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Research Article

A Review On Herbal Medicine Use In The Management Of Tuberculosis

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ARTICLE INFO | **ABSTRACT**

Tuberculosis is indeed a significant global health concern, with a substantial burden in India. This contagious disease spreads in crowded, resource-limited environments through airborne transmission, primarily from coughing or sneezing individuals. Its symptoms encompass hemoptysis, coughing, weight loss, chest pain, blood-tinged sputum, and fever.

India's rich biodiversity offers a promising avenue for potential anti-tuberculosis treatments. Medicinal plants have long been integral to traditional remedies and healthcare in India. These plants contain bioactive compounds such as tannins, alkaloids, phenolic compounds, and flavonoids, which can have therapeutic effects when absorbed into the human body. Several plant species in India have demonstrated anti-mycobacterial properties, making them potential candidates for tuberculosis treatment. Research into these plants and their phytochemical components has the potential to contribute significantly to tuberculosis treatment and prevention. Leveraging India's traditional knowledge and unique flora can offer novel solutions to this global health challenge and potentially reduce the burden of tuberculosis, not only in India but also worldwide. Further investigation and development of these plant-based treatments can offer hope for a more holistic approach to combatting this infectious disease.

Keywords: Phytochemicals, anti-tuberculosis properties, medicinal plant, Mycobacterium tuberculosis.

1. INTRODUCTION

Mycobacterium tuberculosis, the bacterium responsible for tuberculosis (TB), remains a leading cause of death in underdeveloped regions, notably in Asia and Africa. Limited resources for management and treatment perpetuate the disease's prevalence in these areas. According to the World Health Organization (2002), Africa reports the highest TB incidence, contributing to nearly 95% of the global eight million infections. South Africa, with approximately 80% of its population affected, ranks third in TB incidence, following China and India. Over the past 15 years, this rate has surged by 400%, particularly among individuals co-infected with HIV, further highlighting the urgent need for TB control measures in these regions.[1,2,3]
The standard medical treatment for tuberculosis (TB involves a prolonged course of antibiotics. However, adherence to this regimen is often challenging, especially in rural areas, contributing to treatment difficulties. Additionally, the adverse effects of conventional medications, such as gastrointestinal distress, hepatitis, drug interactions, and hearing loss, discourage some individuals from continuing treatment. The emergence of extensively drug-resistant, multi-drug-resistant, and totally drug-resistant TB strains has exacerbated the global health crisis. With M. tuberculosis developing resistance to commonly used antibiotics, many people are now turning to herbal remedies for various medical conditions, seeking alternative approaches to combat this resilient and evolving pathogen.[4,5,6]
Residents of South Africa's Eastern Cape Province have a long history of using traditional plant remedies, including approximately thirty herbs from 21 plant families, to address tuberculosis and related conditions. Traditional healers often combine these plants in polyherbal preparations for treatment. While the specific

constituents of these polyherbal formulations have not been extensively documented, this traditional knowledge is indispensable, as a significant number of TB patients in the region turn to traditional healers for healthcare. Harnessing this expertise is essential in formulating effective strategies for TB treatment and in promoting a comprehensive approach to healthcare that bridges the gap between traditional and modern medicine.[7,8]

INFECTION

Tuberculosis (TB) is a complex disease with distinct phases in its pathogenesis. If TB infection is a contributing factor, it initiates an internal signaling cascade that can either enhance the host's protective response or lead to a pro-inflammatory response. The disease progression can be divided into three primary phases.

The first phase centers on the crucial level of airborne transmission, where infectious droplets from an infected individual are inhaled by a healthy person. Within the initial stages of infection, Mycobacterium tuberculosis (M. tuberculosis) proliferates in the lungs, causing mild discomfort. Alveolar macrophages, key players in infection establishment, are targeted by the bacterium, which employs various strategies to evade and enter these cells.[9,10]

During the ongoing infection, M. tuberculosis evades the cytolytic effects of alveolar macrophages and multiplies within them. Dendritic cells, presenting antigens, transport the information to lymph nodes, where T lymphocytes are activated to form early-stage granulomas. This phase, often referred to as the latent phase, involves limited bacterial growth and extratissue dissemination.

The third and final stage occurs when TB reactivation takes place due to reduced host immunity and the inability to maintain protective responses. The granuloma structure is disrupted, leading to lung cavities and pulmonary TB in these circumstances. The rate of extra-pulmonary TB may also increase as bacteria disseminate.

Understanding these distinct phases in TB pathogenesis is crucial for developing effective treatments and interventions, as well as for preventing the reactivation and spread of this infectious disease.[11,12]

SYMPTOMS & DIAGNOSIS

Tuberculosis (TB) presents a range of symptoms, including coughing, weight loss, chest pain, blood-tinged sputum, and fever. Other manifestations can include weakness, fatigue, drowsiness, shortness of breath, loss of appetite, and wheezing. Some unrelated infections can mimic these symptoms. Therefore, sputum testing is crucial for TB diagnosis.

TB diagnosis relies on clinical characteristics, histology, and the presence of acid-fast bacilli in clinical samples. Skin testing with tuberculin and chest radiography are primary methods for identifying latent TB infection. Advanced diagnostic techniques include ribosomal RNA sequencing, lipid analysis, polymerase chain reaction, restriction fragment length polymorphism, and various rapid diagnostic assays.[13]

Accurate and timely diagnosis of TB is essential for effective treatment and preventing disease spread. Modern diagnostic methods have significantly improved the speed and accuracy of TB detection, allowing for earlier intervention and better management of this infectious disease.[14]

PATHOPHYSIOLOGY

Tuberculosis (TB) presents a range of symptoms, including coughing, weight loss, chest pain, blood-tinged sputum, and fever. Other manifestations can include weakness, fatigue, drowsiness, shortness of breath, loss of appetite, and wheezing. Some unrelated infections can mimic these symptoms. Therefore, sputum testing is crucial for TB diagnosis.

