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REVIEW ARTICLE

Insights on Natural Products and Their Derivatives in Tuberculosis Management

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Abstract

Tuberculosis (TB), a bacterial disease primarily affecting middle- as well as low-income countries, poses a significant public health threat. Natural products have historically been and remain a vital source of fresh medications for treating various diseases. The renewed interest in natural product research is partly a result of the increasing prevalence of drug-resistant *Mycobacterium tuberculosis (MTb)* strains along with adverse outcomes associated with first- and second-line anti-tubercular drugs. The TB complexity and the complications arising from the use of allopathic medications, such as multidrug resistance, highlight the effectiveness of natural medications in this context. Therefore, it is crucial to explore new treatment therapies to effectively mitigate the harmful effects associated with TB. More research is needed on various natural substances, both independently and in combination with currently approved drug regimens, as potential TB treatment options.

Key words: Tuberculosis; *Mycobacterium tuberculosis*; Drug resistance, multiple; Biological products.

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Introduction

Tuberculosis (TB) is one of the deadliest contagious diseases.[1] *Mycobacterium tuberculosis* (*MTb*) continues to be listed among the globally primary reasons for infectious disease-related mortality regardless of 60 decades of therapy and 90 decades of immunisation.[2] As an obligatory aerobe that is acid-fast, non-motile and oxygen-dependent TB exist. Their cell growth rate is moderate and their doubling durations range from two to more than twenty hours.[3] One important characteristic that distinguishes *Mycobacterium* from other bacterial organisms is the complexity of its cell wall.[4] Some other species of *MTb* are *M bovis, M canetti, M africanum* and *M microti*.[5] Numerous essential activities are housed in the mycobacterial cell envelope, which makes it essential for cell activity.[6] The bacterial cell's ability to withstand harsh conditions, its resistance to most antibiotics, its ability to transfer nutrients and its ability to adhere to host cell receptors are all crucial roles played by the cell wall. These organisms are known as "acid-fast" as gram-positive or gram-negative staining fails to detect mycolic acid, a crucial component of the cell wall's structure.[7,8]

Since TB is predominantly transmitted by air, it stands apart from infectious disorders. The process by which TB spreads involves the discharge of bacilli from an infected person's lung within

the immediate surroundings.[9] Subsequently, the organisms undergo inhaling by vulnerable people, usually people with impaired immune systems and close interactions.[10, 11] Later on, as the organisms multiply inside the lungs, they stimulate the immunological system of the host, particularly the phagocytes. As a result, well known as a granuloma is created that is made up of immune cells, including macrophages, T cells and B cells as well as necrotic lung tissue.[12] Granuloma is the pathological manifestation of the host's reaction to a TB infection.[13] Roughly 10 % of all those who were originally afflicted, develop a symptomatic, active and contagious illness. But the majority of individuals (90 %) experience asymptomatic, non-transmissible latent (or dormant) illness.[14] Immune responses to TB infection are indicative of a latent infection with TB even without clinical signs of active TB.[15]

It is possible for individuals having latent TB to reactivate, or go into active illness.[16] Fever, tiredness, appetite loss and weight loss are signs of active TB, which in certain cases results in the spread of bacilli throughout the lungs and beyond. Chronic coughs are common in those with lung ailments and haemoptysis, or coughing up blood is generally seen in individuals with severe lung illnesses.[17] A latent TB infection becoming active is the cause of the reactivation of TB. The organism can reactivate in response to immune-compromising diseases such as diabetes, HIV infection, malnutrition and cancer and can survive for decades inside a granuloma formation.[12] Figure 1 shows the burden of TB among countries across the world.

Around 10 million people worldwide become ill with TB disease each year. TB is the leading infectious killer in the world, killing 1.5 million people annually, despite being preventable and curable. TB is also the primary cause of death for HIV-positive individuals and a significant global contributor to antibiotic resistance. A total of 856,000 people in South Asia became ill with this disease and 84,000 died from it in year 2022, making up 8 % and 7 % of all TB event cases and deaths worldwide.[18] Multidrug-resistant (MDR) TB is regarded as a major warning to society,[19] especially for those who don't have enough access to healthcare. Rifampicin (RIF), one of the leading first-line medications for the treatment of TB, was discovered to be resistant in 600,000 new TB cases, based on estimates from the World Health Organisation (WHO). "First-line" medicines are the medications that the WHO regards as standard therapy for TB.[20]

Even though TB is usually curable, worries have been expressed about the global increase in drug resistance.[21-23] A 6-month course of ethambutol (EMB), isoniazid (INH), RIF and pyrazinamide (PZA), is commonly used to treat active TB; this treatment regimen is known as "R.I.P.E." treatment. Patients with Extensively drug resistant (XDR)-TB have very low probability of a successful course of therapy,[4] which highlights the critical need to discover novel compounds that

