IJPSR (2025), Volume 16, Issue 5 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 26 November 2024; received in revised form, 18 December 2024; accepted, 22 December 2024; published 01 May 2025

SIGNIFICANT PROGRESS IN THE TREATMENT OF EXTRAPULMONARY TUBERCULOSIS: A COMPREHENSIVE REVIEW

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Keywords:

Extrapulmonary tuberculosis, Multidrug-resistant tuberculosis, Novel therapeutics, Adjunctive therapies, Nanotechnology

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ABSTRACT: Extrapulmonary tuberculosis (EPTB) accounts for a significant proportion of TB infections worldwide; however, its diverse clinical manifestations and tissue-specific involvement make diagnosis and treatment challenging. Recent years have seen substantial improvements in both the diagnosis and treatment of EPTB. Bedaquiline, delamanid, and pretomanid have revolutionized the treatment of multidrug-resistant and extensively drug-resistant tuberculosis. These drugs, often used in combination, enhance outcomes for both pulmonary and extrapulmonary diseases. Corticosteroids, immunomodulators like interferon-gamma, and vitamin D supplements effectively reduce inflammation and boost the immune response in severe cases of tuberculosis meningitis or pericarditis. Advanced drug delivery technologies, such as nanoparticles and liposomes, can improve drug bioavailability and target affected areas while minimizing overall toxicity. In resource-limited settings, the Directly Observed Treatment, Short-course (DOTS) strategy helps improve treatment adherence and outcomes. Future goals include personalizing drug regimens based on genetic and resistance profiles and developing shorter, less toxic treatment protocols. Expanding molecular diagnostic tools and laboratory capacity will enhance early detection and treatment. These advancements in EPTB management are expected to improve patient outcomes globally.

INTRODUCTION: Tuberculosis (TB) is a chronic granulomatous disease and a major health problem in about one-third of the world's population in developing countries. It is a bacterial infectious disease caused by the bacillus "Mycobacterium tuberculosis". The World Health Organization reports that tuberculosis is the biggest cause of death from one type of infectious microorganism and ranks in the top 10 causes of mortality globally [1].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.16(5).1262-70

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.16(5).1262-70

Although pulmonary tuberculosis is the most frequent type, non-pulmonary types such as lymphatic, pleural, bone and abdominal tuberculosis are also common and provide special therapeutic difficulties. Extrapulmonary TB can affect both immunocompetent and immune-compromised patients, but it is more common and severe in those with HIV, who have higher risks of latent reactivation and disseminated disease, particularly lymphatic, miliary, and CNS TB [2].

The treatment of non-pulmonary tuberculosis presents unique issues, in particular, because the availability and delivery to sites from which drug therapy is delivered may be limited by the anatomical site. This variability often necessitates individualized strategies that may account for differences including tissue penetration, drug

concentration, and the presence of barriers such as the Blood-Brain Barrier (BBB) in TB meningitis [3]. Here, we review recent developments in immunoprophylaxis, and treatment of latent TB, as there are only protections that have been partly understood mechanisms to overcome these challenges related to how to prevent them from becoming active. Because drug-resistant tuberculosis strains like MDR TB [4] are harder to treat, we need new and effective treatments. The current therapies take a lot of time and may result in adverse consequences that prompt individuals to stop taking their prescribed medications. The resistance of tuberculosis may be further strengthened by such discontinuations, facilitating the propagation of the disease. Therefore, the development of new therapies that are more effective, safer, better potency, and able to fight drug-resistant TB [4], would help people recover more quickly and reduce the spread of the disease. Through the Revised National Tuberculosis Control Program (RNTCP), India has worked to ensure that everyone has access to high-quality TB diagnosis and treatment services since its inception in 1997. By 2015, 90% of all TB cases, including drug-resistant TB, should be detected; additionally, 90% of new cases and 85% of cases that have already been treated should have a favorable treatment outcome (treatment success) [12]. Up to two million lives have been saved by the program's treatment of more than 12 million patients. To date, RNTCP's tiered response plan to combat drug-resistant TB has mostly focused on treatment effectiveness and laboratory capacity [5].

Types of Non-pulmonary TB: Extrapulmonary TB is when TB infections spread outside the lungs and affect other organs and systems in your body. Pulmonary tuberculosis is common, but extrapulmonary symptoms may be life-threatening and should prompt special care [6]. A few of the interesting types of extrapulmonary tuberculosis are:

Meningeal Tuberculosis (TB Meningitis): The membranes encircling the brain and spinal cord are impacted by this severe form of tuberculosis. It is especially common in older and immune-compromised people, and it frequently happens without other extrapulmonary infections. Low-grade fever, chronic headaches, nausea, and tiredness are common symptoms, which can develop into more serious neurological impairments. Because of the significant morbidity and mortality rate linked to this illness, early diagnosis is essential [7].