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The protein C3 plays a crucial role in mycobacterial infection. It attaches to the cell wall, promoting mycobacteria's ingestion by macrophages. Opsonization via C3 occurs rapidly, even in areas unexposed to M. tuberculosis. After macrophage phagocytosis, a series of events determines either active disease, termed primary tuberculosis, or successful containment, leading to latent TB. The outcome depends on host defenses and the delicate balance between exposure and the onset of an immune response. Mycobacteria continue to divide inside macrophages, with a bacterial cell division cycle occurring every 25 to 32 hours, further influencing the infection's course and persistence.[18,19,20]

In the battle against mycobacterial infection, macrophages play a pivotal role. Early on, these immune cells release cytokines and proteolytic proteins to combat the invading microbes. Cytokines then recruit T cells, initiating adaptive immunity at the infection site. Macrophages also present mycobacterial antigens to T cells, setting the stage for a well-coordinated immune response. This phase can last from two to twelve weeks, during which bacteria continue to proliferate until they reach a critical mass. It's at this point that cell-mediated immunity is triggered, often detected through a skin test. Granulomas, characteristic nodular formations, develop around M. tuberculosis colonies. These structures result from the concerted efforts of activated T lymphocytes and macrophages, creating a microenvironment that constrains bacterial growth and reproduction, serving as a defence mechanism in individuals with robust cell-mediated immunity.[21,22]
Tuberculosis, in its aggressive form, leads to widespread inflammation by destroying immune cells at the site of infection, potentially harming the bacilli. To enhance its persistence, M. tuberculosis can modify its protein expression. Within a few weeks, the environment becomes characterized by low oxygen, low pH, and nutrient scarcity, leading to necrosis, a state that forces the bacteria into hibernation, limiting their growth. In individuals with robust immune systems, wounds may undergo fibrosis and calcification, effectively containing the infection. In cases of compromised immunity, TB can progress to a more active, severe form, causing greater damage and posing a significant health threat.[23,24]
In individuals with compromised immune systems, the granuloma structure, which initially contains the bacilli, becomes inadequate. The necrotic tissue liquefies, and the granuloma's wall loses its stability. Subsequently, the semi-liquid necrotic material may discharge into a bronchus or nearby blood vessel, creating an air-filled cavity at the lesion's core. In cases of hematogenous dissemination, globules may break free from blood vessels, potentially infecting others. Such discharges into blood vessels can also lead to extra-pulmonary TB. Likewise, bacteria can enter the lymphatic system and accumulate in the tracheobronchial lymph nodes, where they can form new caseous granulomas, contributing to the spread and severity of the disease.[25,26]

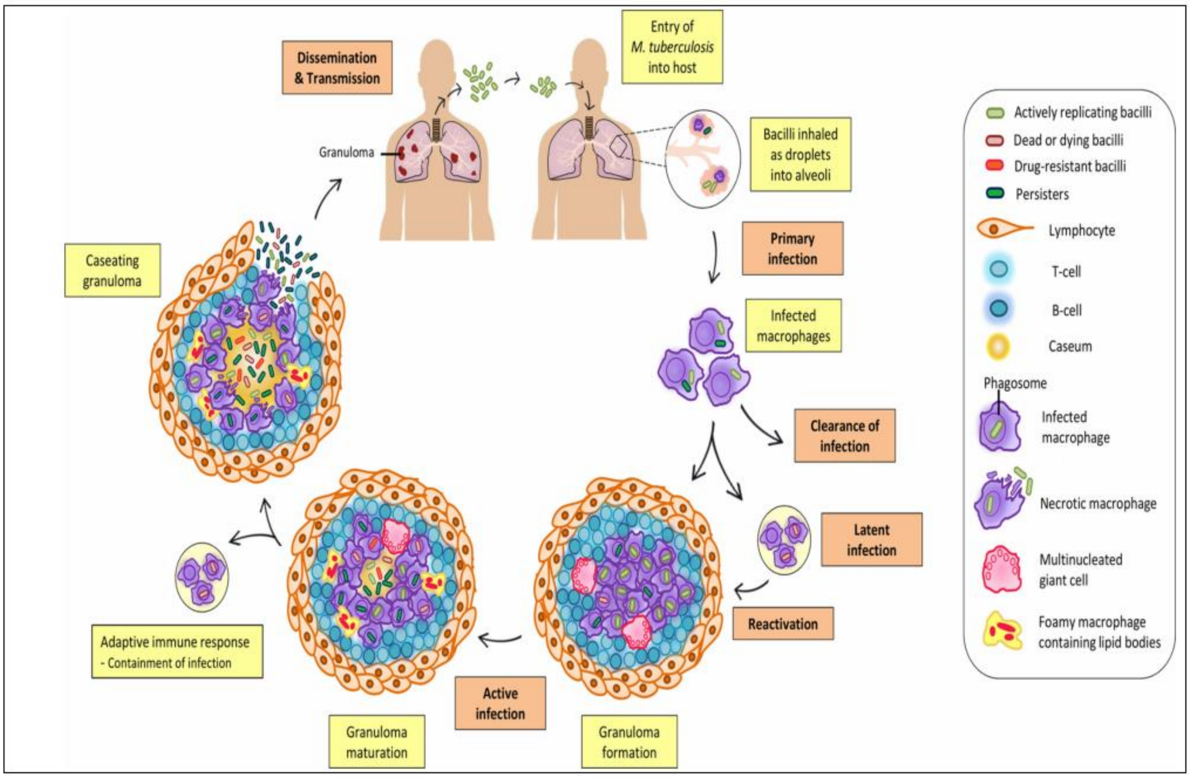

Figure 1. Pathophysiology of tuberculosis

Herbs: as an adjunct to tuberculosis

The WHO recommends a six to nine-month Directly Observed Therapy Short (DOTs) course for tuberculosis treatment. However, the combination of anti-TB drugs can often lead to liver damage due to certain metabolic processes. The primary challenge is to enhance drug efficacy while minimizing side effects. Herbs, used alone or in combination, have shown effectiveness in mitigating medication-related adverse effects. Ethnomedical practices involving plant-based remedies for liver ailments are well-documented. Plants, rich in broad-spectrum secondary metabolites, offer potential for discovering new drug targets to address specific diseases, highlighting the importance of both traditional knowledge and scientific exploration in improving tuberculosis treatment.[27,28]