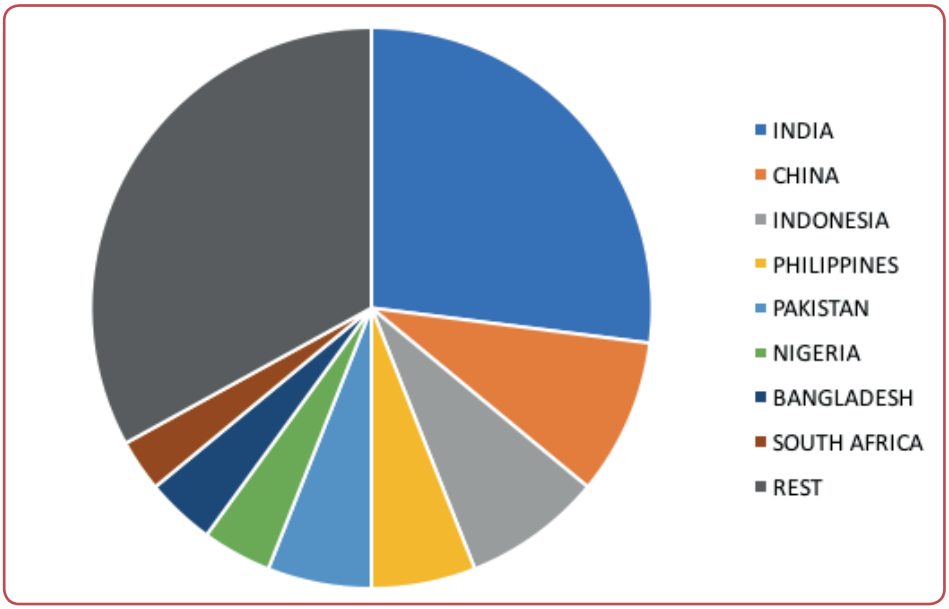

Figure 1: The burden of tuberculosis among countries

are effective against *MTb* strains sensitive to second-line medications. A "completely drug-resistant TB" strain that has minimal chance of responding to therapy has been discussed recently.[7, 10] Moreover, there is an urgent need for agreement on how to define these *MTb* strains, particularly concerning their severity.[11] Thus, finding new anti-tubercular drugs is essential to addressing treatment resistance and eventually eliminating TB.

Pathogenesis of TB

The oxygen-rich macrophages in the lungs are the main target of pathogenic strains of TB infection. *MTb* infection results from a small number of tubercle bacilli distributed in the air that invade the host's alveoli from a patient experiencing active pulmonary TB. This instance of innate immunity results in the quick phagocytisation of the *Mycobacterium* by alveolar macrophages, allowing for its eventual destruction.[24] Bacilli begin to replicate in macrophages if the infection continues and they then spread to endothelium and epithelial cells. In just a few weeks, mycobacteria grow exponentially and spread to other organs through the blood and lymph, affecting other cells in the process.[25, 26] Mycobacterial infection and pathogenesis are signalled by cytokines and other chemical mediators produced by toll-like receptors (TLRs).[27] Consequently, dendritic cells and macrophages associated with monocytes are transferred to the lung infection.

To distribute *Mycobacterium* antigens towards CD^4 and CD^8 T-cells, which effectively stimulate these cells; dendritic cells here take up bacilli and move to lymph nodes. Numerous studies have shown the vital role of CD^{4+} T-cells in the defence against *MTb.* The fact that *MTb* recurs in HIV-positive patients owing to CD^{4+} T-cell depletion further supports the results. Various CD^{4+} cell subsets, including T-helpers and regulatory T-cells, can aid or hinder one another in our attempts to regulate infection. Developed T-cells respond to mediators made by infected cells by multiplying and migrating back to the lung's focal spot of sickness. The TB signature, granuloma, is formed with the culmination of these events of cell movement toward the infection site. For an extensive period, this granuloma development prevents macrophages from disturbing the latent condition of bacilli.[28-30]

An infection can recur if the conditions are appropriate for latent bacilli inside granulomas to be released. Through phagocytosis and receptor binding, mycobacteria were able to infiltrate macrophages through the cholesterol domains of the plasma membrane.[31, 32] While the findings from *in vitro* research are contradicted by *in vivo* investigations, the *in vitro* studies elucidated the function of unique receptors that facilitate macrophage absorption of *Mycobacterium*.[33, 34]

Mycobacteria are taken up *in vivo* by different receptors, like complement receptors. Most *in vitro* experiments indicate that the bacilli have a preference for binding to mannose and complement