Genitourinary Tuberculosis: The kidneys and urinary tract are the main organs affected by this kind. Back pain, fever, and sterile pyuria the presence of white blood cells in urine without a bacterial infection are some of the symptoms that can indicate pyelonephritis.

Men may develop issues including scrotal lumps as a result of the infection spreading to the prostate and other reproductive organs. Salpingo-oophoritis in women can cause persistent pelvic pain and possibly reproductive problems [8].

Tuberculous Lymphadenitis: Often referred to as scrofula, this condition involves the lymph nodes, particularly in the cervical region. It typically arises from the spread of TB from the lungs or other sites. Initially, the lymph nodes may swell and become painless, but as the disease progresses, they can become inflamed, and tender, and may even form draining fistulas [8].

Peritoneal Tuberculosis: This form occurs when TB spreads to the peritoneum, often from abdominal lymph nodes or through direct infection. Symptoms can range from mild abdominal pain and fatigue to severe manifestations that mimic the acute abdomen. It is particularly common in individuals with underlying conditions such as cirrhosis and alcohol use disorder [8].

Bone and Joint Tuberculosis: Although it can affect any organ in the body, TB primarily manifests (especially extra-pulmonary) as spread to weight-bearing joints and bones leading to Pott disease or infection of the spine. Neuropathies, spinal deformities, and unimaginable pain may arise from spinal cord compression. Chronic arthritis can also involve other joints [8].

Gastrointestinal Tuberculosis: Although it usually occurs after a prolonged contraction, TB has been known to impact the gastrointestinal tract. Additionally, it may result in appendicitis-like symptoms, ulceration, and inflammatory bowel

syndrome. Other symptoms include diarrhea, weight loss, and abdominal pain [8].

Cutaneous Tuberculosis: This form occurs when TB spreads to the skin, often resulting from direct extension from an underlying focus of infection. It can present as painless nodules that may ulcerate and form sinus tracts [8]. There are different types of extrapulmonary tuberculosis and each has its corresponding problem and management. These conditions require management so complications can be avoided, making early recognition and intervention important. For healthcare providers who treat patients with extrapulmonary TB, it is important to be aware of its types [6].

Pathophysiology: Mycobacterium TB to organs other than the lungs. Hematogenous spread, granuloma formation, tissue damage and necrosis, and a variety of clinical symptoms are some of the pathophysiology's primary processes. When the bacterium enters the blood vessel and travels to distant tissues, such as lymph nodes, kidneys, bones, and the central nervous system, this is known as hematogenous spread. One important way that extrapulmonary TB develops is through this widely diffused infection [9]. Granules are colloidal aggregates of macrophage and lymphocyte cells that form to confine the infection when the immune system recognizes the pathogen in a particular organ. This triggers an aspect of innate immunity and results in the creation of granulomas. For instance, these granulomas may form in the kidneys' glomeruli and rupture, allowing bacteria to spread further into the renal tubules[10]. Necrosis may result from tissue damage caused by the immunological response. This may lead to kidney function loss in renal tuberculosis by causing ulcers and abscesses [11]. Depending on the locale, extrapulmonary tuberculosis might present with different clinical symptoms. For instance, imaging features typical of renal tuberculosis, such as uneven calyceal outlines due to necrosis, may also be present, and necrotic lymph nodes are frequently seen in cases of lymphatic involvement [12]. Thus, tissue degradation, hematogenous spread, an immune response leading to the development of granulomas, and a variety of clinical symptoms characterize the pathophysiology of extrapulmonary tuberculosis, all of which make identification and therapy difficult.

Drug Resistance: The development of drug resistance is a great challenge in managing EPTB, especially in the background of the high burden of India. The frequency of drug-resistant Mycobacterium tuberculosis in EPTB is largely unknown because obtaining diagnostic specimens can be challenging and laboratories that can do culture and DST for extrapulmonary samples may not exist [13].