Moringa oleifera leaves, rich in phytochemicals like alkaloids, flavonoids, carbohydrates, glycosides, saponins, tannins, and terpenoids, exhibit hepatoprotective properties. Oral administration of M. oleifera leaf extract restores normal liver function in rats with hepatic damage induced by anti-TB drugs INH, PZA, and RIF.[29,30]
The leaf extract of Moringa oleifera improves liver function and restores normal blood enzyme levels like bilirubin, alkaline phosphatase, AST, ALT, and reduces lipid peroxidation. Cassia auriculata root extract significantly reduces elevated levels of ALP, AST, ALT, bilirubin, cholesterol, and protein caused by anti-TB drug-induced hepatotoxicity while maintaining normal Malondialdehyde (MDA) and enzymatic antioxidant levels. Terminalia chebula, a valued medicinal herb, is recognized for its antioxidant and cell membrane stabilizing properties in Ayurvedic pharmacopoeia. These plants offer potential in alleviating liver damage induced by anti-TB drugs.[31,32]
Fruits of Terminalia chebula offer protection against hepatotoxicity induced by anti-TB drugs. Herbal formulations containing T. chebula demonstrate hepatoprotective properties. Rats with oxidative liver injury from RIF and INH benefit from a polyherbal mixture including Eclipta alba, Tephrosia purpurea, Curcuma longa, Picrorhiza kurroa, Withania somnifera, Phyllanthus amarus, Pinus succinifera, Pistacia lentiscus, Orchis mascula, and Cycas circinalis. Clinical research highlights the potential of combining medicinal plants with TB drugs to enhance treatment effectiveness. [33,34,35]
In a 12-week study, three patient groups on anti-TB medication were assessed. The first group received capsules with whole plant extracts from Solanum nigrum, Berberis aristata root, and Aloe vera. The second group received a decoction of Phyllanthus fraternus, and the third group received a placebo starch capsule. Liver enzyme levels and activity in the first and second groups remained within the normal range at the study's conclusion. However, the third group experienced an increase in ALT and AST levels, emphasizing the potential benefits of herbal supplements in mitigating drug-induced liver damage. [36,37]
In studies assessing hepatotoxicity, the liver enzymes AST and ALT were utilized as marker enzymes. Berberis aristata is a source of phytochemicals with hepatoprotective and antitubercular properties. Solanum nigrum is a potent antioxidant that regulates detoxification enzymes and scavenges free radicals. Phyllanthus fraternus also displays hepatoprotective qualities. Aswagandha is used as an adjunctive Ayurvedic treatment for pulmonary tuberculosis, enhancing the bioavailability of PYZ and INH, modulating the immune system, and restoring normal SGPT and SGOT levels within 28 days of treatment.[38,39]

Numerous in vitro and animal model studies involving plants like Cassia auriculata, Ficus religiosa, Lawsonia inermis, Moringa oleifera, Terminalia chebula, Tinospora cordifolia, Withania somnifera, and others provide compelling evidence for the hepatoprotective benefits of medicinal herbs in mitigating liver damage caused by anti-TB medications, underlining their potential role in enhancing the overall safety and efficacy of TB treatment.[40,41]
Clinical studies suggest that a combined approach of anti-TB drugs and Ayurvedic medications may lead to improved survival rates in pulmonary tuberculosis patients. Those on TB medication alone had cure and mortality rates of 11.42% and 40.9%, respectively. In contrast, patients receiving a combination of TB medication and Ayurvedic remedies showed a 41.3% cure rate with only 3.8% mortality. Systematic research also supports the effective use of Ayurveda in pulmonary tuberculosis treatment. Herbal remedies have the potential to prevent hepatotoxicity, enhance therapeutic outcomes, and are generally well-tolerated without toxic or adverse effects.[42,43]

ANTI-TUBERCULOSIS PLANT-DERIVED DRUGS

Herbal products are moreover a promising wellspring of antimycobacterial mixes, which may also have colossal work inside the chemotherapy of TB and other breathing tract sicknesses. In each region, considering the climatic and geographic conditions, extra special remedial floras create and a vital wide variety of them have top notch beneficial properties. On account of the adversarial impacts of cutting edge tablets and medications, plants had been an ordinary valuable asset of medicaments inside the cure of a wide volume of ailments.[44,45]
Helpful vegetation were being applied for a extreme long an ideal opportunity to fix numerous pains which include tuberculosis. Thusly, special pharmaceutical things were given from vegetation fill in as unassuming and safe choice. Infusions, macerations, tinctures and decoctions of remedial plant parts, for instance, leaves, roots, stem bark, stem, blossom and natural objects were used for a full-size long time as conventional prescriptions of TB via close by people a way and wide. The standard records on plants is transforming right into a noteworthy asset in making progressively cutting-edge and better prescriptions. In this review, records on several remedial plant life and its phytochemical ingredients was studied.[46,47]

Boerhaavia diffusa, commonly known as 'Punarnava' in traditional Indian medicine, is a perennial herb found in India's wastelands. Its roots are recognized for their diuretic and laxative properties, traditionally used to treat conditions like anasarca, ascites, and jaundice. The medicinal use of Boerhaavia sp. dates back to ancient times. Phytochemistry has identified numerous plant compounds with therapeutic potential, offering natural remedies for various ailments without significant side effects, contributing to the evolution of herbal medicine throughout history.[48,49]

Treatment for tuberculosis, a common and frequently fatal infectious disease, is extremely difficult and often involves lengthy courses of several medications. Fighting antibiotic resistance is becoming more and more important as multi-drug-resistant tuberculosis becomes more prevalent. Investigating different strategies so becomes essential. *Punarnava* (B. diffusa) was used in conjunction with chemotherapy as an adjuvant in the treatment of 25 patients with pulmonary tuberculosis, according to a study by Surya et al. As a control, another group of twenty-five patients was given only chemotherapy. Patients were observed for two months. The findings showed that patients who took Punarnava in addition to chemotherapy recovered clinically and radiologically more quickly, converted their sputum, gained more weight, and had higher T lymphocyte counts than those who just received chemotherapy.[50,51]