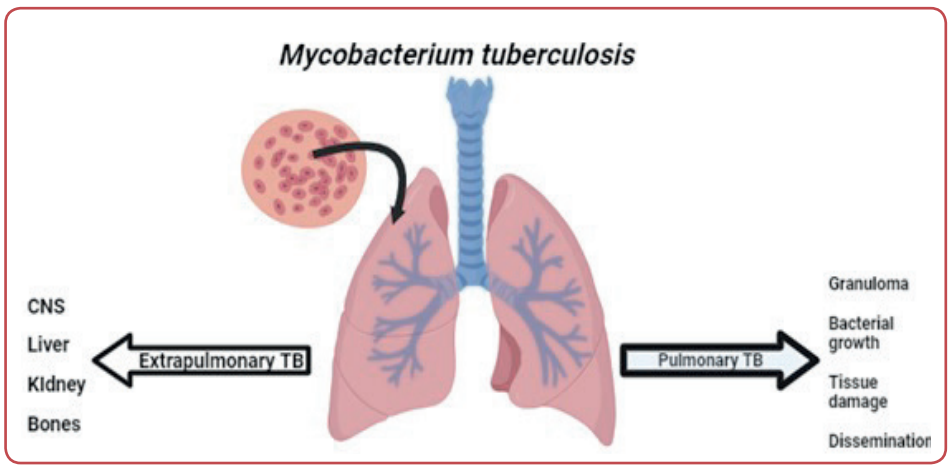

Figure 2: The pathogenetic steps of Mycobacterium tuberculosis

receptors, prone to be safe since they don't generate a lot of superoxides. However, the uptake of Mycobacteria by Fc (fragment crystallisable) receptors, which only slightly contribute to the lack of specific antibodies, sets up precise intracellular trafficking routes and elicits a robust host response.[35] This elucidates the reason for Mycobacteria's incapacity to internalise receptors and demonstrates the minimal influence receptors have on their survival potential (Figure 2).[36, 37]

Current drug therapies

To increase the body's ability to respond to medication and reduce the length of the course of treatment, modern pharmacological therapy includes many drugs. Isoniazid and rifampicin are a pair of the primary medications used today. Rifampicin is essential for the regimen since it ensures the best possible results while reducing treatment durations. The application of isoniazid, rifampicin, streptomycin and ethambutol is a nine-month schedule. Pyrazinamide added to a regimen throughout the initial two months may shorten the duration of the therapy by half to six months while maintaining a cure rate of ninety-five percent or higher, according to research done by the Medical Research Council in the UK.[38]

The way to eradicate TB is to stop the virus from spreading in the first place. This can be achieved by giving treatment priority to patients who have positive sputum smear results, or those who have the potential to transmit the illness. These people can be tested and treated using the directly observed treatment short course (DOTS) method, which is an extremely efficient as well as cost-effective TB management technique that is advised globally. Five components make up DOTS: ongoing financial and political obligations; consistently provided high-quality anti-TB drugs; standardised short-course (SSC) anti-TB treatment administered through direct observation therapy (DOT); standardised recording and reporting; and quality-assured diagnostic procedures.[39]

Problems with the ongoing drug therapy

The TB prolonged period therapy results in low patient compliance and the abundance of drugs might occasionally make it harder for patients to take their regular doses. The negative effects of the current treatment are also rather common and it has been demonstrated to antagonise when used with other medications. Additionally, the high expense of the medications required for the treatment is brought on by the prolonged course of treatment. There is little to no impact of the present multi-drug regimen on latent TB.[40] Also, it has resulted in multidrug-resistant TB. Drug resistance arises from the use of ineffective or improper therapies. This can be brought on by inconsistent drug administration, stopping therapy midway through, or skipping any one of the prescribed medications (a conventional treatment regimen consists of at least two medications).[41]

Second-line drugs like aminoglycosides and fluoroquinolones are effective in treating multidrug-resistant tuberculosis (MDR-TB), however, they are less effective, somewhat more toxic and not very cost-effective.[42] Although second-line drugs are even more costly as compared to first-line drugs, the main issue is that the second-line drugs' treatment duration is nearly twice as long as the standard TB treatment, which makes it more challenging for some individuals to pay for prescription medicines, stick with it through to the end and raises the possibility of the disease spreading and developing resistance that could lead to XDR-TB and ultimately increase mortality.[43] It has been demonstrated that doing research using natural products is a successful approach for finding novel, physiologically active drugs.[44]

Natural drugs as a ray of hope

Natural products are the source of a wide range of bioactives with diverse therapeutic qualities.[45] These products are extensively used as the most effective contemporary medications.[46] As the cornerstone for preserving health, traditional medicines are essential in meeting the basic healthcare needs of developing nations. As per a survey, a minimum of thirty percent of the pharmaceuticals that are presently on the market have their source or genesis in distinct natural resources. As a result, substantial study is still being done on natural derivatives' potential for therapeutic use in modern medicine.[47]

Many well-known anti-TB drugs are derived from natural sources. Recently, researchers have discovered new natural products or their derivatives that show promising antibacterial effects

