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Current Status of Multi Drug Resistance- Tuberculosis: A Major Public-Health Threat

Deepak Kajla[1*], Veerta Sharma[2], Ashi Mannan[2], Tanveer singh[3] and Pankaj Kumar Singh[4]

[1]*Gurugram Global College of Pharmacy, HailyMandi Road, Faukhnagar, Haryana-122506 (Gurugram) India.*
[2]*Chitkara College of Pharmacy, Chitkara University, Punjab, India.*
[3]*Molecular & Integrative Physiology, University of Illinois, Urbana,Illinois, USA.*
[4]*Integrative Physiology and Pharmacology, Institute of Biomedicine, Faculty of Medicine, University of Turku, Turku, Finland.*

[*]dr.deepakkajla@gmail.com (Corresponding Author)

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ABSTRACT

Background: Rifampicin is the most effective first-line antibiotic for tuberculosis (TB). However, drug resistance, particularly multidrug-resistant TB (MDR-TB), poses a significant global health challenge. According to the World Health Organization (WHO), approximately 500,000 new TB cases in 2019 were resistant to treatment, with 78% showing multidrug resistance. India alone accounted for 27% of all MDR or rifampicin-resistant (RR) TB cases reported in 2020. MDR-TB, defined by resistance to at least isoniazid and rifampicin, is primarily driven by poor adherence to treatment, inappropriate antibiotic use, and transmission in crowded settings.

Purpose: This review highlights the increasing threat of MDR-TB and underscores the need for alternative therapeutic strategies, improved diagnostic tools, and updated treatment guidelines to combat drug-resistant TB effectively.

Methods: A literature-based analysis was conducted, focusing on recent WHO reports, updated guidelines, and emerging approaches in MDR-TB diagnosis and management, including molecular diagnostics, novel oral drugs, and adjunctive therapies such as nutritional and traditional support systems.

Results: Recent WHO guidelines emphasize early detection using advanced molecular techniques and the use of repurposed oral anti-TB medications. These strategies show promise in enhancing disease control and patient outcomes. However, the implementation of new regimens requires further clinical evaluation. Integration of supportive care approaches such as nutrition and traditional therapies may contribute to a more holistic management of MDR-TB.

Conclusion: The growing prevalence of MDR-TB and XDR-TB calls for urgent action in diagnosis, treatment, and patient support. While revised WHO strategies offer a promising framework, continued research and clinical trials are vital to optimize therapies and address global TB drug resistance effectively.

1. Introduction

Public health is seriously at danger due to the recent increase of *Mycobacterium tuberculosis* (TB) cases (Laszlo *et al.*, 1997; WHO, 2000). Tuberculosis (TB), a fatal condition caused by *Mycobacterium tuberculosis* (Mtb), is one of the leading respiratory disease-related causes of mortality worldwide (WHO, 2020). In 2023, TB was the leading infectious disease killer, accounting for about 8.2 million new diagnoses and 1.25 million deaths, surpassing COVID-19. German biologist and pharmaceutical researcher Dr. J. L. Schönlein coined the name "tuberculosis" for the first time in 1839 (Robert Koch *et al.*, 2010). For his discovery of *Mycobacterium tuberculosis*, the microorganism that causes TB, Dr. Robert Koch was awarded the Nobel Prize in Physiology or Medicine in 1905. The term "Mycobacterium tuberculosis complex" refers to a group of closely associated bacterial species (News-medical.net, 2010). TB is still a serious global health issue, particularly in light of the rise of multidrug-resistant TB (MDR-TB). MDR-TB strains complicate treatment regimens and lower success rates because they are resistant to at least isoniazid and rifampicin, the two most effective TB medications. The need for better detection and management techniques is highlighted by the fact that less than half of the estimated 400,000 MDR-TB cases in 2023 were identified and treated. *Mycobacterium tuberculosis* (Mtb) is an intracellular parasite that enters the body through the lymphatic and circulatory systems

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and eventually makes its way to the organs. When these aerobic bacteria enter a host that is susceptible, they can spread throughout the atmosphere and result in a number of different issues. One possibility is that the bacteria will be eliminated by the human immune system; otherwise, they may enter a dormant state and result in a latent TB infection. The third possibility is where the latent infection with TB manifests itself (Talbot *et al.*, 2015). Comprehensive public health measures, such as improved diagnostic tools, efficient treatment plans, and strong prevention campaigns, are needed to combat TB and MDR-TB. These tactics must be given top priority by the international community in order to counter the ongoing threat of tuberculosis and its drug-resistant variants.