In a larger study that examined 1,295 extrapulmonary specimens between 2005 and 2012, M. tuberculosis was detected in 189 specimens, and multidrug resistance (MDR) was recorded in 37 cases (19%) [11]. MDR rates ranged from 10% among cerebrospinal fluid (CSF), 6% among urine, 27% among fluids and aspirates, 23% among pus, and 19% among lymph node specimens. Isoniazid resistance was also high (resistance rate 31%) as well as ethionamide (38%). These results suggest that extrapulmonary drug-resistant tuberculosis including MDR-TB affecting different extrapulmonary sites underscores the importance of susceptibility testing in suspected EPTB cases amongst healthcare providers. Furthermore, there is an urgent need to broaden culture and DST access for extrapulmonary specimens to allow appropriate treatment of patients promptly. Moreover, very little is known about drug resistance in EPTB and the need for systematic investigations exploring associations of susceptibility data with epidemiological, clinical, and other risk factors has been expressed. Such information would aid in formulating targeted interventions to effectively control drug-resistant EPTB and optimize patient care. In conclusion, tackling drug resistance in EPTB is vital for efficient TB control and management in high-burden countries [14-15].

TABLE 1: DRUG SUSCEPTIBILITY PATTERNS OF *M. TUBERCULOSIS* IN PULMONARY AND EXTRAPULMONARY SPECIMENS

Extrapulmonary Specimens							
Sample Type	**Smear +ve (%)**	**MTB Culture +ve (%)**	**XDR (%)**	**MDR (%)**	**Resistant to > 1 drug/not MDR (%)**	**SM, INH, RMP, EMB Sensitive (%)**	**Mono-resistance**

CSF (n=76)	15 (19.7)	10 (13)	0	1 (10)	2 (20)	4 (40)	ETH = 3
Urine (n=208)	ND	17	0	1 (6)	3 (18)	8 (47)	OFX = 4, ETH = 1
Fluids & Aspirates (n=186)	17 (9)	11 (5.9)	0	3 (27)	1 (9.0)	4 (36)	SM = 1, RMP = 1, ETH = 1
Pus (n=414)	155 (37)	ND	ND	ND	ND	ND	ND
Lymph Nodes (n=246)	117 (47.5)	58 (23.5)	0	11 (19)	22 (38)	25 (43)	SM = 1, RMP = 2, OFX = 3, ETH = 12
Total (n=1223)	342 (33.6)	189 (15.5)	1 (0.5)	37 (19)	38 (20)	78 (41)	INH = 3, RMP = 5, OFX = 9, SM = 2, ETH = 33
Pulmonary Specimens							
Sample Type	**Smear +ve (%)**	**MTB Culture +ve (%)**	**XDR (%)**	**MDR (%)**	**Resistant to > 1 drug/not MDR (%)**	**SM, INH, RMP, EMB Sensitive (%)**	**Mono-resistance**
Bronchial Wash (n=155)	56 (36)	36	0	7 (19)	5 (14)	17 (47)	OFX = 1, ETH = 6
Gastric Aspirates (n=68)	11 (16)	6	0	2 (33)	0	2 (33)	RMP = 1, OFX = 2
Total (n=223)	67 (30)	42	0	9 (21)	5 (11.9)	19 (45)	RMP = 1, OFX = 3, ETH = 6

MDR, multidrug resistant; XDR, extensively drug resistant; ND, not done; SM, streptomycin; INH, isoniazid; RMP, rifampicin; EMB, ethambutol; KM, kanamycin; ETH, ethionamide; OFX, ofloxacin.

Epidemiology: Tuberculosis (TB) remains a serious disease with an annual burden of approximately 1.3 million new cases and 450,000 deaths. The TB incidence for children aged 0–14 years in England and Wales is 11.9 per 100,000 for all TB cases and a non-pulmonary TB incidence of 1.9 per 100,000 (Public Health England reported unpublished data).

The majority of cases are seen in infants and young children, while it seems that those children aged 5–15 experience a period of relative immunity from primary TB infections which often resolve spontaneously in this age group. The fact that more adults have HIV is driving up childhood TB because if an adult has HIV, they often transmit TB to children much more easily, and a child infected with HIV is easier to infect. In Korea, the number of notified TB cases was 36,089 (71.4/100,000) in 2013; for the same year notification data reported aspects of TB at sites other than the lung as extrathoracic extrapulmonary TB (EPTB), with 7,369 EPTB cases and a rate of 14.6/100,000 representing 20.4% of all TB cases detected. The sites of EPTB can be varied, however, the pleura, lymph nodes, gastrointestinal organs, bones and joints, CNS, and genitourinary tract are by far affected most frequently. The proportion of EPTB cases ranged between 14% (2005–2007) and over 20% (2010–2013), likely reflecting diagnostic difficulties or underreporting. Young age, female sex, Asian or African descent, and HIV infection have been associated with increased risk of EPTB as well [16-17].