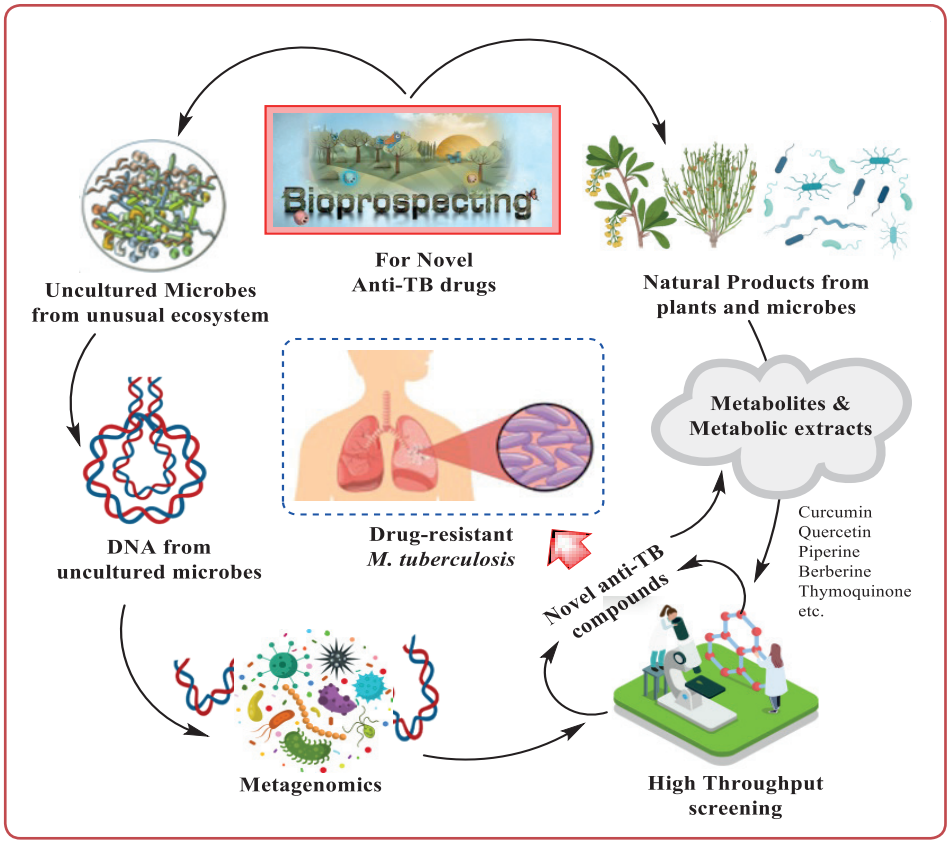

Figure 3: The chemical structures of important phytoconstituents used in tuberculosis management

towards *MTb* (Figure 3). These findings might potentially restore the current clinical procedure for TB treatment, which lacks candidates from new natural product sources. Actinomycin, a natural substance obtained from the bacterium *Streptomyces antibioticus*, was among the first recognised naturally occurring substances that stop *MTb* from developing in cultures.[48] In comparison to synthetic chemicals, various natural substances are more bioactive and possess better pharmacokinetic qualities, such as better absorption, distribution and excretion. Despite facing

Table 1: CPromising natural compounds for tuberculosis treatment

N	Phytochemical constituents	Biological source	Therapeutic activity	References
1	Curcumin	*Curcuma longa*	It prevents the activation of caspase-3 and NF-κB, enhances T cell-mediated immunity, as well as lowers the likelihood of *MTb* reactivation following treatment.	51
2	Quercetin	*Euphoria paralias*	It prevents the isocitrate lyase and glutamine synthetase activity, which are involved in the nitrogen and TCA cycle, correspondingly.	52
3	Phloretin	*Malus domestica*	Phloretin hinders IL-12, IL-1β and TNF-α secretion and diminishes p38 MAPK, ERK and JNK phosphorylation.	53
4	Berberine	*Hydrastis canadensis*	It inhibits microsomal drug-metabolising enzymes. It also causes a decrease in oxidative stress.	54

5	Piperine	*Piper nigrum*	Piperine possesses an efflux-inhibitory effect.	55
6	Tea polyphenols	*Camellia sinensis*	Tea polyphenols that target the cell wall of mycobacteria.	56
7	Artemisinin	*Artemisia annua*	Artemisinin functions by specifically targeting the hem molecule within bacteria, thereby disrupting their ability to sense oxygen levels.	57
8	Griselimycins	*Streptomyces griseus*	It binds and inhibits the mycobacterial DNA polymerase III sliding clamp (DnaN)	58

challenges in natural product discovery, such as the distinctive *MTb* cell wall, complex pathways involved in biosynthesis and reduced solubility of certain substances, there is significant potential for the development of therapies based on natural products for TB in medicinal chemistry fields, pharmacology and biology.[49]

According to recent scientific literature reviews, there are more than 350 plant species employed in the treatment of TB globally and several naturally derived compounds have been extracted and recognised with potent activities towards *MTb*, XDR-TB and MDR-TB.[50] In this section, compiled list of plant metabolites and microbial extracts that have been studied for TB treatment is presented (Table 1).

