REVIEW

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Advances in adjunct therapy against tuberculosis: Deciphering the emerging role of phytochemicals

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Abstract

Eastern countries are a major source of medicinal plants, which set up a rich source of ethnopharmacologically known medicines used in the treatment of various diseases. These traditional medicines have been known as complementary, alternative, or nonconventional therapy across globe for ages. Tuberculosis (TB) poses a huge global burden and leads to maximum number of deaths due to an infectious agent. Treatment of TB using Directly Observed Treatment Short-course (DOTS) therapy comprises multiple antibiotics is quite lengthy and causes serious side-effects in different organs. The length of the TB treatment leads to withdrawal from the patients, which paves the way for the emergence of drug resistance in the bacterial population. These concerns related to therapy need serious and immediate interventions. Traditional medicines using phytochemicals has shown to provide tremendous potential in TB treatment, mainly in the eradication of *Mycobacterium tuberculosis* (*M.tb*), increasing natural immunity, and managing the side effects of anti-TB drugs. This review describes the antituberculosis potential of selected ethnopharmacologically important phytochemicals as potential immune-modulator and as an adjunct-therapy in TB. This review will be a useful reference for researchers working on ethnopharmacology and will open the door for the discovery of novel agents as an adjunct-therapy to tuberculosis.

KEYWORDS
adjunct therapy, cytokines, immunomodulation, *Mycobacterium tuberculosis*, phytochemicals, T cells

1 | INTRODUCTION

Tuberculosis (TB) is a communicable disease caused by slow-growing, acid-fast bacillus *Mycobacterium tuberculosis (M. tuberculosis)*. BCG (*Bacillus Calmette-Guérin*) is the only validated vaccine against pulmonary TB. However, despite years of vaccination and antibiotic therapy, TB remains a threat with 10.5 million new cases reported in 2019.[1] WHO reports that there are documented 10.5 million new cases of TB each year with almost 1.8 million deaths. Needless to say that about one-third of the cases still remain unreported.[2]

M. tuberculosis is inhaled in the form of small aerosol droplets containing the bacilli and is transmitted to healthy

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│  Directly Observed Treatment, Short course (DOTS)- 6 to 9  │
│  months long,  first-line anti-TB agents that form the core │
│          of treatment regimens are:                    │
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Isoniazid	**Rifampicin**	**Pyrizinamide**	**Ethambutol**
Inhibition of mycolic acid synthesis in bacteria.	Binds to the β subunit of bacterial DNAdependent RNA polymerase, thereby inhibiting RNA synthesis.	Prodrug of pyrazinoic acid, which acts by an unknown mechanism; may inhibit synthesis of fatty acids in bacteria.	Inhibits arabinosyl transferases involved in polymerization of arabinoglycan (cell wall).

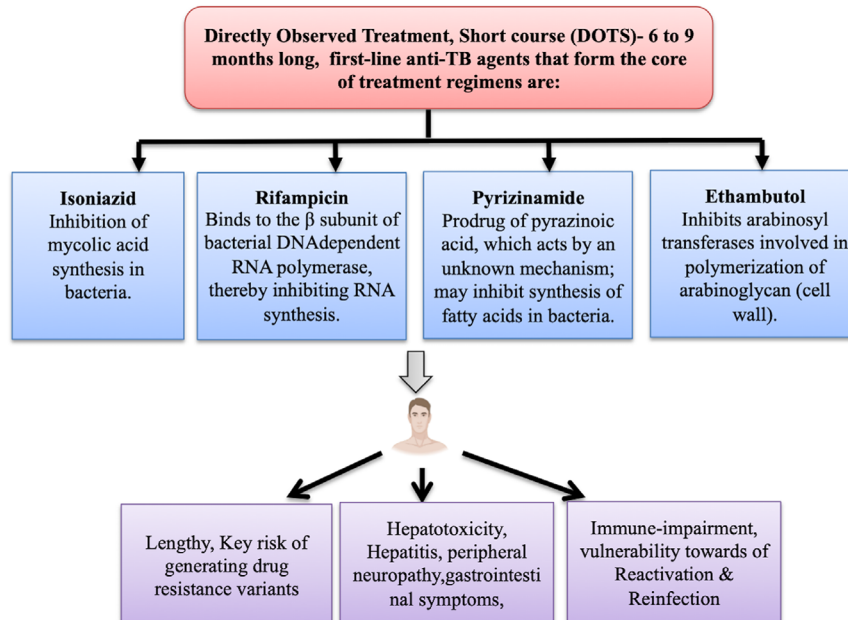| Lengthy, Key risk of generating drug resistance variants	Hepatotoxicity, Hepatitis, peripheral neuropathy,gastrointestinal symptoms,	Immune-impairment, vulnerability towards of Reactivation & Reinfection

FIGURE 1 Tuberculosis treatment and associated side effects

individual from an infected person through the respiratory route via inhalation into the lungs. The bacteria travel through the lungs and reside in the alveoli of the lungs. In 90% of the infected individuals, the infection does not lead to active disease and is called a latent state of infection where bacteria can live for many years in a nonreplicating state. In the remaining 10% individuals, who are in immune-compromised state, the disease may take the active replicating form.[3] Treatment of TB is globally known as "Directly Observed Treatment Short-course (DOTS)." It is a multidrug and a long-term therapy. It consists of many antibiotics that cause severe toxicity and side effects.[4,5] After approximately 4 weeks of treatment with antibiotics, the patient's condition improves significantly, causing him to discontinue the treatment regime, which can give rise to drug-resistant persister populations. Moreover, the treatment is expensive considering the income of the patients in the developing countries and there is a significant risk of the generation of multidrug-resistant (MDR) and extensive drug-resistant (XDR) strains of bacteria.[4,5] In some adverse cases, the side effects of the antibiotics cause liver diseases such as hepatitis with a mortality of 5% and dampens the hosts' T-cell immune response. Frontline anti-TB drugs such as rifampin have adverse side effects like thrombocytopenia and itching, isoniazid causes neuropathy and T-cell reduction. Isoniazid, pyrazinamide, and rifampin cause drug-induced hepatitis with high mortality rate.[5] The side effects of the DOTS therapy have been schematically represented in Figure 1. Therefore, we need an alternative therapeutic approach that may limit the side-effects associated with anti-TB therapy.

