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HERBAL MEDICINES AS AN EMERGING APPROACH FOR THE TREATMENT OF TUBERCULOSIS: A SYSTAMATIC REVIEW

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ABSTRACT

Background: Tuberculosis is an airborne infection known for causing lung damage, and it poses a significant threat to individuals with weakened immune systems or underlying health issues. Conventional allopathic medications have been linked to the emergence of cross-resistance or multidrug resistance in diseases like TB, complicating treatment. Consequently, herbal remedies have gained attention as a potentially more effective approach to treating this disease. Medicinal plants with antituberculotic properties offer pharmacologists a fresh source of medicinal compounds, enabling the development of innovative drugs based on their active components or intermediate metabolites. **Objective:** Recent studies have highlighted the potential of ayurvedic medicines to significantly reduce mortality in certain situations, owing to their compatibility with the body's natural environment. The rising popularity of ayurvedic medicine can be attributed to its minimal toxicity and comparative lack of side effects when compared to allopathic treatments. **Conclusion:** In this review, we focus on the botanical categorization and anti-tubercular properties of medicinal herbs selected from scientific literature. Our main goal is to shed light on these anti-tuberculosis plants, their chemical constituents, and their effectiveness in combating tuberculosis.

KEYWORDS: Mycobacterium tuberculosis; Chemotherapy; Drug resistance; Herbal Medicines.

INTRODUCTION

Tuberculosis is the major public health concern, recording 1.3 million death per year across the globe.[1] According to World Health Organisation, Tuberculosis(Tb) is an infectious disease caused by the bacteria called *Mycobacterium tuberculosis* (Mtb). It is a communicable chronic granulomatous disease which primarily affects the lungs.[2] The modern treatment of (Tb) depends on Rifampicin, Ethambutol, Isoniazid and Pyrozinamide which are costly with serious side effects.[3] The evolution of new "multi-drug resistant"(MDR) strains of *Mycobacterium Tuberculosis*, can be attributed to the developed resistance against both the first line and second line drugs. Thus, there is a necessity of novel innovative approaches to reduce thedisease burden.[1]

For centuries, medicinal plant have been used as a source to prevent and cure many diseases and continued to be hope for several emerging strains and disease.[1] Galen said that there was no disease which plants could not cure.[4] Since antiquity, this boon of mother nature has always contributed humanity with remedies in the form of medicine against disease. Indian scriptures including "Rig-veda, Atharvaveda and Charaka samhita" reveals the abundant benefits of plants. As catalogued by WHO globally, 21,000 plants are widely used for medical purposes. Within India 2500 species have identified as traditional medicine. They are highly significant dueto the presence of numerous phytochemicals.[1]

PATHOGENESIS

Tuberculosis's development in immunocompetent individuals starts with the emergence of cell-mediated immunity, providing resistance to the organism and leading to hypersensitivity to tubercular antigens. Tuberculosis's characteristic features, including caseating granulomas and cavitation, stem from the destructive hypersensitivity within the host's immune response. Since the cells responsible for both protective immunity and damaging hypersensitivity are the same, the emergence of tissue hypersensitivity also signifies gaining immunity to the organism. The sequence of events from exposure to containment of the infection can be outlined asfollows.

- ***Entry into macrophages***

Virulent mycobacteria enter macrophage endosomes through various macrophage receptors,

such as the macrophage mannose receptor and complement receptors. These receptors recognize specific components of the mycobacterial cell walls, facilitating the entry process.

- ***Replication in macrophages***

Following internalization, these microorganisms thwart normal microbicidal responses by hindering the fusion of lysosomes with the phagocytic vacuole. This evasion strategy enables the mycobacteria to persist and reproduce within macrophages. Consequently, the initial phase of primary tuberculosis (within the first 3 weeks) involves substantial bacterial growth in pulmonary alveolar macrophages and air spaces. Eventually, this leads to bacteremia and the dissemination of the organisms to various locations. Despite this bacteremia, individuals in this phase usually remain asymptomatic or experience a mild flu-like illness.

- ***Development of cell-mediated immunity***

Cell-mediated immunity typically develops about three weeks after exposure. During this process, processed mycobacterial antigens are transported to the draining lymph nodes and presented to CD4 T cells by dendritic cells and macrophages. This interaction, guided by macrophage-secreted IL-12, leads to the generation of TH1 subset CD4+ T cells. These cells havethe capacity to secrete IFN-Y, a cytokine crucial for immune response modulation.