Curcumin

Curcumin is a major phenolic pigment extracted from the rhizomes of turmeric (*Curcuma* genus),[59] belonging to the family *Zingiberaceae* and is widely recognised as a multifunctional compound because of its several therapeutic and pharmacological properties (Figure 4).[60] Curcumin turns up as a new beneficial approach against *Mycobacterium abscessus* virulence and resistance to drugs. Curcumin demonstrates synergistic activity with amikacin, ciprofloxacin, clarithromycin and linezolid towards a clinical variant of *M abscessus*, even at reduced inhibiting doses (MIC) of 128 µg/mL. Additionally, curcumin at 1/8th of *M abscessus* MIC significantly ($p < 0.05$) reduces the bacteria's motility. *M abscessus* develops a biofilm that contributes additional virulence and resistance to drugs. Notably, between days 4 and 8, the biomass of matured biofilms is suppressed by curcumin at levels substantially greater compared to MIC.[61]

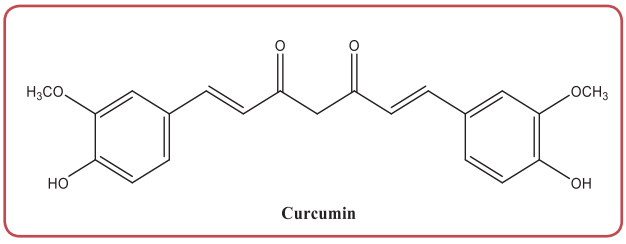

Figure 4: The chemical structure of curcumin

Curcumin induces apoptosis within macrophages, which facilitates the elimination of *MTb*. The quantity of intracellular *MTb* decreased substantially when curcumin at doses of 10, 30 and 50 µM were pre-incubated for an hour before infection by *MTb* H37Rv in human THP-1 monocytes and primary human alveolar macrophages. During two- and four-days post-infection, the amount of *MTb* retrieved was considerably ($p < 0.05$), reduced in curcumin-treated cells than in control cells maintained with 0.05 % DMSO.

Curcumin, however, did not hinder *MTb* development in a dearth of macrophages at levels up to 50 µM, indicating that curcumin stimulates the activity of macrophages to assist *MTb* clearance. The TUNEL test findings of *MTb* -infected THP-1 cells proved that curcumin induced dependent on dosage macrophage apoptosis. Autophagy and curcumin-induced, caspase-3-dependent apoptosis have been identified as the processes involved in the increased elimination of *MTb* in differentiated THP-1 human monocytes and primary human alveolar macrophages.[51] *MTb* induces the NFκB activation, which inhibits the host's immune system from eradicating the infection by inhibiting both autophagy and apoptosis in contaminated human macrophages.[62-64]

Quercetin and rutin

The majority of phenolic compounds found in plant extracts belong to the classes of flavones or flavanones, which are rich in antimycobacterial flavonoids.[65] Flavonoids are secondary polyphenolic plant metabolites known for their various health advantages, like antioxidant, analgesic, antibacterial, anti-inflammatory and anticancer

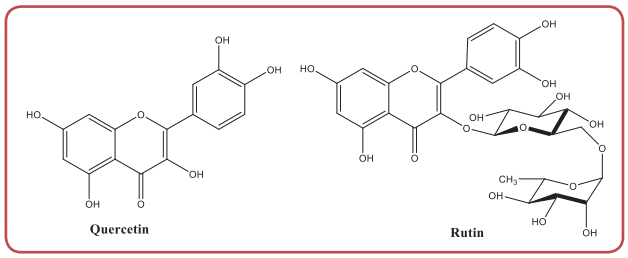

Figure 5: The chemical structures of quercetin and rutin

characteristics. Common dietary sources of flavonoids include red wine, tea, coffee, beer, vegetables, fruits, herbs, leaves, seeds and various medicinal plants, which provide compounds such as quercetin and rutin.[66]

Quercetin is a predominant polyphenolic flavonoid found in edible plants and is well-known for its antioxidant characteristics (Figure 5).[47, 67] The growth inhibitory effects of flavonoids such as rutin and quercetin towards slow-growing mycobacteria (*MTb* H37Rv) were evaluated utilising different assays: broth-microdilution method (BMDM), luciferase reporter phage assay (LRPA) and microplate Alamar blue assay (MABA). Rutin's antimycobacterial activity has been underexplored *in vitro*, whereas this study represents the initial analysis of the effectiveness of quercetin in a test using luciferase reporter phage. Quercetin was found to inhibit the growth reliant on hyaluronan of *MTb* complex in lung cells by targeting hyaluronidase, an enzyme that is essential for using hyaluronan as a source of carbon for the growth of bacteria.[68] Natural products like flavonoids often exhibit selective interactions with biological targets, such as receptors associated with disease states. Quercetin, for example, inhibits sulfotransferase, a key enzyme in sulphur metabolism pathways essential to ensure survivability and virulence of pathogenic bacteria like *MTb*. This inhibition disrupts sulphur metabolism, crucial for lipid metabolism and mycolic acid synthesis, an essential part of mycobacterial cell walls.[69]

