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Review Article

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Herbal Anti-Tuberculosis Medicaments: Highlighting New Advances in Therapeutics

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ABSTRACT

The bacterial illness tuberculosis (TB) is very hazardous. The condition is very contagious, and it is often transmitted from person to person by inhalation of bacteria-carrying air droplets. TB is a disease that mostly affects the lungs, but it may affect other organs as well. It has resulted in an increase in the number of orphans due to parental deaths, which is now estimated to be 10 million, with maternal mortality accounting for 6% -15% of the total, or 15% -34 percent if only indirect effects are included. A clinical technique is used to test for tuberculosis, which checks for present cough, sputum intake, fever, weight loss, and night sweats. A multidisciplinary approach is necessary to find new, critically needed anti-TB medications from natural sources. In such a complex condition, using allopathic pharmaceuticals leads to more significant consequences like cross-resistance, while natural treatments have been shown to be more beneficial in this case. The research of novel medicines for the successful weakening of the unstable sickness connected with tuberculosis is the most important requirement.

Key Words: Tuberculosis, Botanicals, Anti-tubercular, Natural, Phytoconstituents, Therapy

INTRODUCTION

Tuberculosis (TB) is a bacterial infection that is the second largest cause of mortality worldwide. Robert Koch, a German scientist, discovered the organism that causes tuberculosis, *Mycobacterium tuberculosis*, in 1882. 1 Following his discoveries, the development of efficient prescription medications and vaccines provided a long-term solution to the ailment. At one point, the United Nations predicted that tuberculosis will be eliminated worldwide by 2025. 2 Once upon a time, tuberculosis was thought to be a mild ailment that could be cured with medications. The first antibiotic was produced in 1944, and it performed miracles. However, owing to drug tolerance, streptomycin monotherapy began to work, emphasizing the significance of establishing a contemporary treatment that uses a multiple medication system to prevent germs from becoming more resistant. A multi-drug strategy, as well as a number of anti-TB drugs, were quickly established. 3 Despite this, a new kind of antibiotic resistance called multidrug-resistant tuberculosis (MDR-TB) emerged, which is caused by bacteria that are resistant to at least rifampicin and isoniazid, the first-line medications for TB treatment. Extensively drug-resistant tuberculosis (XDR-TB) strains of tuberculosis are resistant to both first- and second-line TB therapies. 4 Antibiotic resistance has become a hot subject among physicians, researchers, government officials, and the general public. Antibiotic research from the past, as well as current understanding of cell biology and antibiotic activity, may be combined to generate infection-controlling medications. 5

CURRENT DRUG THERAPY

To boost the body's ability to adapt to care and decrease the period of treatment, current pharmaceutical therapy utilizes a cocktail of drugs. Two of the most often given first-line treatments are rifampicin and isoniazid. 6 Rifampicin is a more significant part of the regimen since it reduces recovery time and assures the best results. A nine-month therapy includes rifampicin and isoniazid, as well as streptomycin and ethambutol. 7 According to one study done by the Medical Research Council of the United Kingdom, utilizing pyrazinamide in the first two months of the therapy regimen

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reduces the treatment period to six months while maintaining a cure rate of 95% or better. 8 Stopping the virus from spreading is the most effective way to eliminate tuberculosis, which may be achieved by prioritizing treatment for sputum smear-positive patients or anyone who can spread the illness. DOTS (Directly Observed Treatment) may be used to assess and manage these individuals. The short course is a very successful and cost-efficient strategy to TB care that is widely recommended across the globe. 9 DOTS consists of five elements: ongoing political and financial commitment, quality-assured diagnostic protocols, consistent delivery of superior anti-TB medications, supervised documentation and reporting, and systematic short-course (SCC) anti-TB care provided under clear and supportive observation (DOT). 10