A thorough understanding of the host immune response after *M. tuberculosis* infection is essential for the development of effective vaccine strategies and immune therapeutics. *M. tuberculosis* infects the healthy individuals by getting inhaled in form of the bacilli containing aerosol droplets, which are released from an infected person. After getting inhaled, the bacteria travel through the mucosal pathway and reach the alveoli of the lungs. The alveolar macrophages are the first cells that encounter these pathogens and engulf them.[6] These macrophages secrete cytokines and chemokines that recruit other inflammatory cells to the site of infection. Alveolar macrophages together with neutrophils and other inflammatory cells organize themselves into compact structures called granulomas. Granulomas form in the lungs to limit the growth of *M. tuberculosis*. The macrophages and dendritic cells migrate to lymph nodes and present the mycobacterial antigens to the T cells in the lymph nodes. Upon antigen presentation, naïve T cells differentiate into CD4+ and CD8+ T cells and move back to the lungs.[6] These T cells mainly T-helper 1 (Th1) cells and T-helper 17 (Th17) cells eliminate the bacteria by secretion of pro-inflammatory cytokines such as IFN-γ, TNF-α, and cytolytic killing mechanisms, respectively. The granuloma consisting of a core of infected macrophages, surrounded by epithelioid cells, lymphocytes, neutrophils, and mesenchymal stem cells (MSCs) is maintained by a delayed-type hypersensitivity (DTH) response to the bacterial antigens and tumor necrosis factor-alpha (TNF-α).[6,7] In 90% of the infected individuals, the *M. tuberculosis* remains in the granulomatous structure for a very long time in a nonreplicating, asymptomatic state called as the "dormant state."[7] Antigen-specific regulatory T (Treg) cells and T helper 2 (Th 2) cells also get differentiated and counter the pro-inflammatory response in order to maintain homeostasis in the infected host.[8]
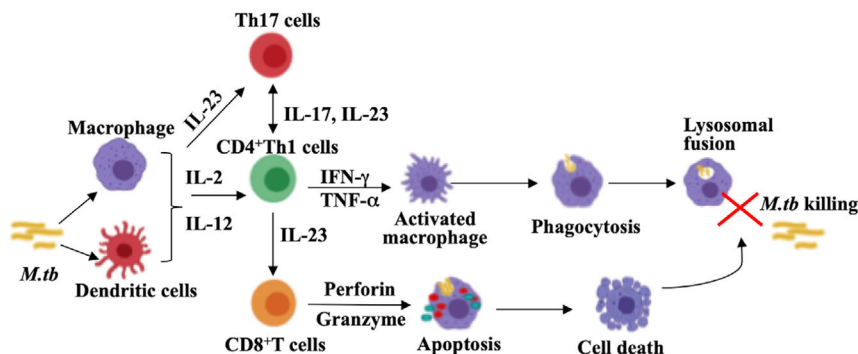
FIGURE 2 The role of T cells in Tuberculosis pathogenesis and bacterial clearance
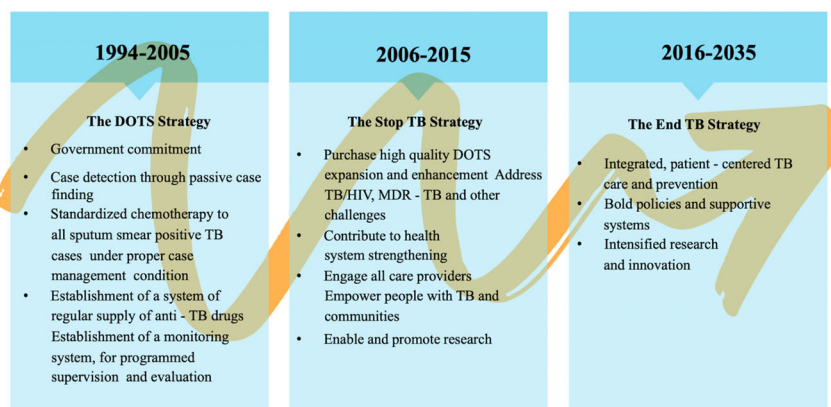

FIGURE 3 Evolution and the pillars of global TB eradication strategies

M. tuberculosis resides in the granuloma in dormant state for decades by utilizing the host lipids and slowing down their replicative genes[9] and wait for an opportunity such as a weakened immune system to reactivate and cause active disease.[8] Elimination of actively dividing bacteria in the macrophages involves the role of macrophages and T helper (Th) cell responses whereas latent *M. tuberculosis* that is supported by the host MSCs requires myriad other factors and responses to get cleared up.[9] Thus, Th1 and Th17 cells are the most important arms of adaptive immunity that are responsible for maximum protection against tuberculosis infection.[10,11] The crucial role of T cells and their secreted cytokines in TB pathogenesis has been described in Figure 2.

The major challenges faced by TB eradication programmes are the failure of BCG vaccination in protection against adult pulmonary TB, the length and side effects of DOTS therapy, slow progress in new drug development approaches, and the emergence of drug resistance in TB strains.[1,5] Therefore, we urgently need an improved alternate therapeutic approach that can overcome these limitations to deal with the deadly pathogen better. This is the utmost requirement of the 2035 end TB goal as set by the WHO. We have described the pillars of global TB management programme in Figure 3. Thus, in such a scenario a therapy that could be derived from natural plants to bal-

ance out the toxicity associated with the drugs used in the DOTS therapy and thereby rejuvenates the immune system, to avoid or prevent disease reactivation is urgently needed and would be very beneficial. These compounds are mainly extracted from the plants that have been used in traditional medicines for ages and have shown promising effects. These compounds may be used either as drug candidates or immunomodulatory agents with therapeutic potential against TB. Here, in this review paper, we would mainly focus on ethnomedical agents/compounds, which have been used as immunomodulators or as an adjunct therapy to reduce the toxicity of the DOTS therapy and induce Th1 response and/or Th17 host protective immune response simultaneously. This review is an effort to summarize such compounds, known as phytochemicals with their detailed mechanism of action.

2 | TREATMENT OF TUBERCULOSIS USING TRADITIONAL MEDICINES DERIVED FROM PLANTS

Tuberculosis is an ancient disease as evident from the skeletal deformities found in the Egyptian mummies belonging to 2400 BC, but it has been only around 2000 years since the first report of TB was documented in India and China.[12] The traditional treatment of TB is practiced

based on indigenous knowledge possessed by the local healers. Earliest known treatment of this disease consisted of natural methods to manage TB and comprised various rituals derived from old traditional practices.[13] Age-old practices related to TB treatment that have been handed down from generation to generation and are still part of TB therapy in various countries of South Africa and Asia.[14–21] These traditional therapies although are not capable of completely eradicating the disease but are quite effective in treating the respiratory disorders associated with TB and reducing the toxicity associated with antituberculosis therapy (ATT) as observed by the treatment provided in the patients by the traditional healers. Researchers all over the globe are trying to find new antimicrobials from rich and medically significant plant secondary metabolites belonging to the Indian subcontinent, South Africa, and other eastern countries.[15,16,18]

Since traditional treatment is practiced mostly on a local scale therefore, the plants used for the treatment vary considerably based on the country or place where it is followed. Researchers from high TB burden countries have reported different plant species used locally by traditional healers for the treatment of TB and as the literature suggests, most widely used plant species in the treatment of TB belong to Asteraceae, Asparagaceae, Amaryllidaceae, Apiaceae, Rutaceae, Solanaceae, and Leguminosae families where plant parts such as roots, leaves, barks bulbs, and fruits contribute to the treatment of the patients.[20,22,23,24]

These plant extracts do not eradicate the bacteria all on their own but they seem to play a very crucial role in managing symptoms related to TB such as prolonged cough, chest pains, fatigue, appetite loss, and fever that increase the level of discomfort in patients. These plant extracts or secondary metabolites exert expectorant, bronchodilator, anti-inflammatory, and antipyretic effects. Since hundred years, plants such as *Tussilago farfara* and *Pulmonaria officinals* are being explored for these properties in the treatment of TB.[25] Treatment of TB through the use of plants/phytochemicals constitutes a comprehensive approach, which could give TB treatment an improved outlook.

3 | PHYTOCHEMICALS USED IN TUBERCULOSIS THERAPY WITH THEIR POTENTIAL ROLE IN ATT

The word "Phytochemicals" refers to a variety of naturally occurring and biologically active substances in plants that have protective or disease curing properties. The word "phytochemical" has been derived from the Greek word "phyton," which means plants.[26] The phytochemicals are basically the chemicals produced in plants mostly as part of protection mechanism utilized by the plants

to help them thrive predators and pathogens. They are the product of primary or secondary metabolism of the plant.[26] These compounds have a history of being used in biomedical therapies and their therapeutic properties are mainly associated with the presence of many different compounds such as carotenoids, flavonoids, isothiocyanates, indoles, monoterpenes, and phenolic acids.[27] The British Nutrition Foundation has classified these phytochemicals into four major categories: terpenoids, phenolics, nitrogen-containing compounds, and sulfur-containing compounds.[27] Till now, an ample number of phytochemicals have been screened but due to the lack of detailed analysis, this area of research has been continuously neglected and therefore needs to be strengthened by new research. Limited studies have been conducted so far in exploring the potential role of phytochemicals in antituberculosis therapy. Many researchers now giving attention to the role of phytochemicals in TB therapy, as this therapy might help improve the effects of DOTS treatment. Some studies report the promising effect of the phytochemicals against *M. tuberculosis* bacteria.[28,29] However, these studies fail to compile the host protective mechanisms or the immunotherapeutic use of these compounds. The domain of phytochemical studies against *M. tuberculosis* is very broad and promising and is therefore in drastic need of further exploration. We know that DOTS therapy while eliminating the bacteria dampens the host immune system. An adjunct drug or compound that could prevent the dampening of the immune cells will prove to be a boon for TB treatment.

In the following section, we have tried to summarize the known phytochemicals, which have been used in TB therapy. We have also discussed the antimicrobial activity of these phytochemicals with special impetus on their use in the prevention and treatment of tuberculosis.