Phloretin

Flavonoids are polyphenolic substances found in plant-based foods like coffee, red wine, fruits, vegetables, legumes and nuts. Phloretin, a polyphenolic molecule and dietary flavone present in apples (*Malus domestica*), has been shown to exhibit various biological activities (Figure 6). These activities include potential anti-inflammatory and antineoplastic actions, achieved through the induction of cytokines, chemokines and other factors by leukocytes (white blood cells).[53]

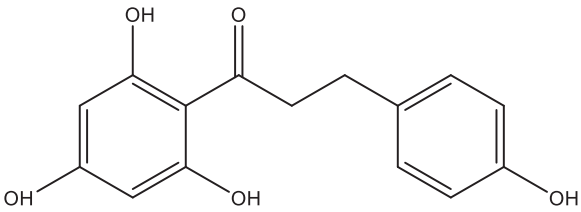

Figure 6: The chemical structures of phloretin

Phloretin has demonstrated antimicrobial activity against *MTb*, potentially reducing inflammation in the lungs. Studies have indicated that interleukin (IL) and tumour necrosis factor-alpha (TNF-α) are just two examples of chemicals causing inflammation whose expression is reduced by phloretin. Furthermore, RT-PCR and immunoblot analysis were employed to assess the impact on LPS-stimulated dendritic cells and interferon-stimulated MRC-5 human lung fibroblasts. These investigations revealed that phloretin inhibits IL-12, IL-11 and TNF-α secretion, as well as the IL-12, IL-1, IL-6, TNF-α and MMP-1 expression. Additionally, phloretin was found to reduce the phosphorylation of ERK and p38 MAPK.[53]

Berberine

Berberine is a bioactive component that is extracted from roots, barks and rhizomes of four families of therapeutic plants: *Annonaceae* (African whitewood), *Rutaceae* (cork tree), *Ranunculaceae* (goldenseal) and *Berberidaceae* (barberry). Berberine is an isoquinoline alkaloid that has antibacterial, antidiabetic, anti-tumour and anti-inflammatory characteristics (Figure 7).[70, 71]

Berberine has been shown to have hepatoprotective effects *in vitro* in an experimental model, in

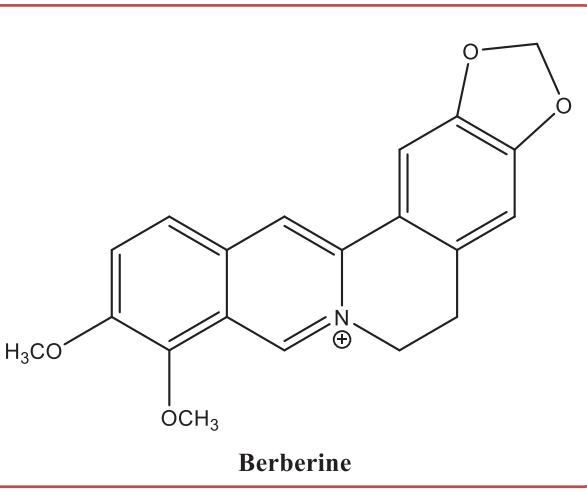

Figure 7: The chemical structures of berberine

part due to its suppression of K/Ca currents and enzymatic microsomal drug metabolism.[72, 73] By inhibiting the generation of COX-2, TNF-α and iNOS, it decreases the level of oxidative stress.[54] It prevents microsomal enzymes that regulate drug metabolism as well as decreases oxidative stress.[74]

Piperine

Piperine is a bioactive compound found in *Piper longum* and *Piper nigrum* (Figure 8). Rifampin (RIF), a cornerstone of TB treatment, can eliminate *MTb* in both extracellular and intracellular environments.[75] Resistance to RIF significantly impacts the duration of TB therapy, which can extend up to two years beyond the standard six-month treatment.[76] The increasing frequency of drug-resistant *MTb* strains underscores the need for innovative global approaches to combat TB. One potential future treatment approach involves incorporating efflux pump inhibitors (EPIs) into anti-TB medication.[77, 78]

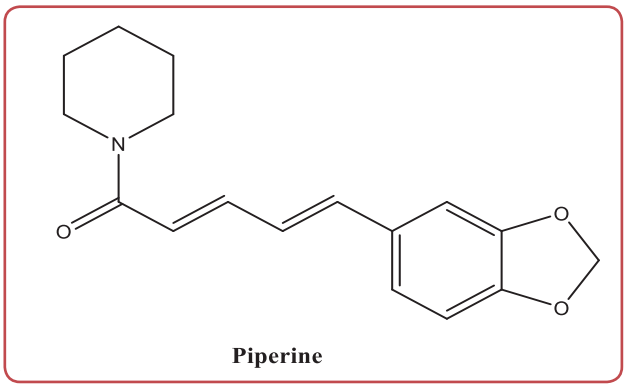

Figure 8: The chemical structure of piperine

Piperine, known for its efflux-inhibitory properties, was investigated in a phase III clinical study in India[79-81] and has shown significant efficacy as an adjunct therapy in TB treatment.[82-84] Piperine's ability to enhance bioavailability by inhibiting CYP3A4 and human P-glycoprotein (P-gp) is a key reason researchers propose it as an adjunctive medication.[85] P-gp, the predominant efflux transporter in the mammalian intestine, significantly limits the oral bioavailability of compounds, while CYP3A4 metabolises numerous medications directly. Therefore, blocking these pathways is crucial for increasing serum concentrations and prolonging the efficacy of anti-TB medications. This work examines the impact of piperine and rifampicin (RIF) by itself and in conjunction with the replication of the EP gene in *MTb* strains that have various drug susceptibility patterns. It also suggests a distinctive mechanism for the beneficial relationship between piperine and RIF.