1.1. Disease Progression in the Body of an Individual

The TB infection manifests itself in four stages:

(I) The first stage of the macrophage response;
(II) The growth stage;
(III) The stage of immunological control;
(IV) The stage of lung cavitations.

These four stages happen over the course of around thirty days. At the beginning of Stage I, the bacterial infection known as TB enters the body by breathing. Macrophages in the pulmonary alveoli attempt to engulf the bacteria. However, if the bacterial load is high or the macrophages are weak, TB bacilli can survive and multiply within them. The TB infection progresses to Stage II after about a week if alveolar macrophages in the lungs are unable to halt the TB bacillus multiplication in Stage I. This fast multiplication of the initial TB bacillus creates the infection and makes macrophages unable to control it. Up to the third week after the first infection, Stage II is ongoing.

When the bacilli cease their exponential proliferation at the conclusion of Stage II, Stage III, when bacterial growth is balanced by immune responses, starts. During this phase, the human body produces more immune cells in an effort to contain the infection and prevent it from spreading. At this stage, granulomas begin to form around infected sites to limit bacterial dissemination. A Ghon focus is a circular complex made up of macrophages and tuberculosis bacilli in the lungs. Vicinal lymph nodes are frequently infected with tuberculosis bacteria (Smith *et al.*, 2003).

If immune defenses are strong, the granuloma stabilizes, preventing bacterial spread. The TB bacilli can be hidden by the lung tissue itself, but they can survive for generations inside the macrophages. If the patient has a robust immune system, the main complex heals and only leaves a tiny cavity; in the worst scenario, it leaves an X-ray-visible scar in the tissue. However, in around 5% of cases, the major complex fails to recover, leading to Stage IV. In this phase, 12 to 24 months after the initial infection, the TB bacilli come back to life and begin to multiply swiftly. The patient finally displays the bulk of the warning signs and symptoms of active TB once the TB bacilli quickly spread. Since sputum may spread live TB germs to other people, the illness is now very infectious (Sharma *et al.*, 2021).

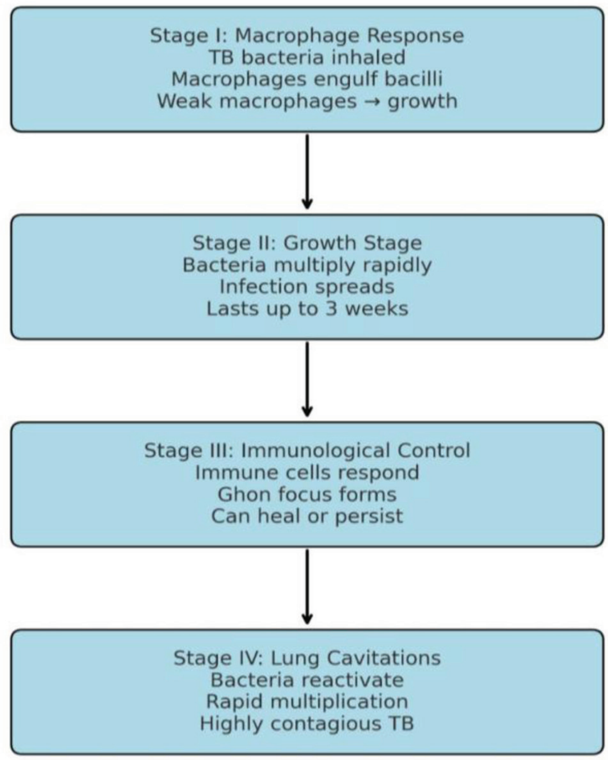

Figure 1: Four Stages of the TB Infection Manifestation

2. Classification

A. It is initially classified as active, military, or latent according on the signs and modes of activity it exhibits.

Both kinetic and miliary forms of TB are agile/active kinds that quickly infiltrate organs.(Sharma *et al.*, 2016; Rfiei *et al.*, 2019) While the condition generally impacts the respiratory system, it has been seen to extend to other organs in a few cases. (Torrelles *et al.*, 2017; Sharma *et al.*, 2018). This chronic, crippling disease has a latent stage that lasts for generations, making it challenging to detect and treat (Atlanta, 2020).