PROBLEMS WITH THE CURRENT DRUG THERAPY

Patient compliance is hampered due to the extended period of TB treatment, and the large number of drugs utilized will make it difficult for patients to take their regular dosages. The present treatment is still prone to side effects and has been demonstrated to interact negatively with other drugs. In addition, the lengthy operation involves a large financial commitment in the pharmaceuticals required for treatment. The new multidrug therapy has little to no effect on latent tuberculosis. It has also led in the development of MDR-TB. 11 When the improper or inefficient medications are utilised, drug tolerance develops. This might be due to drug delivery confusion, stopping the process in the middle, or leaving just one of the medicines delivered in the protocol (standard treatment is at least two drugs). 12 MDR-TB may be treated with second-line drugs such fluoroquinolones, aminoglycosides, and others, but they are ineffective, dangerous, and costly. Second-line drugs are more expensive than first-line drugs, but the main issue is their treatment duration, which is nearly double that of standard TB treatment, making it much more difficult for some patients to afford treatment, continue treatment for the full duration, and increase the risk of disease spread, leading to further resistance development. 13

NATURAL BOTANICAL ANTI-TUBERCULAR PRODUCTS

If the number of cases of XDR-TB and MDR-TB continues to climb, a new antibiotic to combat resistant germs will be required to prevent and eliminate tuberculosis across the globe. Natural sources, which are rich in chemical complexity and have a lot of antibacterial activity, are appealing beginning points in the search for novel and better anti-TB drugs. 14 Herbal products are rarely utilised to their full potential due to a lack of knowledge and study of their chemical makeup. This industry will thrive if appropriate standardized methods are developed to assure product uniformity and transparency. Allopathic pharmaceuticals are evidence-based and give the finest therapies for a suffering person, but they are typically symptomatic, costly, and have harmful side effects when used to treat chronic illnesses15. Natural medications have a larger chemical variety, better hit rates in high throughput screening, and the ability to access the site of action of their target cells. Natural products were traditionally the pedigree of various medicinal agents from which possible leads of heterocycles like pyrans, flavones, chalcones, coumarins, pyrimidones, and oxzolidines were architected to assign the sources of potential candidates for the reduction of various ailments like anti-cancer, anti-inflammatory, anti-microbials, anti-viral, and anti-TB. 16 In the search for novel anti-TB drugs, this has renewed interest in natural resource discoveries. Natural tools have also been proved to be useful in the creation of current drug design models in many tests. They haven't been properly examined in any area, though. Scientists have recently discovered a few botanical products with notable anti-TB potential (**Figure 1**).

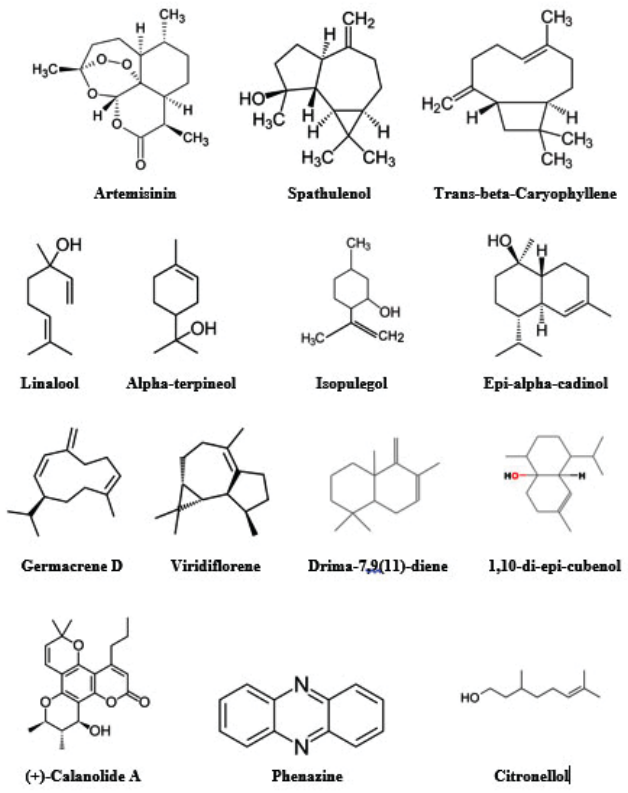

Figure 1: Structures of recently discovered anti-tubercular botanical products.

