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The potential of herbal medicine as a promising complement and synergistic effects with anti-tuberculosis drugs: Term and condition apply

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Editorial

Tuberculosis (TB), a disease that can be both prevented and typically cured, likely became the leading cause of death from a single infectious agent again in 2023, after being surpassed by COVID-19 for three years. Tuberculosis resulted in nearly twice as many deaths as HIV/AIDS. Each year, over 10 million people continue to contract TB, with this number increasing since 2021. Immediate action is essential to eradicate the global TB epidemic by 2030, a goal endorsed by all United Nations Member States and the World Health Organization.[1] Though modern antibiotics like rifampicin and isoniazid have been instrumental in the fight against TB, the emergence of drug-resistant strains and the challenges associated with long-term therapy have led to renewed interest in alternative treatments. In 2022, it was estimated that around 410,000 new cases of multidrug-resistant or rifampicin-resistant tuberculosis (MDR/RR-TB) occurred. Over the past years, recent research into new drugs and treatment medication has led to the improvement and evaluation of several promising new treatment regimens for TB.[2]

One of the promising research domains is the exploration of herbal medicine as a potential treatment and management for TB. Herbal medicine, as a centuries-old practice found across various cultures, involves using whole plants or plant extracts for curing and therapeutic purposes. Several traditional herbal remedies have been known and listed in different pharmacopoeias around the world, with several of them displaying notable antimicrobial compounds.[3] The exploration for novel TB treatments has developed to incorporate plants from traditional medicine globally, such as in Indonesia, Ayurveda (India and surrounds), traditional Chinese medicine, and African herbal medicine.[4-6] Researchers are progressively devoted to investigating these traditional remedies, hoping that they may provide novel approaches to addressing the challenges of tuberculosis, particularly in the context of rapid increase of drug resistance.[7]

Herbal medicines as whole plants or compounds offer several mechanisms of action that could be beneficial in the fight against TB. It might be containing antibacterial material that demonstrates direct antibacterial effects against *Mycobacterium tuberculosis*. These compounds can either destroy the bacteria (bactericidal effect) or inhibit their growth (bacteriostatic effect), making them potential candidates for adjunctive treatment in TB therapy.[3,5] Another mechanism of the herbal compound is immunomodulation, as herbal medicines can help modulate the immune system by enhancing the body's natural defence mechanisms to eliminate the bacteria. This mechanism of action is very important since it can help in clearing the infection more effectively and reduce the risk of complications in TB patients with weakened immunity, as TB patients often suffer from other clinical conditions such as HIV/AIDS and diabetes mellitus.[1,7] Herbal compounds are also can have anti-inflammatory and antioxidant materials, so they can

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reduce tissue damage and improve the healing process, thereby enhancing the effectiveness of conventional treatment regimens.[8,9] Furthermore, herbal medicines can have synergistic effects with anti-tuberculosis drugs. Many herbs work synergistically with conventional antibiotics, enhancing their effectiveness and possibly reducing the risk of drug resistance. Some herbal compounds may also reduce the side effects of TB medications, improving patient adherence to the long treatment regimen, enhancing the effectiveness of standard TB medications, reducing the necessary duration of treatment, or mitigating side effects, all while potentially addressing the problem of drug resistance.[5,10]

One of the most concerning issues in modern TB treatment is the growing prevalence of MDR-TB and extensively drug-resistant tuberculosis (XDR-TB). These forms of TB are resistant to the primary drugs used in TB treatment, namely rifampicin and isoniazid. In these cases, the addition of herbal medicines may help address the challenge of drug resistance by re-sensitizing resistant bacteria. Some herbal compounds have been shown to have an adjuvant effect when combined with standard anti-TB drugs, for example, garlic (*Allium sativum*) contains allicin, a sulphur compound with known antimicrobial properties. It has indicated that allicin can enhance the activity of antibiotics against resistant strains of *Mycobacterium tuberculosis* by disrupting the bacterial cell membrane and interfering with the bacteria's ability to detoxify the drug. This potential for re-sensitizing drug-resistant strains is crucial in treating MDR-TB and XDR-TB.[3,4]

Aside from drug resistance issues, side effects also being one biggest concern in TB management. Anti-TB medications, such as rifampicin, isoniazid, and pyrazinamide, can cause a range of side effects, including liver toxicity, gastrointestinal disturbances, and neuropathy. Some herb medicines can alleviate the side effects of anti-TB drugs The addition of certain herbal remedies could help mitigate these side effects, improving patient adherence to the treatment regimen and overall outcomes, for instance, *Tinospora cordifolia*, an herb known for its immune-boosting and hepatoprotective properties. It has been shown to protect liver cells from damage caused by the hepatotoxic effects of anti-TB drugs, particularly isoniazid and rifampicin. By reducing the incidence of liver toxicity, Tinospora cordifolia may help patients tolerate TB treatment more effectively, in addition, it can potentially reduce the risk of discontinuation or loss of treatment follow-up due to adverse effects of medication.[7] Another herbal material that has an anti-inflammatory effect is silymarin. Silymarin is an extract from the herb *Silybum marianum*, commonly used in the treatment of liver diseases. Research has demonstrated that silymarin exhibits antibacterial activity against *Mycobacterium tuberculosis* and enhances the efficacy of anti-TB drugs, thereby potentially reducing the duration of treatment.[8] Some other effects of herbal medicine is supporting immune function and reducing inflammation. Tuberculosis, as a chronic infection, often leads to severe inflammation in the lungs and other organs, as the immune system tries to combat the infection. Chronic inflammation can impair healing and lead to the formation of granulomas that contribute to tissue damage. Herbal medicines with immunomodulatory and anti-inflammatory properties can support the immune system and help control the inflammatory response.[3,10]

Regardless of the promising potential effects of herbal medicine in TB treatment, several significant challenges persist. Firstly, although preclinical studies in laboratories and animals have demonstrated the potential efficacy of certain herbs, conducting large-scale clinical trials is crucial to establish their safety and effectiveness in humans. Aside from that, variations in the quality of plants, dosage, and methods of preparation can further complicate the consistency of research outcomes. Also, must be noted that it is imperative to thoroughly elucidate the mechanisms by which these herbs exert their therapeutic effects before they can be integrated into mainstream medical practice. While herbal medicines may offer beneficial adjunctive effects, it must be highlighted that they should not be considered replacements for conventional tuberculosis therapies, therefore stopping the treatment. It must be very carefully claimed also, that relying solely on unproven remedies of herbal medicine or delaying appropriate treatment could lead to severe adverse outcomes for patients, even leading to mortality. While the integration and collaboration of herbal remedies into TB treatment regimens requires careful study and clinical validation, the existing studies indicate a promising future for their use as

complementary and supplementary therapies. By leveraging both traditional wisdom and modern scientific research, herbal medications could become an integral part of the fight against tuberculosis, offering a multifaceted approach to combating this persistent and dangerous disease. However, more rigorous clinical trials are necessary to determine the precise role of herbal remedies in TB treatment. If it is proven safe and effective, herbal medicines could play an essential role in the fight against tuberculosis, offering hope to millions of people around the world and achieving the goal of stopping TB.

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