Traditional Treatment Approaches:

Use of Herbals: Traditionally long-standing cultural customs surrounding herbal therapy are reflected in the country's traditional TB treatment methods, which mostly rely on a variety of herbal plants. The systematic review identified several noteworthy plants, including *Zingiber officinale*, *Allium ursinum*, *Myrsinea fricana*, *Croton macrostachyus,* and *Allium sativum*. These plants' roots and leaves, which are thought to have medicinal qualities against tuberculosis, are frequently employed in a variety of treatments. Usually, fresh or dried plant components are used to prepare these herbal treatments, with water serving as the main solvent. To increase the

effectiveness of the therapies, additives like milk, honey, and cow butter are commonly used. These plants' geographic distribution reveals a notable concentration in areas such as Oromia, Tigray, and Amhara, where decades of traditional knowledge about their use have been transmitted [18].

Even though these herbal medicines are widely used, many of them lack scientific proof of their anti-mycobacterial properties. Given that 79.6% of the plants used traditionally have not been tested experimentally or clinically, this reveals a significant research deficit. Therefore, more research is desperately needed to support the traditional claims and investigate these plants' potential for creating potent anti-TB medications. We can improve our comprehension and use of these herbal treatments in the fight against tuberculosis by establishing a connection between scientific study and traditional knowledge [19].

Recent Treatment Approach:

New Drug Developments:

Bedaquiline and Delamanid: These are the two newer drugs that have significantly impacted the management of multidrug-resistant tuberculosis (MDR-TB). Their introduction has provided new options for treating patients who have strains of Mycobacterium tuberculosis resistant to standard first-line therapies [20-21].

The way that delamanid and bedaquiline work makes them good choices for treating multidrug-resistant tuberculosis (MDR-TB). Because of its special mechanism, bedaquiline even works against drug-resistant forms of Mycobacterium TB by blocking ATP synthase, an essential enzyme that is involved in energy production [20]. In contrast, delamanid prevents the bacterial cell wall's vital components, mycolic acids, from being produced, which changes the bacterial activity and eventually eradicates the infection [21]. These medications can help individuals with MDR-TB achieve high success rates, according to clinical trials. The BEAT Tuberculosis study, for example, showed great efficacy with a regimen consisting of bed aquiline and delamanid, with excellent results in a significant number of patients. A 6-month course of treatment with these medications is also very beneficial for MDR/RR-TB, according to the PRACTECAL trial, with better outcomes than traditional therapy. Even though pulmonary MDR-TB has received a lot of attention, there is growing evidence that bedaquiline and delamanid can also be utilized to treat extrapulmonary and other non-pulmonary forms of tuberculosis. These cases are appropriate for them because of their capacity to work against resistant germs and enter a variety of tissues. Furthermore, these drugs' versatility in combination regimens allows for tailored treatments to address the unique requirements of patients with non-pulmonary tuberculosis, which may result in better outcomes in these challenging situations [22-23].

Pretomanid: It is a novel drug that has emerged as a crucial component in the treatment of highly resistant tuberculosis (TB), particularly multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB. Its role in combination therapies is significant for several reasons [24].

Inhibiting the production of mycolic acids, which are vital parts of the cell wall of Mycobacterium tuberculosis, is how pretomanid functions. Because of this function, pretomanid is effective against resistant forms of bacteria since it causes their death [23]. Pretomanid is usually used in conjunction with other drugs, like bedaquiline and linezolid, to optimize the effectiveness of treatment. In clinical trials, a combination of bedaquiline, pretomanid, and linezolid has demonstrated significant success rates in treating very resistant tuberculosis. Due of pretomanid's unique technique of targeting the bacterium, this combination provides broader protection against resistant TB and lowers the likelihood of treatment failure [25].

Adjunctive Therapies:

Immunotherapy: An Emerging Approach: Immunotherapy approaches aimed at augmenting our understanding of immune responses to Mycobacterium tuberculosis (M. tuberculosis) have evolved, with recent applications of interferon-gamma (IFN-γ) therapy to treat both latent and active TB selectively stimulating T-cell-mediated overall immunity. It performed well in terms of immunogenicity by providing a more sustained immune response and long-term memory but only modestly impacted clinical endpoints such as bacterial clearance and resolution of fever in cavitary tuberculosis patients upon human testing.