- ***T cell-mediated macrophage activation and killing of bacteria***

Critical in the activation of macrophages, CD4+ T cells of the Th1 subset release IFN-y. These activated macrophages then unleash various mediators and enhance gene expression, yielding significant downstream outcomes.

1. TNF: Responsible for monocyte recruitment, which subsequently activates and transforms into“epithelioid histiocytes” hallmarking the granulomatous response.
2. Inducible Nitric Oxide Synthase (iNOS): Elevates nitric oxide (NO) levels, promoting the creation of reactive nitrogen intermediates crucial in mycobacterial destruction.
3. Antimicrobial Peptides (Defensins): Toxic to mycobacteria, these peptides are additional weaponry released by activated macrophages. This orchestrated immune response plays a vital role in countering mycobacterial infections.

- ***Granulomatous inflammation and tissue damage.***

Alongside spurring macrophages to eliminate mycobacteria, the TH1 response alsocoordinates the formation of granulomas and caseous necrosis. Macrophages, activated by IFN-y,undergo differentiation into “epithelioid histiocytes,” which aggregate to compose granulomas. Some

of these epithelioid cells might fuse, creating giant cells. For many, this reaction arrests infection before significant tissue damage or illness can arise. Yet, in individuals with compromised immunity due to age or immune suppression, the infection advances, and the persistent immune response culminates in caseation necrosis.

Activated macrophages additionally release TNF and chemokines, encouraging therecruitment of more monocytes. The significance of TNF is evident in patients with rheumatoid arthritis treated with TNF antagonists, who exhibit an elevated risk of tuberculosis reactivation.

In essence, immunity against tubercular infections primarily relies on the actions ofTh1 cells, which activate macrophages to eradicate mycobacteria. This immune defense, though effective, carries the trade-off of hypersensitivity and the consequent tissue damage. Any defects in the various steps of the Th1 T cell response (including IL-12, IFN-Y, TNF, or nitric oxide production) lead to poorly developed granulomas, lack of resistance, and progression of the disease. Individuals with hereditary mutations in any aspect of the Th1 pathway become highly vulnerable to mycobacterial infections.

Reactivation of the infection or exposure to the bacilli in a previously sensitized hosttriggers a swift defensive reaction, accompanied by heightened tissue necrosis. Just as hypersensitivity and resistance emerge in tandem, the waning of hypersensitivity (evident when a M. tuberculosis-infected patient tests negative for tuberculin) is a concerning indication of diminishing immunity to the organism.[2]

ALLOPATHIC TREATMENT FOR TB

The recommended treatment regimen for tuberculosis (TB) entails the use of first- line medications over a course of six months, yielding an 85% success rate. This regimen involves two months of isoniazid, rifampicin, ethambutol, and pyrazinamide, followed by four months of isoniazid and rifampicin. The introduction of first-line drugs (FLDs) like isoniazid, rifampicin, ethambutol, pyrazinamide, and streptomycin in the 1950s and 1970s marked a significant reduction in TB cases, particularly in developed nations. These drugs revolutionized TB treatment. For drug-susceptible pulmonary tuberculosis (DS-PTB), two treatment options are available according to WHO guidelines. The first option involves a 4-month regimen comprising rifapentine, moxifloxacin, isoniazid, and pyrazinamide. Alternatively, a 6-month course includes isoniazid and rifampicin along with pyrazinamide and ethambutol during the initial 2 months.

In the case of drug-resistant tuberculosis (DR-TB), a combination of both first-line and second-line drugs is employed, tailored to antibiotic susceptibility testing results. The second-line drugs (SLDs) used encompass streptomycin, rifampicin, pyrazinamide, ethambutol, cycloserine, ethionamide, kanamycin, and thioacetazone. The treatment of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB is typically more extended, less effective, less tolerable, and more expensive compared to the regimen for drug-susceptible TB. This often involves the use of injectable drugs.

A retrospective cohort study indicated that the proportion of patients with MDR-TBachieving a cure was less than 69%, even with directly observed treatment. This highlights the need for exploring new drugs with novel mechanisms or reduced adverse effects to effectively manage drug-resistant tuberculosis.[11] Table: anti TB drugs and their mechanism of action.