Cassia fistula it is known by various common names such as Pudding-Pipe Tree, Purging Cassia, Golden Shower, and Indian Laburnum, belongs to the legume family Fabaceae, specifically the subfamily Caesalpinioideae. Native to the Indian subcontinent and Southeast Asia, it thrives in regions spanning from India to Myanmar, Thailand, Sri Lanka, and southern Pakistan. This captivating plant serves both ornamental and medicinal purposes. It holds cultural significance as the state flower of Kerala, India, the national tree and flower of Thailand, and the provincial flower of Sri Lanka's North Central Province, adding to its global recognition and appeal.[52,53]
This plant has been traditionally used from ancient Indian Hindu civilization and its description was enlisted in Sanskrit books Charaka Samhita, Sasruta Samhita and Atharva Ved.[50,51]
The anti-tuberculosis activity of *Cassia fistula* was done by Chakraborty A K *et al*. Where they isolated a saponin-polybromophenol (CU1) from *C. fistula* bark through ethanol extract and observed that CU1 interact with RNA polymerase, inhibiting open-complex formation and thereby RNA synthesis. To determine the effect of CU1 on RNA polymerases of *Mycobacterium tuberculosis* they had performed fluorescence based in vitro transcription assay. In this study it was shown that CU1 represses the transcriptional activity of *M. tuberculosis* RNAPσ^{A}holo.[54,55]

***Vetiveria zizanioides* L. (Poaceae):-** Khus or Khas grass, scientifically known as Vetiveria zizanioides, was studied for its antimycobacterial properties using an ethanolic extract and its soluble fractions. The research found that both fresh and spent roots of V. zizanioides were effective against both drug-resistant and drug-sensitive strains of Mycobacterium tuberculosis with MIC of 500μg/ml. But hexane extract of *V. zizanioides* shows most repressed activity against TB with MIC value of 50 μg/ml. This suggests that the reported antibacterial activity of vetiver essential oil could be attributed to compounds like vetiverin and other synergistic substances present in the plant, highlighting its potential in combating tuberculosis.[56,57]

Bee glue: - Bees make this glue by collecting plant secretion or from the sticky exudates on buds of cone bearing trees. Propolis extract from Trigona sp. was shown to be more active than that from Apis mellifera L. Although the amounts of 2'-hydroxyformononetin, odoratin, vestitol, butein, dalbergin, 7-hydroxyflavanone, and pinocembrin vary depending on the plant resin that is mixed with their saliva, both species contain these substances.
Propolis is used in the treatment of sores, wounds, viral infections including HIV, gastro-intestinal problems and it has already been used as a traditional method for curing TB. In vitro studies have proved that Propolis extracts can inhibit the growth of TB bacteria while increasing the efficacy of the already established anti-TB drugs like rifampicin, isoniazid and streptomycin. Propolis has shown to work by lowering the formation of granulomas in infected individuals thereby inhibiting TB development.[58,59]
According to Sawicki et al., propolis extract from Trigona sp. caused modifications in mycobacterial cells' transcriptome and metabolism. Propolis may inhibit mycobacteria's ability to synthesize their cell membranes, which leads to the build-up of free radicals and profoundly alters metabolic pathways associated with redox equilibrium.[60,61]

***Artemisia annua* (Chinese traditional medicine):-** A study has shown that artemisinin, known for its antimalarial properties, has the potential to both treat tuberculosis and enhance the efficacy of conventional TB medications. It prevents TB bacteria from entering a dormant, hard-to-treat state by targeting their heme molecule, which is crucial for sensing oxygen levels. Dormant bacteria are highly drug-tolerant, and the immune system induces dormancy to control bacterial growth. By inhibiting dormancy, artemisinin may help shorten treatment duration and delay drug resistance development. This dual-action approach offers promising prospects for more effective TB treatment and improved patient outcomes in the fight against this infectious disease.[62,63]
Extracts from artemisia plants are effective against Mycobacterium TB regardless of the carbon source that the bacteria uses to develop or whether the bacteria enters a hypoxic growth arrest state. This discovery is important because M. tuberculosis breaks down many carbon sources that it comes into contact with during infection. Because M. tuberculosis relies predominantly on cholesterol as a primary carbon source during infection, cholesterol plays a significant role in the infectivity and virulence of the disease. Additionally, any chemicals or carbon sources that block cholesterol metabolism can inhibit the growth of M. tuberculosis. This eventually throws off central metabolism by causing carbon deficiency and metabolic disruption. With a

minimum inhibitory concentration (MIC) of 290 µg/ml, Artemesia dichloromethane extract in cholesterol can prevent M. tuberculosis from receiving carbon sources.[64,65]

***Tridax procumbens* Linn. (Compositae):-** "Coat buttons," often employed in Ayurvedic liver disease treatment, are derived from flower blooms. The microplate alamar blue assay (MABA) assessed their antimicrobial activity against M. tuberculosis. Flavonoids can depolarize membranes and hinder the synthesis of proteins, RNA, and DNA. This potentially reduced bacterial cell density and led to lysis. Tannin, when used as a prolonged subtherapeutic dose of antimicrobial growth-promoting factor (AGP), is especially useful for the selection of antibiotic-resistant microorganisms. These findings highlight the diverse applications and potential benefits of natural compounds in microbial management and therapeutic strategies.[58,59]

***Capparis moonii* wight (Rudanti):-** Rudanti, also known as Tinospora cordifolia, exhibits antioxidant and immunomodulatory properties, bolstering the body's defences. Rudanti is used by ayurvedic doctors to treat pulmonary tuberculosis because it possesses Rasayana (antioxidant and revitalizing) qualities. It activates the Reticulo Endothelial System (RES) and accelerates healing in tubercular lesions, promoting the formation of new healthy tissue and eliminating harmful cells. When Rudanti powder is incorporated into DOTS (Directly Observed Treatment, Short-Course), it offers hepatoprotection due to its components like stachyhydrin, chebulinic acid derivatives, and gallotannins, which possess antitussive and antibacterial activities. These attributes contribute to its potential in tuberculosis treatment.[60,61]