3.1 | Allicin

Garlic (*Allium sativum*) is a commonly used food ingredient that has been widely acclaimed for its contribution to human health for centuries. Garlic is used in the prevention and treatment of a variety of infectious and noninfectious diseases.[30–32] Garlic is a strong antibacterial agent and can inhibit the growth of both Gram-positive and Gram-negative bacteria.[33] Allicin is the main constituent of garlic with potential antimicrobial properties (Figure 4A). It is an oxygenated sulfur compound, which is chemically known as thio-2-propene-1-sulfinic acid S-allyl ester. Allicin is an inhibitor of sulfhydryl metabolic enzymes. It interacts with the SH- group of the enzymes to exert its antimicrobial effects.[34] Garlic has inexhaustible research history against mycobacterial infection. In 1944, Rao et al reported the reduction in *M. tuberculosis*
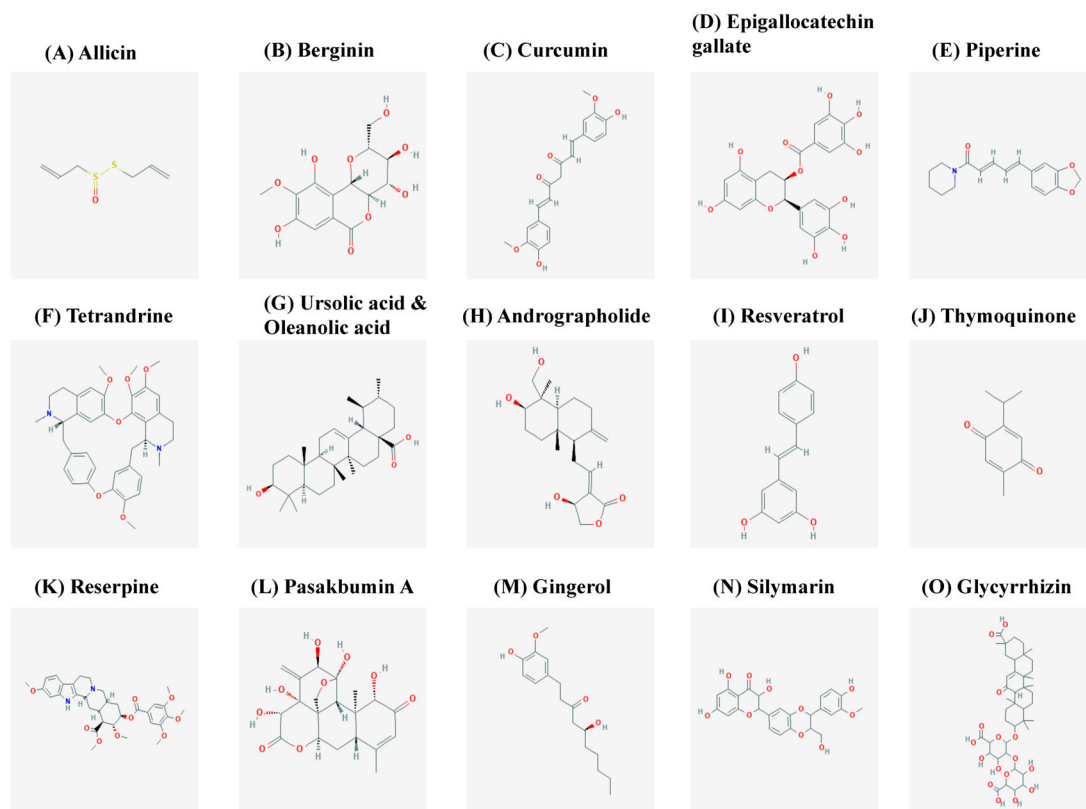
FIGURE 4 Structure of phytochemicals used for the treatment of tuberculosis. (A) Allicin, (B) Bergenin, (C) Curcumin, (D) Epigallocatechin gallate, (E) Piperine, (F) Tetrandrine, (G) Ursolic acid and Oleanolic acid, (H) Andrographolide, (I) Resveratrol, (J) Thymoquinone, (K) Reserpine, (L) Pasakbumin A, (M) Gingerol, (N) Silymarin, and (O) Glycyrrhizin (Adapted from PubChem)

replication upon treatment with allicin. They observed a bacteriostatic effect at low concentrations and a bactericidal effect at higher concentrations of the compound.[35] A further study by Ratnakar et al in 1995 reported that garlic was able to inhibit the growth of isoniazid-susceptible and -resistant strains, H37Rv and TRC-C1193, respectively.[36] In the following years, it was reported that allicin reduces *M. tuberculosis* burden in the host by increasing the activity of the enzyme, glutathione peroxidase.[37] Another interesting in vitro study compared the antitubercular activity of *Allium sativum* with standard antibiotics using the disc diffusion method.[38] These results established that garlic exhibited maximal activity against multiple drug-resistant *M. tuberculosis* as well.[38] In 2006, Hasan et al studied the reduction in Reactive Oxygen Species (ROS) expression induced by the bacilli, upon treatment with allicin.[39] In 2014, Vishwanathan et al reported in an in vitro study that garlic extract and garlic oil both show decent antimycobacterial activity when compared to standard drugs, using zone inhibition method.[40] A recent study by Dwivedi et al has given some strong proofs to establish the therapeutic potential of allicin in the pathogenesis of tuberculosis. Allicin/garlic extract displays direct killing of Mycobacteria and leads to the induction of pro-inflammatory cytokines in macrophages while also limiting *M. tuberculosis* infection inside the cells by interacting with the cell

surface receptors responsible for *M. tuberculosis* entry.[41] Experiments done in mice model establish that treatment of infected mice with allicin/garlic extract leads to a significant reduction in bacterial burden mainly due to host protective Th1 response, which eliminates the pathogens in a much lesser time duration compared to the conventional treatment coarse. Furthermore, garlic extract also has been shown to reverse the immune-dampening effects associated with the use of standard TB drugs.[41] In a nutshell, allicin/garlic extract showed very promising results in infected mice when used alone or as an adjunct to classical antibiotics for both drug-sensitive and -resistant strains. Another compound derived from garlic, known as ajoene, has shown tremendous effectiveness in TB treatment due to its ability to induce autophagy and ROS synthesis.[40–42] The therapeutic value of these compounds and their broad-spectrum antimicrobial activity suggests garlic and its derivatives can be a beneficial addition to ATT.

3.2 | Bergenin

Bergenin is a natural secondary metabolite found in different parts of several plants.[43] It is also known as cuscutin and is a trihydroxybenzoic acid glycoside (Figure 4B). It is

one of the active phytochemicals in herbal and ayurvedic formulations. Bergenin has a myriad of ethanomedical properties like antibacterial, antiviral, antifungal, antitussive, anti-inflammatory, antitumor, antidiabetic, and wound-healing properties.[44] Of late, the effectiveness and properties of bergenin have been studied by different groups in different disease contexts. Nunomora et al did some initial research on the existing anti-inflammatory properties of bergenin.[45] Later, in 2016, Khan et al reported that bergenin has remarkable activity against the chloroquine-sensitive *Plasmodium falciparum* and also shows antioxidant properties.[46] Recently Dwivedi et al have demonstrated the effectiveness of this phytochemical in tuberculosis management. Their investigation revealed that bergenin treatment in infected macrophages led to the activation of the MAP kinase and ERK pathways, which further lead to TNF-α, nitric oxide (NO), and Interleukin-12 (IL-12) production. Further, when observed in murine model, bergenin induces the expression of Th1 and Th17 immune responses and limit the replication of the bacteria.[47] They also studied that a combination therapy of DOTS along with bergenin reverses the immune damage and reduces the duration of clearance of *M. tuberculosis* in mice.[48] Therefore, to summarize cotreatment with bergenin and isoniazid reduces the side effects associated with isoniazid such as immune dampening, while promoting the generation of long-lasting, central memory T-cell responses.[47,48] Notably, bergenin acted well in the elimination of drug-resistant strains as well. Therefore, bergenin can be a prospective adjunct to current TB therapy.