Streptomycin	Reduction in the production ofribosomal protein
Isoniazid	Cellular, lipid, carbohydrate, and NADmetabolism inhibition
Pyrazinamide	Membrane transport disryption andenergy exhaustion
Rifampicin	Inhibiting synthesis of RNA
Cycloserine	Reduction in the production of mycolicAcid
Kanamycin	Decrease in protein synthesis
Ethambutal	Inhibiting the synthesis of RNA
Quinolones	Inhibition of transcription replicationand DNA replication
CA inhibitors	Inhibite the activity of carbonic anhydrases need for Ph regulation
Coumarins	Inhibit protein synthesis and activity ofcarbonic anhydrases

DRUG RESISTANCE IN TUBERCULOSIS

As per the World Health Organization (WHO), in 2016, there was a 4.1% upswing in the incidence of resistant tuberculosis (TB), and approximately 19% of existing patients developed resistance to one or more anti-tuberculosis drugs. Cases of extensively drug-resistant tuberculosis (XDRTB) have been reported in 123 countries, indicating resistance to a minimum of four core anti-tuberculosis drugs. XDRTB can also encompass multidrug-resistant tuberculosis (MDRTB). Notably, 88% of MDRTB cases are concentrated in middle or high-income countries.Within this category, 60% are distributed across China, India, Brazil, Russia, and Africa. In certainEastern European nations, MDRTB constitutes more than one-third of total tuberculosis cases. Back in 2012, over 90% of reported MDRTB cases emanated from just 30 countries. The escalatedoccurrence of MDRTB can be attributed to the increased prevalence of HIV infection.

SEVERE SIDE EFFECT OF EXISTING ANTI-TB MEDICINES

Antituberculosis drugs can cause hematological reactions, gastrointestinal intolerance, hepatitis, renal failure, and dermatological reactions. These unfavorable repercussions should be discovered soon in order to decrease linked illness and death.

Rifampin has following few of the most dangerous adverse effects include hemolysis, thrombocytopenia, and kidney failure. Anti-rifampin antibodies are absorbed by platelets, causing thrombocytopenia, which leads to platelet loss after complement fixing. PAS has so many gastrointestinal side effects that it is no longer prescribed to adults as a primary medicine. The liver damage caused by isoniazid and rifampin seems to be supplementary. Because they arenot synergistic, neither one nor the other should be given to individuals even without liver disease who are alcoholics. Retrobulbar neuritis is the most serious adverse effect of ethambutol l. Patientstaking Dilantin and isoniazid must be advised regarding the danger of Dilantin over dosage since isoniazid is seen to hamper the metabolism of diphenylhydantoin.[13]

A POSSIBLE AVERSE EFFECT ASSOCIATED WITH ANTI-TB CHEMOTHERAPHY

CHEMOTHERAPEUTIC AGENTS	ADDVERSE EFFECT
Streptomycin	Renal damage, vestibularand auditory nervedamage
Isoniazid	Hepatitis
Rifampicin	Thrombocytopenia, pain, vomiting, nausea
Pyrazinamide	Arthralagia, hepatitis
Ethambutal	Neuritis, colour blindness
Cycloserine	Convulsions, dizziness, depression, psychotic reaction
Ethionamide	Diarrhea, abdominal nerve damage,nephrotoxicity
Kanamycin	Vertigo, auditory nerve damage, nephrotoxicity
Thioacetazone	Skin rash, exfoliative dermatitis

DRUG INTERACTION

Interactions between anti-TB agents and other drugs can lead to significant clinical implications. Such interactions become especially problematic for individuals co-infectedwith HIV, particularly those undergoing treatment with antiretroviral drugs or medications targeting various bacterial, viral, or fungal infections.

Among these interactions, a majority involve rifampicin and similar rifamycins. These substances induce hepatic cytochrome enzymes responsible for metabolizing numerous drugs, resulting in decreased active drug levels. Table 4 outlines the primary drugs influenced

by these interactions. Notably, the administration of rifamycins to patients on antiretroviral therapy poses notable challenges. Given the frequent revisions of antiretroviral regimens, it is advisable to refer to the current guidelines issued by the United States Centers for Disease Control in Atlanta, GA.