***Calophyllum lanigerum*:-** Calanolides, 4-substituted dipyranocoumarins, are one of the main constituents of C. lanigerum leaf extract. Its efficacy against acid-fast bacillus Mycobacterium TB, including strains of the bacteria resistant to antibiotics and several drugs, has been demonstrated by research. M. tuberculosis is significantly inhibited by C. lanigerum leaf extract (IC50 3.02–3.64 µg/mL). This pyranocoumarin successfully inhibited M. tuberculosis's intracellular replication in macrophages when tested at concentrations below the in vitro minimum inhibitory concentration (MIC). It was hypothesised that calanolide A, like the antitubercular medication rifampicin, may quickly stop the production of RNA and DNA, which would stop the synthesis of proteins. At a MIC of 3.13 µg/ml, (+)-Calanolide A has the highest effectiveness against tuberculosis.[62,63]
Calanolide (+)-A is a non-nucleoside reverse transcriptase inhibitor (NNRTI) known for its potential as an anti-HIV-1 medication. Research has revealed its effectiveness against all strains of Mycobacterium tuberculosis, including drug-resistant strains. Calanolide (+)-A works by swiftly inhibiting the synthesis of proteins, RNA, and DNA in Mycobacterium tuberculosis, making it a promising option for TB treatment.[64,65]

***Salvia aratocensis*: -** The two primary essential oils identified in S. aratocensis are epi-alpha-cadinol and 1, 10-di-epi-cubenol, a sesquiterpene. The essential oil of the plant, containing 1, 10-di-epi-cubenol (a sesquiterpene), has demonstrated effectiveness against Mycobacterium tuberculosis strains, including drug-resistant variants. This highlights its potential as a valuable option in the treatment of tuberculosis.[66,67]

***Salvia aratocensis* (Lamiaceae):-** The essential oil, epi-alpha-cadinol, obtained through hydrodistillation from this plant, exhibits antimycobacterial properties and has proven effective against multidrug-resistant tuberculosis (MDRTB).[68,69]
In a study using those essential oils, Bueno et al. discovered that the MIC values for M. tuberculosis Beijing genotype strains were less than 125 microg mL(-1) and between 200 and 500 microg mL(-1) for nontuberculous mycobacterial strains.[70,71]

Salvia multicaulis

One of the most potent nor-diterpenoid 12-demethylmulticauline found in S. multicaulis root has a minimum inhibitory concentration (MIC) of 0.46 µg/ml and has strong in vitro antimycobacterial action against M. tuberculosis. It is almost as potent as rifampin and shows more activity than ethambutol, the first-line treatment for tuberculosis. A number of other terpenoids are also present that exhibit antimycobacterial activity. For example, the sesquiterpene dehydrocostuslactone has a minimum inhibitory concentration (MIC) of 2 mg/ml. This is followed by the sterol ergosterol-5,8-endoperoxide, which has a MIC of 1 mg/ml, and (E)-phytol, which has a MIC of 2 mg/ml.[72,73]

Eriope blanchetii

The native Brazilian plant Eriope blanchetii produces large amounts of three triterpene acids, mainly betulinic acid, oleanolic, and ursolic acids. By using chromatographic techniques, Silva et al. were able to extract these chemicals from the aerial sections of the plant. Comparing their 1H- and 13C-NMR spectra with published data for the respective methyl ester derivatives was necessary for structural elucidation. An investigation on the antimycobacterial activity of cinnamonate-based esters of the triterpenes betulinic, oleanolic, and ursolic acids was conducted by Tanachatchairatana et al. In this case, betulinic acid's 50 µg/ml MIC showed little antimycobacterial action. With a MIC of 6.25 µg/ml, the p-coumaroyl analogue, another derivative of betulinic acid, had excellent efficacy. The majority of oleanolic acid group's analogues exhibit strong antimycobacterial action, with the exception of cinnamonate ester, which has a MIC of 50 µg/ml. The MIC for p-coumarate ester is 6.25 μg/ml. With MIC of 12.5 μg/ml, the parent chemical in the ursolic acid group demonstrated antimycobacterial action. The MIC value of 6.25 μg/ml indicated the strong activity of the p-coumarate ester.[74,75]

Withania somnifera

In the Indian Ayurvedic medical system, it is used as a rasayana. When using an aqueous extract, the anti-TB activity ranges from 0.01 to 1.0 mg/ml. Ashwagandha, at a dose of 500 mg twice day and Chyawanprash 10g thrice daily for 28 days, also aids in the bioavailability and toxicity reduction of anti-TB medications. Vyas et al. evaluated the adjunct qualities of a Rasayana drug in 133 TB patients receiving RNTCP through a single-blind controlled experiment. This Rasayana mixture contained, among other things, capsule forms of Amalaki, Guduchi, Ashwagandha, Yashtimadhu, and Pippali. The 60-day study was limited to individuals with sputum-positive Category I PTB or additional PTB cases who were older than 13 years. Comparing the treatment group to the control, the chemical was found to reduce PTB symptoms. Notably, the Rasayana with ashwagandha showed a 7.7% rise in body weight along with notable reductions in cough (83%), fever (93%), dyspnea (71.3%), and hemoptysis (87%).[76,77]

CONCLUSION

The urgent need to develop new drugs for combating tuberculosis has prompted extensive research into the potential of traditional knowledge as a source of innovative and effective phytotherapeutic agents. With the increasing resistance of microbial pathogens against a wide range of antibiotics, herbal remedies have emerged as a promising alternative. Traditional healing systems worldwide have relied on various plant species, aquatic organisms, and even parasites, offering a vast reservoir of active compounds and remedies.[78,79]

However, the journey from traditional knowledge to modern medicine is not without challenges. Extracting, purifying, and identifying bioactive compounds from complex plant extracts can be a significant obstacle in natural product research. Nevertheless, the findings of recent studies underscore the critical role of plant extracts in developing safer and more potent medications for combating drug-resistant strains of Mycobacterium tuberculosis, which pose a severe threat to human health.[80,81]

Over time, traditional knowledge has created a repository of home remedies that have stood the test of time, proving to be effective and relatively safe. This accumulated wisdom provides a solid foundation for exploring the use of home remedies in contemporary healthcare. The incorporation of this knowledge, coupled with modern scientific techniques, offers a promising avenue for developing novel drugs to alleviate the global burden of tuberculosis and other infectious diseases. In the face of evolving microbial threats, harnessing the power of nature through traditional knowledge may hold the key to safer and more effective treatments.[82,83]