3.3 | Curcumin

Curcumin, also known as "Indian Yellow Gold" is a polyphenol, diferuloylmethane, which is responsible for the bright yellow-orange color of the Indian spice turmeric (*Curcuma longa*) (Figure 4C). Turmeric is the most commonly consumed spice in India. It has been used in India and China since time immemorial, in traditional treatments and as an antibiotic.[49] The compound "curcumin" was isolated by German scientists Vogel and Pelletier in 1815.[50] Curcumin has numerous healing properties that have been a topic of research by scientists all over the world.[51,52] The most studied activity of curcumin in the past years are its antitumor effects and antibacterial properties.[53] In 1949, Schraufstätter and Bernt described the bactericidal activity of curcumin against various bacteria including the TB causing pathogen, *M. tuberculosis*.[54] The antibacterial potential of curcumin has gained tremendous attention in the past few decades owing to its extraordinary antibiotic properties.[55,56] Curcumin has anti-inflammatory and antioxidative potential and targets several pathways important for bacterial survival.[57]

Curcumin is beneficial in the treatment of diseases such as cancer, diabetes, kidney disorder, and neurocognitive disorders by modulating the expression of Nrf2 gene. The anti-inflammatory role of curcumin is exhibited mainly via the downregulation of NF-κB gene signaling and its downstream genes and proteins.[58,59] In cancer, curcumin downregulates the expression and activity of cyclooxygenase (COX-2) gene along with reduced activity of inducible nitric oxide synthase (iNOS) by suppressing the transcription factor NF-κB. This in turn has a role in suppression of progressing tumorigenesis.[60,61] It acts effectively to eliminate *M. tuberculosis* in TB-infected patients. Therefore, it would be very interesting to further explore the action mechanism of this phytochemical in tuberculosis treatment. Curcumin is also reported to prevent anti-TB drug-induced hepatic damage.[62] It exhibits dose-dependent inhibition of intracellular growth for *M. tuberculosis*, H37Rv.[63] It is a potent inducer of apoptosis, which is an effector mechanism used by macrophages to kill intracellular pathogens. The antimicrobial potential of macrophages is increased upon treatment with curcumin, by an upregulation in the expression of apoptosis and autophagy genes.[64]

Although curcumin has myriad health benefits, it is relatively unstable and has poor bioavailability because of being rapidly eliminated from the body.[65] To overcome this limitation, Baldwin et al synthesized monocarbonyl analogs of curcumin and tested for their efficiency in reducing the replication of *M. tuberculosis* and *Mycobacterium marinum* (Mm) and found a remarkable reduction in the number of Mm and *M. tuberculosis* using several analogs.[66] This study paved the way for synthesis of more structural analogs that could interact better with the frontline anti-TB drugs. Another modification of curcumin that is nanoparticle-formulated curcumin was generated by Tousif et al and studied for its effect against active TB in mice model. Nanocurcumin exhibits a fivefold increase in bioavailability compared to curcumin extracted from turmeric and is around ~200 nm in size.[67]

As is the demand of TB treatment, curcumin nanoparticles effectively reverse the hepatotoxicity conferred by antitubercular drugs and reduce the incidence of reinfection and reactivation in mice. Thus, it compensates for the major shortcoming of the DOTS therapy by shortening the time required to achieve complete clearance of the bacilli from the lung and thereby diminishing the probability of generation of drug resistance among *M. tuberculosis* strains.[67] Therefore, an adjunct therapy comprising nanocurcumin together with DOTS therapy could be included in the treatment of tuberculosis.[67] Lately, they further tested curcumin nanoparticles for their possible role in augmenting the effectiveness of *Mycobacterium bovis* (BCG) vaccine. They found that

curcumin nanoparticles improve the host protective ability of BCG by generation of strong and lasting memory response by inducing T-central memory (TCM) cells of the Th1 and Th17 lineages.[68] Most recently Jahagirdar PS et al coencapsulated rifampicin and curcumin in polymeric nanoparticles and used it in infected macrophages. These nanoparticles improved *M. tuberculosis* clearance from the macrophages validating that these rifampicin-curcumin nanoparticles may be a promising therapy in future.[69] These studies open new dimensions to implement the host-protective role of curcumin in tuberculosis treatment.

3.4 | Epigallocatechin-3-gallate

Tea is an extensively consumed drink worldwide. Among the different varieties of tea consumed, black tea and green tea possess maximum antioxidant properties.[70] Many studies have validated the role of polyphenols in tea, in improving the levels of oxidative stress, in different disease conditions.[71,72] Epigallocatechin gallate (EGCG) is one of the principal polyphenolic compound found in the leaves of the green tea plant known as *Camellia sinensis* (Figure 4D). Green tea leaves have been reported to possess anticancer, anti-inflammatory, and antioxidant properties.[73] According to a study by Ahmed et al, EGCG suppresses the IL-1 beta-induced activity and expression of COX2 and nitric oxide synthase-2 (NOS-2) in human chondrocytes.[74] Another study related to chronic kidney disease suggests that EGCG attenuates oxidative stress and inflammation via regulation of NF-κB and Nrf2/HO-1 signaling pathways.[75]

EGCG has shown to be quite impressive in the treatment of tuberculosis. Epidemiological evidence supports the role of tea drinking in the reduced incidences of TB. Research done on the effect of green tea polyphenols on TB suggests that regular consumption of green tea reduces the risk of active TB in infected individuals.[76,77] However, the reason for the association between tea drinking and tuberculosis is still not clear. Catechin called epigallocatechin-3-gallate has been mostly studied in terms of its effects on TB treatment. In murine model studies and in TB patients, green tea extract has been utilized as adjuvant therapy in tuberculosis treatment owing to its ability to reduce oxidative stress.[78,79] Green tea extract also decreases the risk of delay in sputum smear conversion in pulmonary TB patients possibly by having an impact on the integrity of the mycobacterial cell wall.[80,81] Recently Grüber et al discovered that EGCG could possibly bind to mycobacterial ATP synthase and cause the inhibitory effects such as dysregulated energy production and cell wall biosynthesis.[82] Another study by Anand et al has revealed the effect of polyphenols derived from green tea on the TACO

gene, which has been studied for its involvement in inhibition of phagosome maturation during *M. tuberculosis* infection.[83] This study describes that epigallocatechin-3-gallate downregulates the transcription of TACO gene in human macrophages by inhibiting the Sp1 transcription factor, which led to inhibition of mycobacterium survival within macrophages.[83] These studies emphasize that green tea polyphenol specifically EGCG may be used as an adjunct in the prevention of tuberculosis infection and help in reversal or reduction in the side-effects of the strong antibiotics used in the TB treatment regime. Its role as an immunotherapeutic should also be explored so that this polyphenol can be incorporated in the treatment procedure.

3.5 | Piperine

The pharmacological activities of black pepper (known as the king of spices) are because of the presence of various phytoconstituents in it, which confer antipathogenic properties to it. Of all the available phytoconstituents, an alkaloid, piperine is the most important (Figure 4E). Piperine is a natural compound present in *Piper nigrum* and *Piper longum* and is reported to have anti-inflammatory, antimicrobial, antifungal, antioxidant, and anticarcinogenic effects.[84] It forms an essential component of traditional medicines for ages. Piperine has always been a center of attraction in research due to its potential of being an enhancer of bioavailability of drugs through the inhibition of CYP3A4 and human P-glycoprotein, particularly cytochrome P450-mediated pathways.[85,86] In tuberculosis treatment, piperine acts as an inhibitor of bacterial efflux pumps and an immunomodulatory compound.[87] Piperine is efficient against the multidrug-resistant strains along with eliminating drug-sensitive strains.[88] Chabamide is a dimer of piperine and is isolated from the stems of *P. chaba*. This dimer exhibits antituberculosis activity against *M. tuberculosis*.[89] Piperine induces the activity of the proinflammatory Th1 response, thereby, increasing lymphocyte proliferation and increased NO secretion by the macrophages. The cotherapy of piperine and rifampicin (RIF) shows a 1.4-0.8 log decrease in the bacterial number in the lungs of mice, which is significantly higher than RIF alone.[89] Therefore, piperine can be administered in a combination treatment along with anti-TB drugs owing to its upregulation of Th1 immune response, to improve the overall drug response in immune-compromised patients.[90] Piperine has also been studied to exhibit a strong EtBr efflux inhibitory effect in *M. smegmatis*, which possibly makes it an inhibitor of the intrinsic EP system in mycobacteria.[91] A study by Sharma et al shows that piperine reduces the the minimum inhibitory