These guidelines provide updated recommendations regarding the safe and effective use of rifamycins in conjunction with antiretroviral treatments.[14]

Table: Principal Drugs Whose Effects Are Opposed By Rifampicin.

Antiretroviral agents	-	Opioids
Azathioprine	-	Oral contraceptive
Corticosteroid	-	Phenytoin
Cyclosporine	-	Propranolol
Diazepam	-	Quinidine
Digoxin	-	Theophylline
Haloperidol	-	Tolbutamide
Imidazole	-	Warfarin

HERBAL MEDICINES

The primary approach to treating tuberculosis involves chemotherapy, utilizing a combination of five drugs administered over six months for individuals with drug-susceptible TB. This duration can extend to eight months for patients with drug-resistant tuberculosis (DR-TB). Managing drug-resistant TB entails using costly second-line drugs that often lead to severe side effects, contributing to non-compliance issues. Moreover, interactions between anti-TB medications, particularly rifampicin, and certain antiretroviral drugs (ARVs) have further complicated the care of TB in those living with HIV.

Traditional medicinal plants have a historical role in tuberculosis treatment and hold potential as a source of bioactive compounds for creating alternative remedies against mycobacterial diseases. The World Health Organization (WHO) emphasizes that 80% of the global population relies on traditional medicine (IM) for primary healthcare. Additionally, reports indicate that 170 out of the 194 WHO Member States incorporate traditional and complementary medicine (T&CM). By integrating traditional wisdom with contemporary scientific methods, a promising avenue emerges for developing affordable, secure, innovative, and effective therapies.[15]

In the current review, traditional anti-TB medicinal plants are classified across 90 families, encompassing 230 genera and 277 species. Notably, the leading 11 families, each with over 7 plant species, comprise Fabaceae (21 species in 18 genera), Asteraceae (20 in 16 genera), Euphorbiaceae (14 in 11 genera), Lamiaceae (13 in 11 genera), Rutaceae (14 in 10 genera), Combretaceae (9 in 4 genera), Piperaceae (9 in 1 genus), Zingiberaceae (8 in 3 genera), Annonaceae (7 in 6 genera), and Apiaceae (7 in 7 genera).

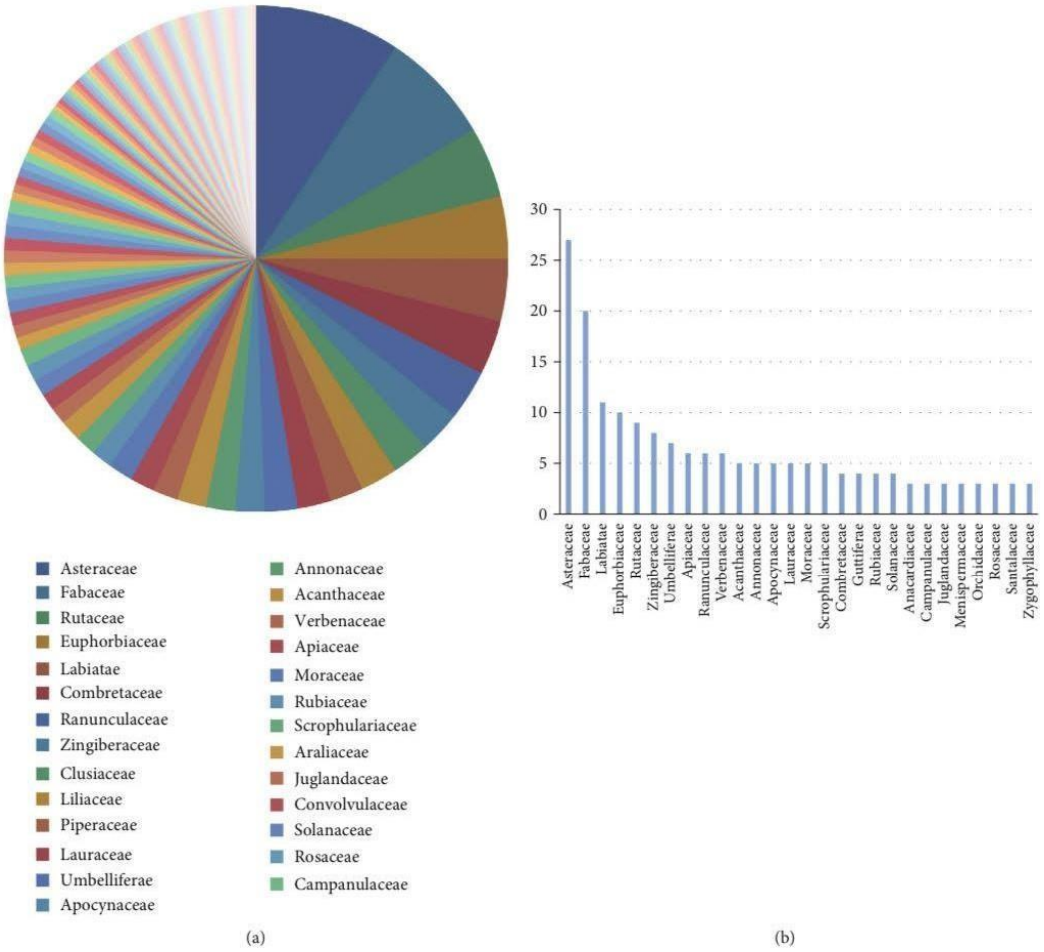
Additionally, 40 plant families are singularly reported. Noteworthy is the presence of 6 species from the Terminalia genus in the Combretaceae family, hosting up to 6 anti-TB plant species. Furthermore, a distinct genus, Piper, contains about 9 anti-TB plant species. Among the traditional anti-TB medicinal plants discussed in the review, the top 10 frequently employed plant parts are leaves (83 instances), roots (61), aerial parts (32), barks (30), stems (14), whole plants (9), seeds (9), fruits (8), rhizomes (8), and flowers (7).