Tea polyphenols

Southeast Asia is believed to be the region where the tea plant, *Camellia sinensis*, was first found and nurtured. Chinese history states that the first recorded use of tea was made by Emperor Shen Nung in 2737 BCE.[86] This marks the beginning of tea consumption. Tea is high in flavonoids, particularly catechins and their derivatives and is also packed with other beneficial compounds.[87] These polyphenolic substances, which include epicatechin gallate (EGCG), are thought to be involved in the health benefits associated with tea. Researchers are investigating the potential use of tea polyphenols from green and black teas as add-ons to vaccinations.[88] Additionally, they are also researched for potential utilisation for a range of illnesses, such as the avoidance of obesity, dental caries and cardiovascular disease.[89] Tea polyphenols are also being studied by experts studying infectious diseases to treat infections like TB. Tea polyphenols that target the cell walls of mycobacteria were the subject of a second investigation.[90]

Luria-Bertani (LB) broth was used to incubate *Mycobacterium smegmatis* mc2 155 and the bacteria were exposed to different doses of EGCG that were extracted from green tea. Later, electron microscopy, high-performance liquid chromatography (HPLC) and liquid chromatography-mass spectrometry (LC-MS) were carried out on isolated mycobacterial cells. The researchers discovered that 20 µg/mL was the optimum EGCG level for tearing down the cell walls of bacteria.[54]

Electron microscopy reveals structural impairment in the cell wall of *Mycobacterium* caused by escalated levels of EGCG. The quantity and configuration of EGCG inside LB media were authenticated using HPLC and LC-MS, two laboratory methods for segregating mixtures. In a separate investigation, the influence of triclosan and green tea catechins on TB bacteria was assessed. Triclosan, a wide-ranging antimicrobial and antifungal agent utilised for over three decades, obstructs lipid production by impeding the vital enzyme InhA.[91] InhA is necessary for the mycolic acid structure of the mycobacterial cell wall and suppressing it compromises the mycolic acid structure, resulting in cellular impairment or demise.[92] To target the TB InhA enzyme, researchers opted to utilise both triclosan and green tea in their TB experiments.[93]

Artemisinin

The plant *Artemisia annua* is the source of artemisinin (Figure 9). It's an herb used in traditional Chinese medicine. A study found that artemisinin could both cure and improve the effectiveness of the common medications used to treat TB. By keeping the TB bacteria from going latent, it functions as an anti-TB agent. The

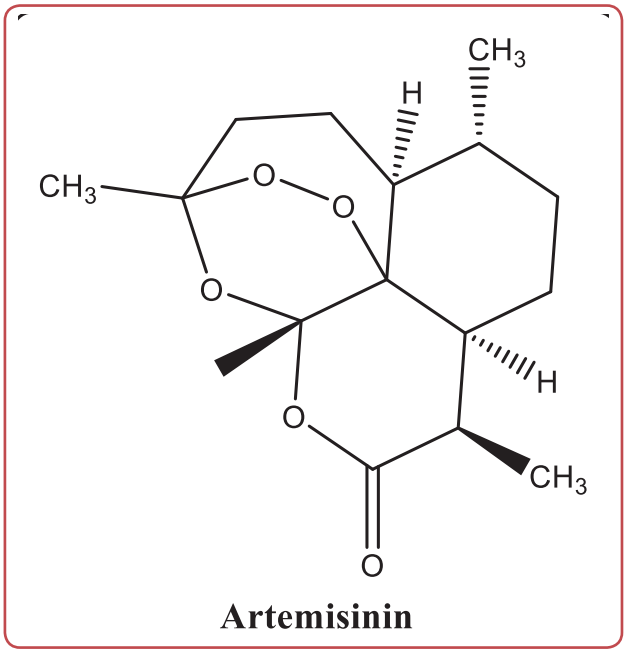

Figure 9: The chemical structure of artemisinin

immune system typically produces dormancy in bacteria to regulate their growth and prevent infection, making it difficult to eradicate the germs in this form. Conversely, the latent microorganisms develop a strong tolerance to medications. By preventing bacteria from detecting the presence of oxygen, artemisinin prevents them from entering dormancy and eventually dying. This is achieved by specifically targeting the hem molecule in bacteria.[57]