concentration (MIC) and improves the antimicrobial action of rifampicin in all bacilli tested.[92] In the presence of rifampicin, *M. tuberculosis* RIF-R showed overexpression of efflux pump Rv1258c. Piperine along with rifampicin inhibits the expression of Rv1258c and thus may improve the bacterial killing efficiency of rifampicin.[92] A recent investigation has proposed that piperine slows down *M. tuberculosis* growth through RNA polymerase inhibition, which is additional knowledge from what was previously known.[93] Lately, the role of piperine as a bioenhancer in tuberculosis treatment is being studied upon. Risorine, a novel combination of rifampicin (200 mg), isoniazid (300 mg) along with bioenhancer piperine (10 mg), has been reported to be highly useful and safe in the treatment of TB.[94] Risorine furnishes more rifampicin in blood compared to the gastrointestinal (GI) tract as well as maintains higher blood levels compared to the conventional rifampicin, and with a better safety profile.[95] To put it all together, piperine has immense therapeutic applications and can be recognized as an important nutraceutical in tuberculosis treatment owing to the essential adjunct role it has shown to play during the treatment course.

3.6 | Tetrandrine

Tetrandrine is a natural compound that is extracted from *Stephania tetrandra* root. This phytochemical, is a member of isoquinolines and a bisbenzylisoquinoline alkaloid (Figure 4F). *Stephania tetrandra* plant has been extensively used in the Chinese medicinal system since ages.[96] Several studies have studied the efficiency of tetrandrine as an inhibitor of calcium channels and an inducer of apoptosis.[96,97] This compound has been reported to be effective in various bacterial and inflammatory health issues.[98–100] This phytochemical also lowers the plasma glucose level by increasing glucose utilization in hepatocyte for glycogen synthesis. Although quite effective in the treatment of many diseases, its effectiveness in the treatment of tuberculosis is not very well documented. Few studies have also been conducted on the role of tetrandrine in the reversal of drug resistance in a group of both isoniazid and ethambutol-resistant clinical strains.[98] Tetrandrine treatment together with isoniazid or ethambutol was effective in reducing the minimum inhibitory concentration of the dual-resistant strain from drug resistance to the sensitive level for both drugs. This study suggested that the combination therapy of tetrandrine with frontline anti-TB drugs, isoniazid or ethambutol increased the efficacy of the drug and may help in decrease in the drug dosage, thereby minimizing the ill-effects associated with the drug.[101] However, since there is a lot of ambiguity in the mechanism of action of tetrandrine and its immunogenic

potential is mostly unknown; more studies are needed in order to explore its maximum potential in TB cure.

3.7 | Ursolic acid (UA) and oleanolic acid (OA)

Ursolic acid (UA) and oleanolic acid (OA) are ubiquitous triterpenoids found in many kinds of medicinal plants such as *Chamaedora tepejilote* and *Lantana hispida* (Figure 4G). More than 700 research articles have discussed its role in disease management, making it a triterpenoid of huge importance.[102] These triterpenic acids have been commonly used in the treatment of respiratory ailments such as cough, bronchitis, colds, and pneumonia.[102] UA and OA have several biological and pharmacological effects, including antibacterial,[103,104] antiviral,[105] antiparasitic,[104] antioxidant,[106] and antitumoral activities.[107] Recent researches have revealed the immunomodulatory and mycobactericidal effect of these triterpenoids on TB pathogenesis.[108,109] UA reportedly activated NF-κB signaling pathway and subsequently enhanced the level of NO, ROS, and TNF-α while reducing the level of TGF-β1.[110–112] The combination of UA and TB drugs has shown to display synergistic interaction in the treatment of TB.[113] A study by Sonia López-García et al states that OA and UA have immunomodulatory effects on *M. tuberculosis*-infected macrophages.[113] OA and UA reduce *M. tuberculosis* growth in macrophages by enhanced production of NO, TNF-α, and ROS. This is also accompanied by overexpression of certain cell membrane receptors like CD36 and TGR5.[114] These are scavenger receptor and G-protein coupled receptors responsible for lipid accumulation and mediating bile acid synthesis. It has been reported that these triterpenes exert their antimycobacterial effects by the conversion of macrophages from M2 to M1 phenotype.[114] Both compounds, alone and in combination, have been studied to be effective against intracellular bacteria even at low doses; with a higher expression of IFN-γ and TNF-α in the lungs compared to untreated control. Therefore, UA and OA have antimicrobial activity together with an immune-stimulatory potential that can be used for the control of mycobacterial infection.[113]

3.8 | Andrographolide

Andrographolide is a bicyclic diterpenoid compound (Figure 4H) found in *Andrographis paniculata*, which has been widely used in traditional medicines across Asian countries as an immune booster. It has antibacterial,[115] antimalarial,[116] analgesic,[117] antihepatotoxic,[118] and immunomodulatory properties.[119] Studies in the murine

model have shown that andrographolide has been effective in significantly reducing Experimental Autoimmune Encephalomyelitis (EAE) symptoms. A recent study by Liao et al has shown the potential of this diterpenoid in the treatment of steroid-resistant airway hyperresponsiveness in patients with asthma.[120] The immune-stimulatory properties of *Andrographis paniculata* pave way for its role in the treatment of gastrointestinal and respiratory tract infections.[121,122] These studies make this compound very promising to be used against *M. tuberculosis*. However, very less research has been carried out globally to examine its in vitro and in vivo potency in the case of *M. tuberculosis*. Though andrographolide has shown to be cytotoxic against *M. microti*, *M. bovis*, and *M. canettii*, studies for its role in the treatment of *M. tuberculosis* are limited.[123,124] In a study by Prabhu et al, docking analysis and molecular simulation establish aminoglycoside 2-N-acetyltransferase (AAC) as a possible target of andrographolide in *M. tuberculosis*.[125] AAC is an enzyme that plays a key role in acetylation of an important intermediate of mycothiol synthesis, which is a major reducing agent in mycobacteria in-charge of regulating the cellular redox potential.[126] Apart from this, AAC may catalyze the acetylation of the 2′ hydroxyl or amino group of a broad spectrum of aminoglycosides and thereby confer resistance to aminoglycosides.[127] This in silico study gives us a direction to explore the vital role of andrographolide as an antimycobacterial agent that targets aminoglycoside 2-N-acetyltransferase in *M. tuberculosis*. As it has immunomodulatory characteristics, further in vivo studies and clinical trials are needed to substantiate its crucial role as a promising drug or adjunct in tuberculosis treatment.

3.9 | Resveratrol

Resveratrol is a natural polyphenolic phytochemical (Stilbenoid) that is extremely enriched in red wine, the skin of grapes, peanuts, and some berries (Figure 4I). It is synthesized by the plant in response to a pathogenic attack or under stress conditions. This stilbenoid is found to be the focal point of a plethora of investigations because of its extensive use in treatment of different diseases. It has been used worldwide in the treatment of viral diseases, cancer, and neurological diseases owing to its anti-inflammatory, antioxidant, and chemotherapeutic properties.[128–131] It has antimycobacterial activity against nonvirulent strains of TB such as H37Ra and BCG. Hong Yang et al have reported in an in vitro study that pretreatment with resveratrol in *M. tuberculosis*-infected macrophages, inhibits the activation of pathways such as TAK1, MAPK, and NF-κB and therefore resulting in the reduction in the levels of proinflammatory cytokines.[132] Furthermore, it has been observed that mice treated with resveratrol are more resistant to *M. tuberculosis* infection compared to untreated control as they harbored less bacterial loads, and lower lung impairment as seen through histological studies.[132] In 2019, Rosa et al developed isoniazid-resveratrol cocrystals (INH-RES) to increase the solubility, stability, and bioavailability of resveratrol for the treatment of cutaneous TB, locally and found it to be effective in disease cure.[133] But, to date, we do not have much research done on the immunomodulatory and bactericidal effects of this compound. It would also be of great interest to further study the contribution of this compound in TB disease.