REFERENCES

1. Dimayuga RE, Garcia SK. “Antimicrobial screening of medicinal plants from Baja California Sur, Mexico”, *J Ethnopharmacol*, vol. 31, 181– 192, 1991.
2. WHO. (World Health Organization). WHO: Global Tuberculosis Programme. Global Tuberculosis Control. WHO Report. World Health Organization, 1998.
3. Sloan DJ, Davies GR, Khoo SH, “Recent advances in tuberculosis: new drugs and treatment regimens”, *Curr Respir Med Rev*, vol 9, 200-210, 2013.
4. Kardos N, Demain AL. “Penicillin: the medicine with the greatest impact on therapeutic outcomes, Appl”, *Microbiol. Biotechnol*, vol. 92, 677-687, 2011.
5. Schatz A, Bugie E, Waksman SA, “Streptomycin, a substance exhibiting antibiotic activity against gram-positive and gramnegative bacteria”, *Proc. Soc. Exp. Biol. Med,* vol. 55, 66-69, 1994.
6. Spellberg B, Shlaes D. “Prioritized current unmet needs for antibacterial therapies”, *Clin. Pharmacol. Ther*, vol. 96, 151-153, 2014.
7. Sivaraj R, Rahman PKSM, Rajiv P, Vanathi P, Venckatesh R. “Biosynthesis and characterization of Acalyphaindica mediated copper oxide nanoparticles and evaluation of its antimicrobial and anticancer activity”, *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, vol. 129, 255-258, 2014.
8. Hill AF. Economic Botany. A textbook of useful plants and plant products. 2nd edn. McGarw-Hill Book Company Inc, New York, 1952.
9. Gupta AK, Tandon N, editors. Reviews of Indian medicinal plants. New Delhi, India: Indian Council of Medical Research; 2004.
10. Sharma SK. Medicinal plants used in Ayurveda. New Delhi, India:National Academy of Ayurveda, Ministry of Health and Family Welfare, Government of India; 1998.
11. Balunas MJ, Kinghorn AD. “Drug discovery from medicinal plants”, *Life Sciences,* vol. 78, 431-441, 2005.
12. Fabricant DS, Farnsworth NR. “The value of plants used in traditional medicine for drug discovery”, *Environmental Health Perspectives*, vol. 109, 69-75, 2001.
13. Sharma SK, Mohan A. “Tuberculosis: From an incurable scourge to a curable disease - journey over a millennium”, Indian *J Med Res*, vol. 137, issue 3, 455-93, 2013.

14. Ahmad S. "Pathogenesis, immunology and diagnosis of latent Mycobacterium tuberculosis infection", *Clin Dev Immunol*, vol 2011, 814943, 2011.
15. Dartois V. "The path of antituberculosis drugs: from blood to lesions to mycobacterial cells", *Nat Rev Microbiol,* vol. 12, issue 3, 159-67, 2014.
16. Cooper AM. "Cell-mediated immune responses in tuberculosis", *Annu Rev*, vol. 27, 393-422, 2009.
17. Dutta NK, Karakousis PC. "Latent tuberculosis infection: myths, models, and molecular mechanisms", *Microbiol Mol Biol Rev*, vol. 78, issue 3, 343-71, 2014.
18. Kaplan G, Post FA, Moreira AL, Wainwright H, Kreiswirth BN, Tanverdi M. "Mycobacterium tuberculosis growth at the cavity surface: a microenvironment with failed immunity", *Infect Immun,* vol. 71, issue 12, 7099-108, 2003.
19. Ulrichs T, Kaufmann SH. "New insights into the function of granulomas in human tuberculosis", *J Pathol*, vol. 208, issue 2, 261-9, 2006.
20. Bozzano F, Marras F, Maria AD. "Immunology of tuberculosis", *Mediterr J Hematol Infect Dis, vol.* 6, issue 1, e2014027, 2014.
21. Rieder HL, Chen-Yuan C, Gie RP, Enarson DA. Clinical Tuberculosis. International Union against Tuberculosis and Lung Diseases. 3rd ed. Oxford: Macmillan Education; 2009.
22. Sudre P, ten Dam G, Kochi A. Tuberculosis: a global overview of the situation today. Bull World Health Organ. 1992;70(2):149-159.
23. Amin A, Vartanian A, Yegiazaryan A, Al-Kassir AL, Venketaraman V. Review of the effectiveness of various adjuvant therapies in treating mycobacterium tuberculosis. Infectious Disease Reports. 2021; 13(3): 821.
24. Debnath PK, Chattopadhyay, et.al. Adjunct therapy of Ayurvedic medicine with anti-tubercular drugs on the therapeutic management of pulmonary tuberculosis. Journal of Ayurveda and Integrative Medicine. 2012; 3(3): 141–149.
25. Holland DP, Sanders GD, Hamilton CD, Stout JE. Costs and cost-effectiveness of four treatment regimens for latent tuberculosis infection. American Journal of Respiratory and Critical Care Medicine. 2009; 179(11): 1055–1060.
26. Khan KH. Roles of Emblica Officinalis (Amla) in Medicine. 2014; 3(6): 604–615.
27. Khusro A, Aarti C, Barbabosa-Pliego A, Salem AZM. Neoteric advancement in TB drugs and an overview on the anti-tubercular role of peptides through computational approaches. Microbial Pathogenesis. 2018; 114: 80–89.
28. Kurane SB, Singh VB, Waghmare SD. Rehabilitation of pulmonary tuberculosis patient with Kharjuradi Ghrita and Pranayama: A study. International Journal of Research in Health Sciences. 2014; 2(3): 755–760.
29. Mueller-Wieland K. Tuberculosis and nutrition. Deutsches Medizinisches Journal. 1961; 12: 145–149.
30. Samal J. Ayurvedic management of pulmonary tuberculosis: A systematic review. Journal of Intercultural Ethnopharmacology. 2016; 5(1): 86–91.
31. Saroya AS. Herbal drugs as therapeutic agents. Herbal Drugs as Therapeutic Agents. August 2014; 1–214.
32. Shingate PN DP, KD. New Method Development for Extraction and Isolation of Piperine from Black Pepper | International Journal of Pharmaceutical Sciences and Research. International Journal of Pharmaceutical Sciences and Research. 2013; 4(8): 3165–3170.
33. Starke JR. Modern approach to the diagnosis and treatment of tuberculosis in children. Pediatric Clinics of North America. 1988; 35(3): 441–464.
34. Tandon N, Yadav SS. Contributions of Indian Council of Medical Research (ICMR) in the area of Medicinal plants/Traditional medicine. Journal of Ethnopharmacology. 2017; 197: 39–45.
35. Verma S, Singh SP. Current and future status of herbal medicines. Veterinary World. 2008; 1(11): 347–350.
36. Xu Y, Liang B, Kong C, Sun Z. Traditional Medicinal Plants as a Source of Antituberculosis Drugs: A System Review. BioMed Research International. 2021
37. Semenya SS, Maroyi A. Medicinal plants used for the treatment of tuberculosis by Bapedi traditional healers in three districts of the Limpopo Province, South Africa. African Journal of Traditional, Complementary, and Alternative Medicines: AJTCAM / African Networks on Ethnomedicines. 2013; 10(2): 316–323.
38. Mathew TS. Performance of the Alcohol Use Disorders Identification Test among Tuberculosis Patients in Russia. Substance Use & Misuse. 2010; 45(4): 598-612.
39. Singh M, Kaur M, Silakari O. Flavones: an important scaffold for medicinal chemistry. European Journal of Medicinal Chemistry. 2014; 84: 206–239.
40. Cantrell CL, Franzblau S, Fischer N. Antimycobacterial plant terpenoids. Planta Medica. 2001; 67(8): 685–694.
41. Abedinzadeh M, Gaeini M, Sardari S. Natural antimicrobial peptides against Mycobacterium tuberculosis. Journal of Antimicrobial Chemotherapy. 2015; 70(5): 1285–1289.
42. Katoch VM. "Newer diagnostic techniques for tuberculosis", *Indian J Med Res*, vol. 120, issue 4, 418-28, 2004.
43. Steingart KR, Ramsay A, Dowdy D, Pai M. "Serological tests for the diagnosis of active tuberculosis: relevance for India", *Indian J Med Res,* vol. 135, issue 5, 695-702, 2012.