IFN-γ was chosen because of its function in priming macrophages and boosting the immune control of intracellular pathogens such as TB. Other immunomodulatory agents, like antagonists of TNF-α and interleukin-1, have been attempted to treat life-threatening inflammatory reactions caused by TB [26].

Corticosteroids: Reducing Inflammation: Since, inflammation can result in serious consequences, corticosteroids are frequently used to treat regimens for patients with spinal tuberculosis or tuberculous meningitis. According to studies, corticosteroids are linked to a 30% lower death risk for TB meningitis patients who are HIV-negative. Additionally, they lessen hospitalization and restriction in cases of tuberculous pericarditis. In these situations, the goal of using corticosteroids is to improve patient outcomes by lessening the negative effects of excessive inflammation. Though being used for the treatment of tuberculosis, it has some adverse effects which include immunosuppression, hyperglycemia, hypertension, osteoporosis, adrenal suppression, weight gain, and mood changes. They may also increase the risk of infections, delay wound healing, and lead to gastrointestinal issues like ulcers [27].

Vitamin D Supplementation: A Complementary Therapy: Some studies have proposed that vitamin D may be involved in enhancing immunity against tuberculosis. One of the proposed mechanisms is through antimicrobial peptides such as cathelicidinwhich could increase the antimicrobial activity of immune cells and may play a role in controlling M. tuberculosis infection. However, despite this vitamin D supplementation might be beneficial in TB treatment as evidenced by some studies clinical trial evidence for the systematic addition of vitamin D in therapy has been limited or absent. Therefore, vitamin D might have a role as an adjunct therapy but its clinical efficacy and appropriate use need to be determined in TB [28].

Novel Drug Delivery Systems: Novel drug delivery systems (NDDS) improve the targeted distribution of anti-tubercular medications to afflicted locations, such as lymph nodes and skin, providing creative ways to treat extrapulmonary tuberculosis (TB). These systems, which include liposomes and nanoparticles, enhance medication stability, regulate release rates, and lessen systemic side effects, all of which contribute to improved therapeutic success and patient compliance. A promising development in addressing the drawbacks of conventional TB treatments is NDDS [29].

Nanotechnology and Drug Encapsulation: By improving the accuracy and effectiveness of treatment, nanoparticles present encouraging developments in targeted drug delivery for diseases like tuberculosis (TB). By altering surface characteristics, such as by adding ligands or antibodies that bind specifically to target cell receptors, these particles can be designed for targeted delivery. This approach ensures the drug reaches the specific area needed, minimizing off-target effects [30]. For chronic illnesses like tuberculosis, which necessitate long-term therapeutic levels without regular dosage, encapsulating medications within nanoparticles also permits regulated release, allowing for a continuous release of the medicine over time [31]. Furthermore, by delivering medications straight to the infection site (such as the skin or lymph nodes), nanotechnology helps minimize systemic exposure and the negative effects that go along with it [30-31].

Anti-TB medications, which usually have poor solubility and depend on passive permeability administration, can also be made more stable and soluble by using nanoparticles. To reach tissues like lymph nodes or skin, where efficient medication penetration is essential, nanoparticles enhance solubility, which in turn improves drug absorption and bioavailability [30].

Treatment of Rifampicin-susceptible, Isoniazid-Resistant Tuberculosis: Rifampicin, ethambutol, and pyrazinamide are commonly used in combination with fluoroquinolone to treat isoniazid-resistant, rifampicin-susceptible tuberculosis (TB). This strategy is supported by data indicating that adding fluoroquinolone may increase treatment success rates. However, because of the low level of evidentiary certainty, the recommendations for this treatment are conditional. Certain guidelines recommend restricting the use of pyrazinamide to the first two months of treatment for individuals with noncavitary disease or a low bacterial load.

Since, the presence of certain mutations can affect the regimen's efficacy, individualized treatment strategies may be required when new drug resistance is predicted or proven. All things considered, maximizing treatment outcomes requires careful assessment of the patient's unique resistance patterns and clinical status [32].