3.10 | Thymoquinone

Nigella sativa (black cumin) is a medicinal plant having the main active compound thymoquinone (2-isopropyl-5-methyl-1, 4-benzoquinone) (Figure 4J). This compound has potent antibacterial, anti-inflammatory antioxidant, antimutagenic, antitumor, and hepatoprotective effects.[134,135] Thymoquinone is the main constituent of the volatile oil extracted from *Nigella sativa* plant. It has proved to restrain the development of pathogenic bacteria by inhibiting the formation of biofilms, which shelter the microorganism from harmful factors of the environment such as the host immune system and antibiotics.[136] Besides, when used in a synergistic therapy with standard drugs, it reduces the minimum inhibitory concentration of the drugs.[137] Additionally, it has been used as an antifungal agent against some significant parasitic pathogens including *Candida albicans*.[138,139] It has not much been used as an antimicrobial and a lot of research is needed to exploit its potential in the treatment of infectious agents. Thymoquinone is reported to have in vitro antitubercular activity and has proved to be significantly effective against drug-resistant *M. tuberculosis* strains by inhibiting the hepatotoxic effects of anti-TB drugs.[140,141] The study delineated antimycobacterial effects of thymoquinone, which successfully hinders the replication of *M. tuberculosis* H37Rv and the extremely drug-resistant, XDR strain inside Raw 264.7 macrophage cell line. It also has been described to inhibit secretion of pro-inflammatory cytokines and NO in different cell lines after bacterial infection.[142] However, we still have very preliminary research on the use of thymoquinone as an adjunct therapy in TB, which needs to be elaborately studied in future.

3.11 | Reserpine

Reserpine is an alkaloid that is extracted from the roots of *Rouwolfia serpentine* plant (Figure 4K). It is efficacious in

the treatment of high blood pressure and other heart diseases by reducing arterial pressure. The antihypertensive effects of reserpine are due to the antinoradrenergic effects it possesses.[143] It blocks the vesicular monoamine transporters such as catecholamines and irreversibly inhibits the internalization and stowage of dopamine in the synaptic vesicles making it very helpful in treating hypertension and psychiatric disorders.[144,145] Reserpine also has shown the ability to inhibit the formation of biofilms by inhibiting the metabolic processes of the bacteria forming the biofilm.[146] Its role as an efflux pump inhibitor makes the bacteria susceptible to drug treatment.[147] Additionally, it has been reported that reserpine when administered together with a standard antibiotic led to the reduction in the MIC of the antibiotic, such as tetracycline by fourfold in treatment of *B. subtilis* infection.[148] Reserpine has shown significant effects on the pathogen's resistance to various anti-TB drugs during mycobacterial infections. This efflux pump inhibitor increases the susceptibility of both BCG and *M. tuberculosis* strains to the drug isoniazid and also to pyrazinamide by blocking the pyrazinoic acid efflux pump.[149,150] Jaiswal et al, in 2017, have observed that in the presence of reserpine, there was a reduction in the MIC of isoniazid and it was effective against both drug-susceptible and drug-resistant isolates.[151] Another study used the derivatives of reserpine in the treatment of *M. tuberculosis* owing to its extraordinary antioxidant properties.[152] It has also been employed for the elimination of nonreplicating *M. tuberculosis* through the use of its efflux pump inhibitor action.[153] However, there is no work done on its role as a potential immune booster. It has been reported that reserpine acts by blocking catecholamines. Grailer et al[152] and Nguyen et al[154,155] have reported in different studies that catecholamines acts on the immune system. It acts on the host by promoting activation of M2-like macrophage activation. Catecholamines act on both MyD88-dependent and MyD88-independent signaling pathways through the activation of TLRs.[154,155] There is no knowledge of how this drug acts on the host immune system. Therefore, reserpine can be categorized among the phytochemicals, which need immediate attention from the researchers as it is a natural compound with minimum or no side effects. If it can be explored as immune booster, it would probably solve the cons associated with the DOTS therapy.

3.12 | Pasakbumin A

Pasakbumin A is a natural compound extracted from the medicinal plant, *Eurycoma longifolia*, which is a commonly used in the treatment of fever, malaria, ulcers, and TB (Figure 4L).[156] Apart from these above-mentioned pharmacological activities, *Eurycoma longifolia* is widely known for its anticancer potential.[157] However, the contribution of specific compounds extracted from *E. longifolia* that control intracellular *M. tuberculosis* growth has not been explored adequately. Few recent studies throw light on the role of Pasakbumin A in tuberculosis as it has anti-TB activity against the virulent *M. tuberculosis* strain. Research done till date, state that pasakbumin A works through the activation of ERK1/2-intermediated signaling pathways and autophagy.[158] A combination of pasakbumin A together with rifampicin has been used to clear the bacteria remarkably by high TNF-α production and autophagy in *M. tuberculosis*-infected macrophages.[158] This study anticipates the imperative domain of pasakbumin, as a much potent drug that has the capacity of being used as a new drug or as an alternate treatment in TB therapy. More substantial research is required to establish it as an anti-TB drug.

3.13 | Gingerol

Ginger is a common plant that grows in Asia and Africa and is found abundantly in China and India (Figure 4M). It is traditionally used to treat various ailments such as headaches, colds, cough, flu, asthma, arthritis, muscular discomfort, and any sort of inflammation.[159,160] Now, scientific studies have also proven the medicinal usage of ginger to cure symptoms associated with TB.[161,162] The use of ginger in a variety of diseases is solely because of the compounds present in it, such as gingerols, shogaols, gingerdiones, gingerdiols, and paradols.[163] As known by the available literature, garlic extracts exhibit weak antibacterial properties but it is the essential oils obtained from ginger rhizomes that are known to be significantly antibacterial. A random study conducted in pulmonary TB patients revealed that a combination therapy of ginger together with DOTS gave significantly encouraging results.[164] A recent paper has reported that [6]-Gingerol has immense potential to be used as an adjunct drug, along with isoniazid, an antibiotic of the DOTS regime. Gingerol showed excellent activity against drug-resistant and dormant bacilli.[165] Some investigators also confirm that the bioactive phytochemicals present in ginger lower the level of effective lipid mediators such as prostaglandin and leukotriene in the treated individuals via lowering the levels of 5-lipoxygenase or prostaglandin synthase, which further leads to a decrease in the production of proinflammatory cytokines highlighting its likely effectiveness in limiting the inflammation associated with tuberculosis treatment.[166–168] The use of gingerol may help the patients avoid steroid treatments and thus their associated side effects. Therefore, it would be very intriguing to look

at the immune-modulatory consequences of including gingerol as an adjunct therapy in the TB treatment, which may add to the efficacy of the therapy.

3.14 | Silymarin

Silymarin is the biologically active compound derived from the seeds of milk thistle plant (Figure 4N). Milk thistle has been used since ages in treating liver ailments.[169] The flavonoid silymarin consists of three phytochemicals, silybin, silidianin, and silicristin. Of the three phytochemicals, silybin is the most important for the effectiveness of this compound in treatment of diseases.[170] Silymarin is used in patients with a history of alcohol use and also in drug-induced liver injuries. It is also recommended in incidences of mushroom poisoning and in chronic hepatitis B.[171–173] Silymarin has proved to possess significant hepatoprotective activity, as revealed by various animal model studies. It has come out to be quite safe without any major side-effects, which makes it a phytochemical with quite promising adjuvant potential to be used in anti-TB treatment.[174,175] Researchers have established that silymarin has the potential to be used as a prospective drug to inhibit liver damage, reestablish the membrane potential and restore the function and expression levels of hepatic enzymes.[176,177] The hepatoprotective effects of silymarin have been confirmed in many studies. Nevertheless, its experimental efficacy in minimising the level of liver damage induced by ATT is a topic of conflict among the researchers. Luangchosiri and group performed clinical trial studies to demonstrate the efficacy of silymarin in treatment of active TB patients.[176] They found that silymarin displayed a positive hepatoprotective effect after 4 weeks of drug administration. They reported that liver damage in the silymarin-treated group was significantly lower than in the control group. However, contrary to the previous report, Marjani et al[169] and Zhang et al[178] did not observe any significant consequence of using silymarin in drug-induced hepatitis patients. However, we need more research and clinical trials before we establish the role of silymarin in TB drug-induced hepatotoxicity because of the variation in result due to limitation in sample size and variation in the population studied. Silymarin has been reported to possess significant anti-inflammatory and immune-modulatory capacity as well. Silymarin has been described to contribute in TB treatment by increasing the expression level of pro-inflammatory Th-1 cytokines. It has shown to eliminate both the MDR and drug-sensitive *M. tuberculosis*. However, the mechanism responsible for the fundamental activity of the extract of silymarin is still not known.[179,180] The antioxidant properties associated with this compound and the research done to date make it very

crucial to be studied more extensively so that its immune-modulatory role can be further confirmed. This phytochemical demonstrates great promises and may be studied in reinfection and reactivation studies.