Griselimycins

Griselimycin is a cyclic peptide that was initially reported through Berteaux and Noufflard-Guy-Loe in 1965 (RP 11072) (Figure 10). They reported to have isolated it from the *Streptomyces griseus* and *Coelicus* species and have shown its antibacterial action against mycobacteria.[94] When rifampicin became available for the treatment of TB in 1968, efforts to enhance the substance's adverse pharmacokinetic characteristics had not succeeded and interest in it ceased. Müller et al recently re-examined the compound and

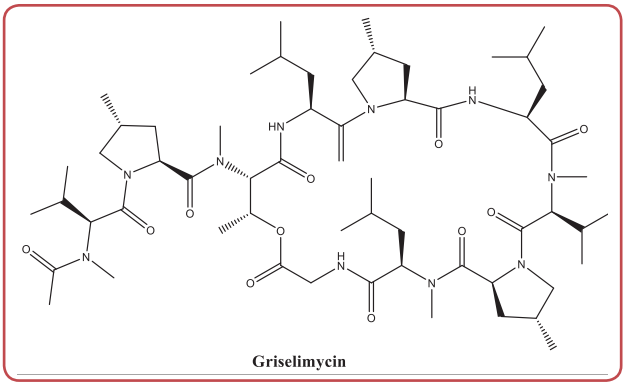

Figure 10: The chemical structure of griselimycin

found that Pro8's metabolic stability was much enhanced by the addition of alkyl substituents to its pyrrolidine ring. Certain compounds, such as cyclohexyl griselimycin, were shown to have enhanced antimicrobial activity against *MTb*.[95]

Challenges of natural products in TB treatment

There are several variables that may affect the effectiveness and safety of novel TB treatments, making it difficult to translate laboratory results into clinical practice. Bioavailability is a major issue since it determines how much of a drug is able to reach the bloodstream and have an impact on the body. Optimal bioavailability is essential for TB treatments, but there are a number of things that may get in the way. For example, a drug's formulation may greatly impact its absorption; substances with promising results in labs might not be designed to be as bioavailable as they might be in people. Furthermore, there is a great deal of individual variation in medication absorption due to physiological variables like patient metabolism, gastrointestinal health and the presence of food. Another issue is the drug's stability; some effective compounds may break down before they have a chance to work, especially if they're water, light, or heat sensitive.

Locating the ideal dosage is another essential part of putting laboratory results into clinical practice. To get the most out of a treatment while avoiding side effects, finding the optimal dosage is crucial. Nevertheless, there are several obstacles in the way of this procedure. For instance, because of variations in metabolism and pharma-

cokinetics, doses that work in animal models may not work in people. A person's medication metabolism may be influenced by their age, weight, organ function and genetic polymorphisms, among other variables; hence, individualised dosing approaches are necessary. Since ineffectiveness and side effects might result from doses that are too low or too high, it is critical to define a therapeutic window that is both safe and effective.

Another important worry that can restrict the adoption of novel medicines and impact patient compliance is the possibility of side effects. People respond differently to novel substances and some of those chemicals may have dangerous effects that weren't considered in the first research. Because of the protracted nature of therapy for chronic diseases like TB, it is all the more important to identify these hazards as soon as possible to ensure patient safety. Constant vigilance is required for the treatment and monitoring of adverse effects when co-morbidities like diabetes or HIV are present.

It is not without its own set of difficulties to incorporate novel TB therapies into current regimens. In order for patients to have access to new medicines, the therapies must be compatible with existing treatment procedures. There is a risk of subtherapeutic levels or increased toxicity due to pharmacokinetic interactions between new therapies and current TB treatments. The risk of drug resistance should also be considered when introducing new medications, particularly when combined with those that are currently in use. Access to new medicines and the treatment landscape as a whole may be complicated by the delay and potential regional variation in updating clinical recommendations to reflect new results.

In conclusion, there are several obstacles to overcome concerning bioavailability, dose, possible adverse effects and combinations with current medications as they pertain to the practical use of test results for the treatment of TB. For innovative TB treatments to be safely and efficiently deployed, researchers, doctors and regulatory agencies must work together to overcome these obstacles. Only then can patients fighting TB see improved results.

Conclusion

This review offers a detailed overview of plant species and various natural products that contain compounds inhibiting TB. It highlights the active chemical components of these natural substances, their anti-mycobacterial properties and other natural products and potential anti-TB plants used globally. Despite the anti-TB properties of many natural products, studies and research on people and animals remain required to identify the cytotoxicity with their extract and active components. Transforming natural ingredients into innovative, highly efficient TB formulations and administering novel drugs at the appropriate time could potentially halt the global TB epidemic. Utilising anti-TB natural products is essential to achieving the WHO's plan to stop the TB pandemic worldwide, which seeks to cut the number of new infections by 90 % and deaths caused by TB by 95 % between 2015 and 2035. These products are less expensive and offer a promising approach to the global fight against TB. Employing natural anti-TB medications will help impoverished families avoid the crippling costs associated with TB. Biomedical professionals should recognise that nature's untapped supply of potential anti-mycobacterial drugs is crucial for a robust global campaign against TB.

Ethics

This study was a secondary analysis based on the currently existing data and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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