The scope of this review was confined to medicinal plants containing anti-TB properties. The identified plants with such components encompassed 156 species, 123 genera, and 64 families. Notably, the leading families included Fabaceae (13 species, 10 genera), Rutaceae (10 species, 7 genera), and Lamiaceae (9 species, 7 genera). Consequently, a greater number of genera within these families exhibited anti-TB attributes.

Numerous plants contained multiple components exhibiting anti-TB activity, and this review exclusively includes the reported active compounds. provides a comprehensive listing of 335 compounds subjected to anti-TB testing.

These compounds can be categorized into 11 primary classes, comprising terpenes (37 types), ketones (31), acids (14), alcohols (10), esters (9), hydrocarbons (9), quinones (8), furans (7), phenols (6), and quinolones (3).

The review also organizes the typical structures of these 335 compounds.



Classification of traditional anti-TB medicinal plants with effective crude extracts and the compounds. (a) Botanical families consisting of the anti-TB medicinal plants. There are 108 families including 230 genus and 277 species in this summary. (b) Genus number (>2) of the anti-TB medicinal plant families.[16]

In the past, medicinal plants played a role in tuberculosis treatment. For instance, practices included inhaling smoke from burnt leaves of Artemisia afra, utilizing the whole plant of Myrothamnus flabellifolius, employing leaves of Carica papaya, Zanthoxylum capense roots, andinhaling seeds of Combretum hereroense 3 to 4 times daily.

Patients would inhale steam from infusions of Artemisia afra and Lippia javanica by covering their heads with a blanket. Leaves of Citrus lemon, Artemisia afra, and Mentha sp. were burned and inhaled 2 to 3 times daily. These Ayurvedic treatments typically lasted for about two weeks to a month, adjusted based on patient responses and tolerance to the formulation and administration.

Medicinal plants house phytochemicals arising from primary and secondary metabolic processes. Extensive literature outlines the therapeutic potential of these compounds, spanning various classes like flavonoids, carotenoids, indoles, isothiocyanates, monoterpenes, and phenolic acids. The treatment regimen for tuberculosis, known globally as "Directly Observed Treatment Short-course (DOTS)," is associated with severe toxicity and side effects.

MTB infection suppresses the Th1 response, resulting in decreased proinflammatory cytokines and heightened anti-inflammatory cytokines. Reduced protective CD1+ T cell levels and DOTSside effects raise reinfection and reactivation risks.

Enhanced efficacy of anti-tubercular treatment is achieved by incorporating anti-inflammatory drugs alongside the standard regimen. However, prolonged usage of these drugs leads to severe side effects, discouraging such approaches.