44. Frieden TR, Sterling TR, Munsiff SS, Watt CJ, Dye C. “Tuberculosis”, *Lancet,* vol. 362, 887-899, 2003.
45. Jensen PA, Lambert LA, Iademarco MF, Ridzon R; “Centers for Disease Control and Prevention. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care settings, 2005”, *MMWR Recomm Rep*, vol. 54 RR-17, 1-141, 2005.\
46. American Thoracic Society and Centers for Disease Control and Prevention. Diagnostic standards and classification of tuberculosis in adults and children. *Am J Respir Crit Care Med*, vol. 161, issue 4, 1376-1395, 2000.
47. Korf JE, Pynaert G, Tournoy K. “Macrophage reprogramming by mycolic acid promotes a tolerogenic response in experimental asthma”, *Am J Respir Crit Care Med*, vol. 174, issue 2, 152-160, 2006.
48. van Crevel R, Ottenhoff THM, van der Meer JWM. “Innate immunity to Mycobacterium tuberculosis”, *Clin Microbiol Rev*, vol 15, 294-309, 2002.
49. Nicod LP. “Immunology of tuberculosis”, *Swiss Med Wkly*, vol. 137, issue 25-26, 357-362, 2007.
50. Li Y, Petrofsky M, Bermudez LE. “Mycobacterium tuberculosis uptake by recipient host macrophages is influenced by environmental conditions in the granuloma of the infectious individual and is associated with impaired production of interleukin-12 and tumor necrosis factor alpha:, *Infect Immun*, vol. 70, 6223-6230, 2002.
51. Ferguson JS, Weis JJ, Martin JL, Schlesinger LS. “Complement protein C3 binding to Mycobacterium tuberculosis is initiated by the classical pathway in human bronchoalveolar lavage fluid”, *Infect Immun*, vol. 72, 2564-2573, 2004.
52. Porth CM. Alterations in respiratory function: respiratory tract infections, neoplasms, and childhood disorders. In: Porth CM, Kunert MP. Pathophysiology: Concepts of Altered Health States. Philadelphia, PA: Lippincott Williams & Wilkins; 2002:615-619.
53. Goyot-Revol V, Innes JA, Hackforth S, Hinks T, Lalvani A. “Regulatory T cells are expanded in blood and disease sites in patients with tuberculosis”, *Am J Resp Crit Care Med*, vol. 173, 803-810, 2006.
54. Rosenkrands I, Slayden RA, Crawford J. “Hypoxic response of Mycobacteria tuberculosis studied by metabolic labeling and proteome analysis of cellular and extracellular proteins”, *J Bacteriol*, vol. 184, 3485-3491, 2002.
55. Knechel NA. “Tuberculosis: pathophysiology, clinical features, and diagnosis”, *Crit Care Nurse*, vol. 29, issue 2, 34-43, 2009.
56. Dheda, K, Booth H, Huggett JF. “Lung remodeling in pulmonary tuberculosis”, *J Infect Dis,* vol. 192, 1201-1210, 2005.
57. Kuete V, Tabopda TK, Ngameni B, Nana F, Tshikalange TE, Ngadjui BT. “Antimycobacterial, antibacterial and antifungal activities of *Terminalia superba* (Combretaceae)”, *S Afr J Bot*, vol. 76, 125-31, 2010.
58. Cowan MM. “Plant products as antimicrobial agents”, *Clin Microbiol Rev,* vol. 12, issue 4, 564-82, 1999.
59. Debnath PK, Chattopadhyay J, Mitra A, Adhikari A, Alam MS, Bandopadhyay SK. “Adjunct therapy of Ayurvedic medicine with antitubercular drugs on the therapeutic management of pulmonary tuberculosis”, *J Ayurveda Integr Med,* vol. 3, issue 3, 141-9, 2012.
60. Gupta R, Thakur B, Singh P, Singh HB, Sharma VD, Katoch VM. “Anti-tuberculosis activity of selected medicinal plants against multidrug resistant *Mycobacterium tuberculosis* isolates”, *Indian J Med Res*, vol. 131, 809-13, 2010.
61. Sharma D, Yadav P, Jaya. An Overview of Phytotherapeutic Approaches for the Treatment of Tuberculosis. *Mini Rev Med Chem*, vol. 17, issue 2, 63-83, 2017.
62. Ramachandran SS, Balasubramanian S. Plants: A source for new antimycobacterial drugs. *Planta Med*, vol. 80, issue 1, 9-21, 2014.
63. Ramos DF, Leitao GG, Costa FN, Abreu L, Villarreal JV, Leitao SG. “Investigation of the antimycobacterial activity of 36 plant extracts from the Brazilian Atlantic Forest”, *Braz J Pharm Sci*, vol. 44, 669-74, 2008.
64. Saikia D, Parveen S, Gupta VK, Luqman S. “Anti-tuberculosis activity of Indian grass KHUS (Vetiveria zizanioides L. Nash)”, *Complement Ther Med,* vol. 20, issue 6, 434-6, 2012.
65. Kaura T, Sharma P, Gupta GK, Ntie-Kang F, Kumara D. “Treatment Of Tuberculosis By Natural Drugs: A Review”, *Plant Archives*, vol. 19, 2168-76, 2019.
66. Valcic S, Montenegro G, Mujica A.M, Avila G, Franzblau S. “Phytochemical, morphological, and biological investigations of propolis from Central Chile”, *Zeitschrift Fur Naturforschung C,* vol. 54, 406-416, 1999.
67. Jackson M, McNeil M.R, Brennan P.J. “Progress in targeting cell envelope biogenesis in Mycobacterium tuberculosis” *Future Microbiol*, vol. 8, 855-875, 2013.
68. Zhang D, Lu Y, Liu K, Liu B, Wang J, Zhang G. “Identification of less lipophilic riminophenazine derivatives for the treatment of drug-resistant tuberculosis”, *J Med Chem*, vol. 55, 8409-8417, 2012.
69. Saraf S, Dixit VK. “Hepatoprotective activity of Tridax procumbens”, *Fitoterapia*, vol. 62, 534-536, 1991.
70. Dzoyem JP, Hamamoto H, Ngameni B. “Antimicrobial action mechanism of flavonoids from Dorstenia species”, *Drug Discoveries and Therapeutics*, vol. 7, issue 2, 66-72, 2013.
71. Lin YM, Zhou Y. “Chalcones and flavonoids as an antituberculosis agent”, *Bioorg Med Chem*, vol. 10, 2795-02, 2002.
72. Saukkonen JJ, Cohn DL, Jasmer RM, Schenker S, Jereb JA, Nolan CM. “An official ATS statement: hepatotoxicity of antituberculosis therapy”, *Am J Respir Crit Care Med*, vol. 174, issue 8, 935-52, 2006.