DOTS Therapy: Under the Revised National Tuberculosis Control Programme (RNTCP) in India, a therapeutic regimen that is generally based on DOTS is provided. This regimen is particularly effective against extrapulmonary tuberculosis (EPTB). DOTS is well-known for its ability to increase adherence and results while simultaneously reducing drug resistance. This is accomplished by ensuring that medical professionals monitor the consumption of scripts. Categories I, II, and III are included in this plan. Category I is for new patients, while Category II was phased out in 2011 and is for patients who did not react to treatment. One of the ways that DOTS treats pulmonary tuberculosis (EPTB) is by treating the disease in areas other than the lungs, such as the lymph nodes and the central nervous system. A study found that the completion percentage of therapy for patients with EPTB was 84%, with a greater success rate in HIV-negative patients (86%) compared to HIV-positive patients (66%). This finding highlights the necessity of developing individualized solutions for certain vulnerable groups. The restricted diagnostic parameters for EPTB and the impact of HIV co-infection are two of the challenges that must be overcome. DOTS continues to play an important role in the care of tuberculosis in India, its primary objective being to enhance adherence and outcomes while simultaneously handling difficult cases [33].

Future Prospective for the treatment of non-pulmonary Tuberculosis: Personalized, quicker, and more effective treatment methods are becoming increasingly the focus of advancements in treating non-pulmonary tuberculosis. Personalized medicine, which is informed by genetic insights, is helping to personalize therapies that reduce side effects and optimize outcomes. One example is adjusting the dose of isoniazid based on the NAT2 genotype [34]. Additionally, research is being conducted to develop shorter, more well-tolerated regimens by combining medications such as rifapentine and levofloxacin. The objective of this research is to shorten the treatment period without sacrificing its efficacy and reduce the problems associated with tuberculosis. The development of a more holistic treatment paradigm is being advanced through the use of clinical trials that examine new drug combinations (for example, delamanid and linezolid) for patients who have comorbidities [36]. In general, these improvements represent a change in the management of nonpulmonary tuberculosis that is more patient-centered and energy-efficient, and they hold the possibility of improved results.

The RNTCP calls for expanding the number of approved drug susceptibility testing (DST) and culture labs throughout India to scale up laboratory capacity. There were 25 accredited laboratories as of March 2011, and there are plans to greatly increase this number. To guarantee prompt and precise diagnosis of MDR TB, the project intends to improve specimen transit infrastructure, implement high-throughput molecular DST, and optimize sputum processing. For a wider population to receive quality-assured diagnosis and treatment, this growth is essential [37].

By reducing the frequency of treatment, long-acting injectables like bed aquiline have the potential to enhance patient adherence, particularly in cases with nonpulmonary tuberculosis that have been present for an extended period [35]. In addition, dependable biomarkers and host-directed therapies, such as adjuvant immune-modulating drugs, are being investigated because they have the potential to enhance immunological responses.

CONCLUSION: Non-pulmonary tuberculosis (TB) requires a targeted approach due to its unique distinguishing traits, especially in terms of diagnosis and therapy management. The growing worry about drug resistance to therapy, and specifically multiple drug-resistant TB (MDR-TB), does, draw attention to the absence of prompt diagnosis and adequate management. The rationale behind accomplishing this aim is to increase the likelihood of a successful outcome by using a customized medicine strategy, in which we customize therapies to meet the needs of each patient and help maximize efficacy while reducing needless exposure to negative effects.

Scaling up the availability of drug susceptibility testing is still crucial for managing resistant cases effectively. However, no single group will be able to address the complexities of non-pulmonary TB alone and multidisciplinary approaches including healthcare providers, researchers, and policymakers need to coalesce around decentralized strategies. Continued investment in research for new therapeutic options and effective public health initiatives will be key in reducing the disease burden, ultimately leading to improved outcomes for individuals affected by non-pulmonary TB.

ACKNOWLEDGMENT: We want to express gratitude to everyone who helped construct this article on extrapulmonary tuberculosis (EPTB). We applaud the researchers who have contributed considerably to our understanding of EPTB diagnosis and therapy. Thank you to the institutions and organizations that provided excellent resources and assistance throughout the research process. We also recognize the assistance of our colleagues and mentors, who provided valuable input and guidance that helped us refine our viewpoints and improve the quality of this work. Finally, we want to thank the patients and communities afflicted by tuberculosis for their experiences and fortitude, which motivate us to improve healthcare results. This article is about the ongoing attempts to combat tuberculosis and improve the lives of those affected by the disease.

CONFLICT OF INTEREST: No financial or other conflicts of interest are acknowledged by the writers.

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How to cite this article:
Islam K, Hussain A and Nayak A: Significant progress in the treatment of extrapulmonary tuberculosis: a comprehensive review. Int J Pharm Sci & Res 2025; 16(5): 1262-70. doi: 10.13040/IJPSR.0975-8232.16(5).1262-70.