(+)-Calanolide A

(+)-Calanolide A is a naturally occurring chemical obtained from *Calophyllum lanigerum*, a Malaysian plant. It's a non-

nucleoside reverse transcriptase inhibitor, which is an anti-HIV-1 drug (NNRTI). The chemical is effective against all types of *M. tuberculosis*, including resistant forms, according to the study. (+)-Calanolide A works by rapidly suppressing DNA, RNA, and protein production. This chemical has similar effects to the common tuberculosis drug Rifampicin, which also inhibits RNA production. 17

1,10-di-epi-cubenol

1,10-di-epi-cubenol, a naturally occurring molecule belonging to the Sesquiterpenes family that accounts for 14.2% of the essential oil obtained from the plant *Salvia aratocensis*, is an active component. It's been demonstrated to work against *M. tuberculosis* strains as well as germs resistant to standard anti-TB drugs. 18

Alpha-terpineol

Alpha-terpineol is a monoterpene alcohol generated mostly from alpha-pinene, which is a more easily accessible monoterpene. This oil comes from the *Eucalyptus citriodora* tree. It's widely used in cosmetics, fragrances, and flavorings. It possesses anti-TB capabilities and has been demonstrated to be effective against MDR-TB and TB with XDR-TB. 19

Artemisinin

The plant *Artemisia annua* is used to make artemisinin. It's a Chinese herb that's utilized in traditional Chinese medicine. According to a study, artemisinin has the potential to cure tuberculosis while also improving the efficacy of standard treatments. It functions as an anti-TB agent because it prevents the TB bacterium from becoming dormant. Dormancy is a difficult-to-kill state in which bacteria fight themselves against low-oxygen circumstances established by the immune system to control bacterium development and prevent infection. On the other hand, dormant bacteria acquire a high degree of opioid tolerance. Artemisinin attaches to the heme molecule in bacteria, preventing it from recognizing oxygen levels and so entering dormancy and death. This may shorten recovery time while also delaying the formation of opioid resistance. 20

Citronellol

Citronellol, also known as dihydrogeraniol, is a naturally occurring acyclic monoterpenoid derived from the myrtaceae family's *E. citriodora*, popularly known as lemon eucalyptus. Citronellol possesses anti-TB capabilities in the air, both plain and in different artificial combinations, and it might be utilized as an inhalation medicine to decrease the number of sick persons and prevent TB transmission. 21

Drima-7,9(11)-diene

Turnera diffusa, commonly known as damiana, is a member of the passifloraceae family endemic to southern Texas. Drima-7,9(11)-diene is produced from the essential oil of *T. diffusa*, popularly known as damiana. The essential oil contains numerous compounds, including drima-7,9(11)-diene, which may be useful in the treatment of tuberculosis and MDR-TB, according to a paper. The essential oil from this vine may be extracted by hydrodistillation. 22

Epi-alpha-cadinol

The Columbian plant *Salvia aratocensis*, which belongs to the Lamiaceae family, produces *epi-alpha*-cadinol, a sesquiterpenoid alcohol. The essential oil derived by hydrodistillation from this plant possesses anti-TB characteristics and is also effective against MDR-TB, according to a paper. 23

Germacrene D

Geracrenes are naturally occurring volatile chemicals that are classified as sesquiterpenes. Germacrene D is extracted from *Lippia americana*, a Columbian plant. This compound's insecticidal and antimicrobial effects are well known. Germacrene D has the ability to inhibit both TB-causing bacteria and MDR-TB-causing bacteria, according to a paper on the influence of essential oil from *L. americana* on M. tuberculosis variant strains. 24

Isopulegol

Isopulegol is a monoterpene alcohol derivative that may be extracted from a range of plants, including the myrtaceae species *E. citriodora*. It is utilized as a fragrance and flavoring ingredient, but according to a research, it also possesses anti-TB properties. It is an inhalation medication that may be used to treat and prevent tuberculosis and other airborne infections. 25

Linalool

Linalool is a terpene alcohol molecule found in a wide range of plants, including *E. citriodora*. Linalool has a variety of commercial applications, the most well-known of which is its pleasant scent. Linalool has the ability to treat *M. tuberculosis* by inhalation therapy, according to a review, and has a crucial role in TB prevention as well as other bacterial, fungal, and viral infections. 26