3.15 | Glycyrrhizin

Glycyrrhizin is a triterpene glycoside, the major active compound present in the roots of the perennial plant *Glycyrrhiza glabra*, also commonly known as licorice (Figure 4O).[181] Its active components are glycyrrhetinic acid, flavonoids, hydroxyl coumarins, and b-sitosterol. *G. glabra* has been used in traditional medicines for the treatment of various diseases and is recognized since ancient times for its ethnopharmacological properties. Glycyrrhizin is most widely used in the treatment of liver problems, as an anti-inflammatory, laxative, antidepressive, and antidiabetic and for the treatment of stomach ulcers.[182–183] This is due to the anti-inflammatory and immune-boosting properties of glycyrrhizin. Several investigators have documented the role of glycyrrhizin in the treatment of liver diseases such as reducing inflammation, liver fibrosis, and promoting tissue regeneration. It has been reported to possess anti-inflammatory and antiapoptotic effects by the suppression of TNF-α and caspase-3.[184] Glycyrrhizin also leads to the upregulation of proliferating cell nuclear antigen (PCNA), suggesting its role in tissue regeneration, in case of liver injury.[185] These properties make glycyrrhizin useful as an anti-inflammatory agent, as an antitumor treatment, and for the treatment of viral infections such as hepatitis B and SARS and in parasitic infections. Due to its use in treatment of different diseases, the researchers have started to look into the antimicrobial potential of glycyrrhizin and have evaluated its potential against both drug-sensitive and -resistant strains of microorganisms.[186] It has been found to possess significant antimicrobial properties against both Gram-positive and Gram-negative bacteria. It has also been used in the treatment of *H. pylori* infection and in the treatment of peptic ulcers.[186] Glycyrrhizin has also been studied to inhibit the propagation of methicillin-resistant *S. aureus* (MRSA) by its bacteriostatic and bactericidal activity.[186] Recently, the role of glycyrrhizin in the treatment of intracellular pathogen, *M. tuberculosis* has been deciphered albeit to a limited extent. It has shown to reduce the MIC of the drugs used in conventional TB therapy when used in combination.[186] However, still we do not know the mechanism employed by glycyrrhizin for its anti-TB effectiveness. The initial results of it acting as bactericidal agent, are convincing enough to further investigate the potential of this phytochemical as an adjunct in ATT. All of these discussed compounds are summarized in Table 1.

TABLE 1 List of phytochemicals having antimycobacterial properties

Name of Phytochemical	Plant of origin	Mechanism of action against *M.tb*	References
Allicin	*Allium sativum* (Garlic)	Antimycobacterial, stimulates Th1 response, antihepatotoxic	30-42
Bergenine	Different parts of a number of plants (*Shorea robusta*)	Anti-inflammatory, induces Th1, Th17 immune response, reduces the length of treatment	43-48
Curcumin	*Curcuma longa* (Turmeric)	Antibacterial, immunomodulatory, enhances BCG efficacy	49-69
Epigallocatechin gallate	*Camellia sinensis* (Green Tea)	Reduces oxidative stress, impacts integrity of mycobacterial cell wall, antioxidant	70-83
Piperine	*Piper nigrum* (Black pepper)	Antimycobacterial, NO production, stimulates Th1 response	84-95
Tetrandrine	*Stephania tetrandra*	Reversal of drug resistance	96-101
Ursolic acid and Oleanolic acid	*Chamaedora tepejilote, Lantana hispida*	Antimicrobial, immunomodulatory, promotes th1 response	102-114
Andrographolide	*Andrographis paniculata*	Antihepatotoxic, antibacterial, immunomodulatory	115-127
Resveratrol	Grapes, berries, peanuts	antibacterial, increases resistance to *M.tb* infection	128-133
Thymoquinone	*Nigella sativa* (Black cumin)	Effective against drug-resistant strains, hepatoprotective	134-142
Reserpine	*Rouwolfia serpentine*	Efflux pump inhibitor, increases the susceptibility of bacteria to antibiotics	143-155
Pasakbumin	*Eurycoma longifolia*	Autophagy inducer, antibacterial	156-158
Gingerol.	*Zingiber officinale* (Ginger)	Anti-inflammatory, antibacterial, antioxidant	159-168
Silymarin	*Silybum marianum* (Milk thistle)	Hepatoprotective, anti-inflammatory, immunomodulatory	169-180
Glycyrrhizin	*Glycyrrhiza glabra* (Licorice)	Anti-inflammatory, immune booster	181-186

4 | THE ROLE OF PHYTOCHEMICALS IN TUBERCULOSIS MANAGEMENT: AN IMMUNOLOGICAL AND HOST HEPATO-PROTECTIVE PERSPECTIVE

Tuberculosis is a disease characterized by both microbial infection and tissue inflammation. The innate immune cells particularly the macrophages and dendritic cells encounter *M. tuberculosis* in the lung alveoli and initiate an early antimycobacterial immune response in order to prevent the progression of the disease.[187] However, *M. tuberculosis* has evolved a number of strategies to keep the host immune system at wonder. Susceptible individuals may have suppression in the level of T helper type 1 cells (Th1) responses, which is a result of reduction in the production of IL-12. Less Th1 response leads to reduced levels of proinflammatory cytokines and high expression levels of anti-inflammatory cytokines.[188] The side-effects of DOTS therapy on the host, including the sharp decline in protective CD4+ T-cells makes the host vulnerable to reinfection and reactivation of the disease.[189] However, the use of anti-inflammatory drugs along with conventional antibiotic treatment controls the inflammation associated with the disease and increases the overall effectiveness of ATT.[190] But, because of continuous use of these anti-inflammatory drugs or steroids the host encounters severe side-effects; making such treatment nonadvisable for the patients. Therefore, immunologists all over the world are looking for an approach, which could lead to upregulation of Th1 immune response selectively, with the simultaneous downregulation of the Th2 immune response.[191] Any such compound, natural, or synthetic that can act as an inducer of selective immune response is referred to as an immunomodulator.[192] Immunomodulators alone are not capable of getting rid of the bacteria but act on the host immune system to make it more potent in eliminating the pathogen. Recently, the use of plant-based compounds as immunomodulators has gained huge importance. A lot of research is being done in evaluating the usefulness of plants and compounds derived from them in boosting the immune system against *M. tuberculosis*. These compounds are used with the sole purpose of balancing the proinflammatory cytokines and anti-inflammatory cytokines, which is disturbed by the bacilli for its favoured survival in the host system.[192] Of the known phytochemicals or plant secondary metabolites whose immunomodulatory properties are very well established are very few. Most of the secondary metabolites have not been tested for their immune-boosting potential and their role in preventing the reactivation of the disease. As their role in the prevention of hepatotoxicity and improving the overall health of the patient is gaining huge attention, these compounds may in future qualify to be used in synergistic treatment approach, along with the conventional DOTS regimen for improving the overall quality of the treatment and reducing the side effects involved with the ATT.