Consequently, researchers are exploring molecules with potential to selectively boost Th1 response while downregulating Th2 immune response, thereby modulating the immune system.

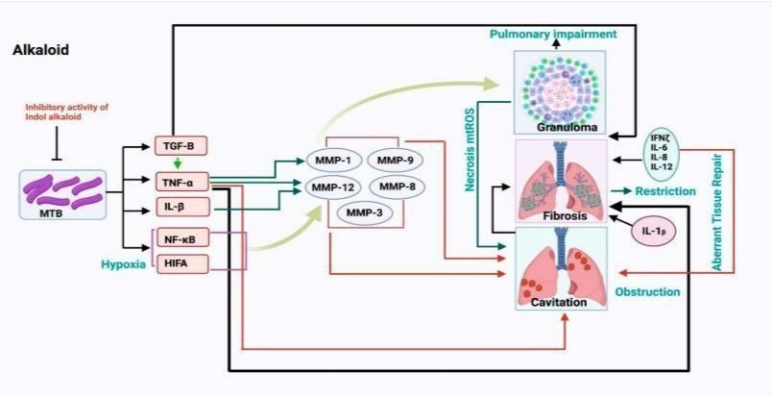
Plant-derived compounds show promise as potential immunomodulators. The alcoholic extract from Coleus scutellarioides (Miana leaves) serves as an immunomodulator, enhancing the proinflammatory T-lymphocyte response and elevating IFN-y and TNF-a levels. Bergenin, a secondary metabolite found in various plant parts, induces Th1 and Th17 responses and impedes bacterial replication in murine models.

When combined with isoniazid, bergenin mitigates isoniazid-induced immune damage, fosters lasting central memory cell responses, and shortens MTB clearance time.

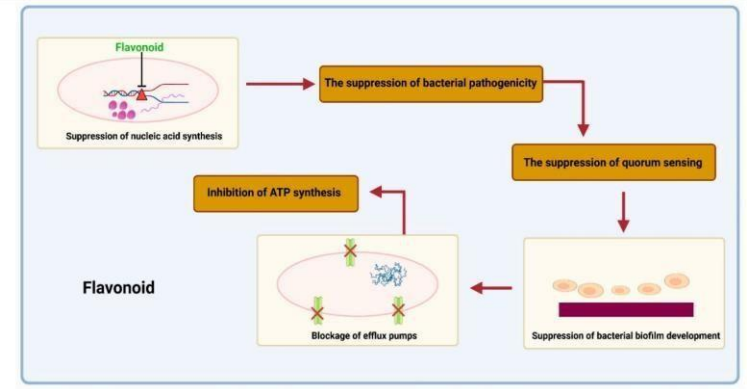
Silymarin sourced from Sylibym marianum seeds similarly boosts the Th1 response across drug-sensitive and drug-resistant strains. Additional immunomodulators from plants encompass allicin (from garlic), piperine (an extract of Chanca piedra/Phyllanthus niruri), curcumin (from turmeric), gingerol (from ginger), and Rubiaceae species extracts. These compounds also exert antioxidant and anti-inflammatory effects.

As adjuncts to DOTS, they may be employed synergistically, offering alternatives tosteroids for inflammation management. Numerous phytocompounds have been previously isolated

andidentified for their anti-TB properties. These substances encompass alkaloids, flavonoids, and terpenoids.