Phenazine

Phenazines are aromatic chemicals produced by several species in the actinobacteria phylum. Riminophenazines, which are derived from lichens, have been studied as a potential anti-TB drug for many years. These compounds are once again being explored as lead chemicals for TB treatment due to clofazimine's anti-TB effectiveness. Clofazimine is a drug that has been demonstrated to be helpful in the treatment of leprosy. It has also proven clinical success in the treatment of tuberculosis, particularly MDR-TB. Clofazimine does not

create tolerance and so prevents resistance to isoniazid in the treatment of tuberculosis. Several new riminophenazine compounds have been produced and studied with the goal of decreasing lipophilicity and enhancing activity, such as B746 and B4157. 27

Propolis

Propolis is a natural substance created by honeybees for the building of hives. It is a complex resinous compound also known as bee glue. Bees collect plant secretions or sticky exudates from cone-bearing tree buds to make this glue. The chemical structure of propolis changes depending on when it is gathered. Propolis has long been used to treat wounds, burns, respiratory infections like HIV, and gastrointestinal problems, and it is still used to treat tuberculosis. Propolis extracts have been found in vitro to inhibit the growth of tuberculosis germs while also enhancing the efficacy of anti-TB drugs including rifampicin, isoniazid, and streptomycin. Propolis has been found to slow the progression of tuberculosis (TB) by lowering the development of granulomas in infected people. Enzymes involved in the bacteria's vital physiological processes might be promising targets for developing new anti-TB drugs. 28

Spathulenol

Spathulenol is a fragrant, viscous organic tricyclic sesquiterpene alcohol compound with a somewhat bitter and spicy taste. It originates from the myrtaceae family's *E. citriodora*, often known as lemon eucalyptus or lemon eucalyptus. It is utilized as a flavoring ingredient and aroma despite its capacity to heal and prevent airborne bacterial infections such as tuberculosis and MDR-TB. 29

Trans-beta-Caryophyllene

Trans-beta-Caryophyllene is a naturally occurring bicyclic sesquiterpene having a cyclobutane and a 9-membered ring. The plant *L. americana*, which belongs to the verbenaceae family, is used to make it. This phytoconstituent, which accounts for around 11.3 percent of the hydrodistillation extract, has been demonstrated to be effective against *M. tuberculosis* and MDR-TB strains. 30

Viridiflorene

The sesquiterpenoid chemical virdiflorene is made up of 5,10-cycloaromadendrane. It may be obtained from a number of plants, including the damiana shrub, which grows in the United States and Mexico. According to one study, virdiflorene has the potential to treat tuberculosis and multidrug-resistant tuberculosis. The essential oil produced by hydrodistillation was tested against *M. tuberculosis* strains in this study. 31

CONCLUSION

The country is being ravaged by a rising strain of tuberculosis tolerance, as well as a lack of effective medicine manufacture. With little hope of eradicating this fatal illness anytime soon, there is a pressing urgency to put a stop to it. Natural sources seem to be the safest alternative, since they provide a high level of antimicrobial activity against a broad range of infections as well as a wide chemical diversity. A vast number of naturally occurring candidates have reached the end of their development. New natural medicines with enhanced modes of action are required to address this. Rather than healing, it is better to prevent. When faced with a terminal sickness that has no treatment for a certain length of time, negligence is not an option. TB can be prevented by getting the correct immunizations and blocking the illness from spreading to healthy people. To provide effective treatment to MDR-TB and XDR-TB patients, a country's government must be able to manage its budget in order to provide enough services to all those who are financially disadvantaged. Both governments and service providers must collaborate to make MDR-TB monitoring and prevention as straightforward as feasible. The DOTS, as well as other TB care organizations and clinics, must improve XDR-TB and MDR-TB surveillance and assure the availability of high-quality anti-TB drugs. To rid the world of this deadly virus, everyone must band together and work as a team, overcoming all hurdles. The government must address the issue of inadequate anti-TB medicine supply by focusing on TB infection prevention, which will help to minimize disease spread and, as a result, greater resistance. Surveillance technology must be enhanced, and more resources must be dedicated to the research, development, and marketing of innovative medical processes, medications, and vaccines.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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AUTHOR'S CONTRIBUTION

The author did the literature survey from standard databases, collected all essential elements, and wrote this manuscript.

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