Alcoholic extract of *Coleus scutellarioides* (Miana leaves) induce the proinflammatory T-lymphocyte response by
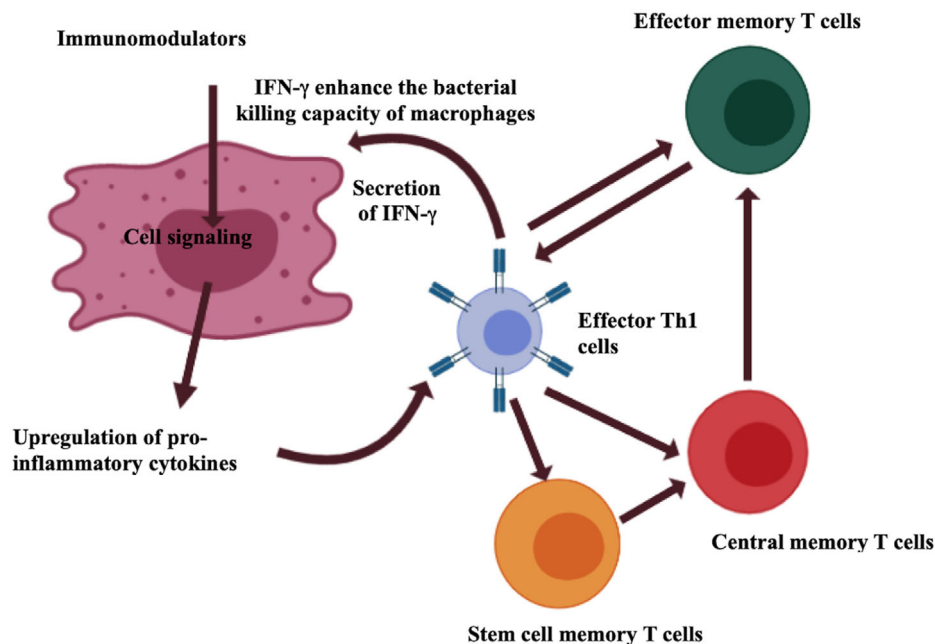
FIGURE 5 The mechanism of action of immunomodulators against TB

increasing the levels of IFN-γ and TNF-α, thus acting as an immunomodulator.[192] The killing of *M. tuberculosis* by treatment of miana extract is not due to direct inhibition of bacterial proliferation; instead, it is a result of host immunomodulation by the compound.[192] Similarly, immunomodulatory activities of other plant secondary metabolites have been described. Garlic induces a strong protective Th1 response while also eliminating the susceptible as well as the drug-resistant strains. Silymarin, extracted from the seeds of *Sylibym marianum*, induces a remarkable expression of Th1 immune response related cytokines both in treatment of drug-sensitive and -resistant strains.[193] Other examples of phytochemicals with reported immunomodulatory effects are piperine, an extract of chanca piedra (*Phyllanthus niruri*), extracts of Rubiaceae species, allicin from garlic, curcumin from turmeric, and gingerol from ginger. They have shown to act by restoring the Th1/Th2 balance, while acting as antioxidants, anti-inflammatory agents, and immunomodulators and increasing the expression level of proinflammatory cytokines and NO.[194] The mechanism of action of immunomodulators on the host system has been described in Figure 5. Phytochemicals such as curcumin may be used as an alternative to steroids used in the management of inflammation during ATT based on the finding that curcumin nanoparticles have been used restore the number and differentiation capacity of T-cells after isoniazid treatment, both in vitro and in mice model. It has also been reported to prevent "apoptosis" in immune cells, which is stimulated by antibiotics; by the activation of the caspase-3 pathway.[58] Moreover, the incorporation of curcumin nanoparticles to the DOTS therapy has been studied to induce the activation and progression of TCM and thereby prevented reinfection and reactivation of the disease in mice.[195] Administration of antibiotics during ATT leads to serious side-effects in the host, such as hepatotoxicity and immune impairment.[195] Certain phytochemicals due to their healing and antioxidant properties such as garlic, aqueous onion (*Alium cepa*) extract, silymarin, and nanocurcumin lead to a significant reduction in liver lesions induced by isoniazid, which has further been confirmed by the lower expression level of liver enzymes such as alanine transaminase, alkaline phosphatase, and aspartate transaminase, which indicate improvement in the condition of ailing host liver as reported in the literature available for the medicinally important plants.[196,197]

Therefore, as studied for some phytochemicals, the antimycobacterial action is mainly due to their immunomodulatory properties and their ability to prevent the adverse effects of antibiotic treatment. If more such studies are conducted to further explore the bacterial clearing capacity of more phytochemicals and their mechanism of action, this may contribute significantly to the effectiveness of DOTS therapy, by reduction in the duration of TB treatment regimen, thus increasing the effective bacterial clearance and simultaneously diminishing the chances of emergence of drug resistance in the bacteria. Any contribution these phytochemicals make may add to the improvement of an existing therapy or pave way for other novel therapies. This might be a

big step in eradication of TB from the population. The effect of using these plant secondary metabolites as immunomodulators or as an adjunct therapy along with the DOTS treatment has various consequences for the host.

5 | CONCLUSION

The phytochemicals derived from plant extracts are useful not only in eliminating the bacteria but as discussed in the review may serve as prospective adjunct agents that help in reducing the after-effects of the classical antimycobacterial drugs. These plant-derived products assist in reinstituting the balanced level of the pro-inflammatory and anti-inflammatory cytokine response of the host, which is disturbed by the bacteria upon infection. Furthermore, studies on compounds with anti-MDR-TB and XDR-TB activity may contribute to the management of TB very significantly as drug development against MDR- and XDR-TB is the need of the hour, owing to its high prevalence and difficult management. The plant-derived phytochemicals can also be given as personalized treatment to patients suffering from other diseases along with TB; like silymarin can be given along with DOTS to a hepatitis patient who gets infected with TB simultaneously. Many of these phytochemicals and the compounds derived from them can be administered as inhalation therapy along with DOTS to increase the effective drug concentrations within the lungs and thereby reduce the incidence of off-target side-effects and systemic toxicity. Although, clinical trials involving combination use of some phytochemicals with the conventional ATT have shown to be very beneficial in TB cure, but still the full potential of phytochemicals still remains undeciphered. There are several limitations, which prevent the successful use of these phytochemicals such as lack of knowledge about their interaction with normal human diet and conventional drugs and less clarity of their mechanism of action. However, these challenges could be overcome by advancing multidisciplinary and high throughput research using bioinformatics, molecular biology, and immunological approaches before it is used on animal models.

Seeing the immense potential this therapy has, it could definitely be recommended for use in the anti-TB drug regimen in future to improve the effectiveness of the existing TB treatment procedures. In conclusion, we have presented many leads in this review article for mining of new drug candidates as boosters of host-directed therapy against the most deadly pathogen *M. tuberculosis.*

6 | OUTLOOK AND FUTURE PERSPECTIVES

Despite highly active research on the development of novel drugs against TBs we have quite a few drugs that have been approved for the treatment of TB in the last few decades,[198] taking into consideration the fast emergence of drug-resistant strains. It has been reported that the new anti-TB drugs in clinical trials such as Sequella (SQ109), piperazine-benzothiazinone (PBTZ169), and benzothiazinones (BTZ043) have the pharmacophore of piperine, which is a phytochemical.[199] Therefore, a plant-based drug molecule could be used as a research candidate for anti-TB treatment. Isoniazid despite having enumerable side effects cannot be replaced because of its effectiveness and target binding specificity. However, any new drug that could reduce the inherent side effects of isoniazid when given in combination could revolutionize TB drug development program. Moreover, phytochemical cotherapy along with isoniazid and other anti-TB drugs leads us toward a potent anti-TB drug development approach and is less time and expenditure demanding compared to searching of a leading anti-TB drug candidate. These advantages pave a promising future for the use of these phytochemicals in TB treatment.

CONFLICT OF INTEREST
The author's confirm that there are no conflicts of interest.

ETHICS APPROVAL
No ethical approval was required for this study.

DATA AVAILABILITY STATEMENT
We hereby declare that this review will be openly available for all.

AUTHOR CONTRIBUTIONS

The authors confirm contribution to the paper as follows: study conception and design: Ved Prakash Dwivedi; data collection: Samreen Fatima, Anjna Kumari; analysis, interpretation, and critical revision for important intellectual content: Samreen Fatima; draft manuscript preparation: Samreen Fatima, Anjna Kumari. All authors reviewed the results and approved the final version of the manuscript.

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