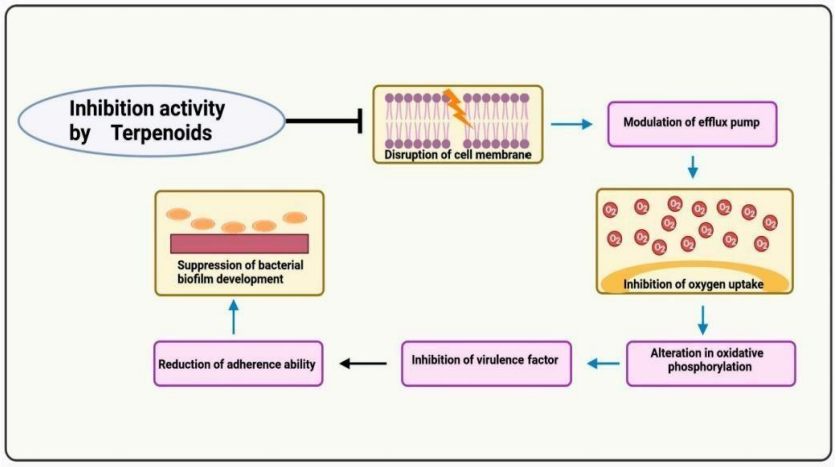


The isolated compound from the plant shows inhibitory activity on MTB. The MTB cells in hypoxia conditions produce HIFA, NF-B, IL-1B, and TNF-a, and these proteins lead to the production of MMP-12, MMP-3, MMP-1/MMP-8, and MMP-9 inhibitors. The production of these matrix metalloproteinases leads to cavitation in the lungs, or MMP-12 and MMP-1 together produce granuloma, which leads to pulmonary impairment or necrosis, leading to cavitation followed by obstruction. Cavitation causes fibrosis in between the mechanism of aberrant tissue repair.



The detrimental suppression of bacterial pathogenicities by Ravonoids. Toxins, quorum sensing, dikydrofolate reductase (DHFR), helicases, and gyrase / topoisomerase inhibitors suppress nucleicacid synthesis. The capacity to produce biofilms then inhibits the synthesis of the cell envelope. Subsequently, it involves blocking the enzyme fatty acid synthase (FAS-5) and peptidoglycan production (suppression of Ala-Ala dipeptide synthesis, inhibition of peptidoglycan cross- linking). Additionally, flavonoids can block efflux pumps, which may result in the reversal of antimicrobial resistance. Then, the bacterial respiratory chain's ATP

synthase and NADH- cytochrome c reductase activities are inhibited.



Mechanism of action of terpenoids. Terpenoids disrupt the cell membrane. Theeftux purp is modulated, which might reverse antimicrobial resistance. The oxygen uptake process is blocked, resulting in the inhibition of oxygen. The oxidative phosphorylation process is altered, inhibiting other virulence factors. The fatty acid synthase enzyme and peptidoglycan production are blocked,suppressing biofilm production.[17]

NUTRITIONAL VALUE (Patients need nutrition)

Dietary guidance combined with energy-boosting supplements showed positive effects on body weight and physical well-being in tuberculosis patients during the early stage of therapy. Studies suggest that vitamins and minerals, such as thiamine, vitamin B6, vitamin C, vitamin E, vitamin A, and zinc, can enhance immune responses and the efficacy of antitubercular drugs. Research with 110 TB cases demonstrated higher lymphocyte proliferation in vitamin- supplemented groups compared to the control. Additionally, improved patient follow-up was associated with bacilli-free sputum and smaller lung lesions.[13]

CONCLUSION

Utilizing medicinal plants and plant-based products presents a compelling alternative for combatting bacteria and mitigating side effects of standard anti-mycobacterial drugs. Given the rise of drug-resistant TB strains, the urgency to explore new remedies has grown significantly. Traditional medical philosophies in India hold a wealth of knowledge to create novel TB treatments. The pursuit of phytodrugs is crucial for effective TB management. Although bio therapeutics of phyto chemicals are gaining attention in various diseases, their

potential for TB treatment requires more research, including understanding mechanisms, bacterial clearance, and immune modulation. By adopting a multidisciplinary approach and integrating promising phyto drug candidates, we can address drug resistance, enhance DOTS therapy, and improve patient outcomes. This approach gains importance given the limited antibiotics and emerging TB resistance forms. Incorporating plants and their products into TB treatment offers an exciting avenue for novel health management strategies. While DOTS effectively clears bacteria, it compromises the immune system; using phytochemicals as adjuncts could boost immunity, providing an eco-friendly alternative to antibiotics. However, it's crucial to exercise caution with alternative medicines. Traditional remedies, while promising, must undergo rigorous testing for safety and efficacy. Scientific scrutiny of phytodrugs in TB treatment is imperative to ensure optimal patient care. In conclusion, harnessing local treatments and beneficial herbs in TB care shows great promise. India's traditional medical practices offer a rich foundation for innovative TB therapies. Exploring phytodrugs and plant-based products to complement standard drugs could yield more positive outcomes and sustainable treatments. With continued research, we envision a future where TB ceases to pose a significant public health threat.[17]

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