73. Ali M, Ramachandram R, Rafiullah MRM, Singh O, Siddiqui AW, Mir SR. “Prevention of Carbon Tetrachloride-Induced Hepatotoxicity by the Ethanol Extract of *Capparis moonii* Fruits in Rats”, *Pharmaceutical Biology*, vol. 42, issue 4-5, 286-8, 2008.
74. Chakraborty AK, Saha S, Poria K, Samanta T, Gautam S, Mukhopadhyay J. A saponin-polybromophenol antibiotic (CU1) from Cassia fistula Bark Against Multi-Drug Resistant Bacteria Targeting RNA polymerase. Curr Res Pharmacol Drug Discov. 2022 Feb 3;3:100090. doi: 10.1016/j.crphar.2022.100090. PMID: 35198968; PMCID: PMC8844791.
75. Nayak P, Thirunavoukkarasu M, A review of the plant *Boerhaavia diffusa*: its chemistry, pharmacology and therapeutical potential, JPHYTO, 2016; 5(2):83-92.
76. Bueno J, Escobar P, Martínez JR, Leal SM, Stashenko EE. Composition of three essential oils, and their mammalian cell toxicity and antimycobacterial activity against drug resistant-tuberculosis and nontuberculous mycobacteria strains. Nat Prod Commun. 2011 Nov;6(11):1743-8. PMID: 22224302.
77. e Silva Mde L, David JP, Silva LC, Santos RA, David JM, Lima LS, Reis PS, Fontana R. Bioactive oleanane, lupane and ursane triterpene acid derivatives. Molecules. 2012 Oct 17;17(10):12197-205. doi: 10.3390/molecules171012197. PMID: 23075816; PMCID: PMC6268083.
78. Cantrell C L, Franzblau S, Fischer N H, Antimycobacterial Plant Terpenoids, Planta Med 67 (2001) 685-694.
79. Tanachatchairatana T, Bremner J B, Chokchaisiri R, Suksamrarn A, Antimycobacterial Activity of Cinnamate-Based Esters of the Triterpenes Betulinic, Oleanolic and Ursolic Acids, Chem. Pharm. Bull. 56(2) 194—198 (2008).
80. Nahar L, Talukdar A D, Nath D, Nath S, Mehan A, Ismail F MD, Sarker S D, Naturally Occurring Calanolides: Occurrence, Biosynthesis, and Pharmacological Properties Including Therapeutic Potential, *Molecules* 2020, 25, 4983; doi:10.3390/molecules25214983.
81. Nagar L, Lamo R, Dwivedi K N, Comprehensive Ethnopharmacological Review Of *Rudanti (Capparis Moonii* Wight), IJPSR, 2020; Vol. 11(2): 556-562.
82. Saikia D, Parveen S, Gupta VK, Luqman S. Anti-tuberculosis activity of Indian grass KHUS (Vetiveria zizanioides L. Nash). Complement Ther Med. 2012 Dec;20(6):434-6. doi: 10.1016/j.ctim.2012.07.010. Epub 2012 Aug 29. PMID: 23131375.
83. Kiani B H, Alonso M N, Weathers P J, Shell S S, Activity against Mycobacterium tuberculosis in Physiologically Relevant Carbon Sources and Hypoxia, Pathogens 2023, 12(2), 227.