B. Resistance-based classification

In Mtb, resistance to antimicrobial drugs can develop quickly. For the treatment of TB, first-line treatments such an isoniazid, rifampicin, pyrazinamide, and ethambutol are often recommended drugs (Pinto *et al.*, 2011). Antibiotic-resistant Mtb isolates can develop primary or acquired drug resistance as a result of a number of causes, including the antibiotic-resistant cell wall (Li *et al.*, 2009) Mtb efflux pumps (De Rossi *et al.*, 2006)and mutations in Mtb genes (Nguyen *et al.*, 2006).

Drug resistance appears to occur independently of other drugs and happens one drug at a time through unrelated pathways, which causes resistance to accumulate gradually over time. (Mitchison *et al.*, 1998; Jindani *et al.*, 1980). Based on resistance, there are the following types of tuberculosis:

- **Multidrug-resistant (MDR) TB:** Infections caused by Mtb strains that have become resistant to at least two of the first-line medications, such as isoniazid and rifampicin, are referred to be multidrug-resistant (MDR) tuberculosis (TB) (Pinto *et al.*, 2011). Treating MDR-TB becomes more difficult without these two potent drugs as fewer potent and possibly less well-tolerated second-line drugs must be employed in place of first-line ones (Frieden *et al.*, 1995). Patients suffering with tuberculosis that is multidrug-resistant (MDRTB) frequently have advanced illness, thick-walled cavities, and medication-resistant lung lesions that have persisted for a long time (Mukherjee *et al.*, 2004).
- **Widespread medication resistance (XDR) TB:** Apart from resistance to several drugs, there is also resistant to any fluoroquinolone and at least one of all three injectable second-line drugs (capreomycin, kanamycin, and amikacin). When MDR-TB bacteria developed resistance to fluoroquinolones and second-line injectable drugs in 2006, the term extensively drug-resistant tuberculosis, or XDR was coined.
- **Monoresistance**: The inability to respond well to a particular first-line antitubercular drug.
- **Polydrug Resistance:** The inability to respond to a greater number than one primary anti-tuberculosis drug, with the exception of isoniazid and rifampicin.
- **Rifampicin Resistance (RR):** Phenotypic or genotypic methods can detect rifampicin resistance, which may or may not be associated with resistance to other anti-TB drugs. It includes all types of rifampicin resistance, such as widespread, poly-, multi-, and mono-drug resistance (Kwonjune *et al.*, 2015).

3. Demographic Burden of MDR-TB

The continued development of MDR-TB is currently one of the most urgent and difficult problems affecting the global tuberculosis control effort (Skrahina *et al.*, 2012). TB is largely a disease of poverty, with over 80% of infections being found in Asia or Africa.

In 2012, there were around 450,000 new infections of MDR-TB infection and 170,000 fatalities recorded. MDR-TB affects 3.8% of TB patients with a recent diagnosis and 20% of patients who have had previous therapy (Skrahina *et al.*, 2012). With the greatest and ranked second percentages of MDR-TB patients globally, respectively, China and India have concerning rates (Zhao *et al.*, 2012). Globally, 9.6% of MDR-TB patients are estimated to have XDR-TB (Kwonjune *et al.*, 2015).

In 2013, there were an estimated 480000 (350000–610 000) cases of multidrug-resistant TB worldwide; of those, 9% had highly drug-resistant tuberculosis. Out of an expected 480 000 cases, precisely 136,000 cases of TB that are resistant to multiple drugs have been identified to the WHO in 2013 (WHO, 2014).

Treatment is beneficial for over 70 percent of patients in the UK with resistant to multiple drugs TB (Furin *et al.*, 2011).

In its most recent report, the World Health Organization's (WHO) stated that over 1,400,000 individuals had passed away from the infection known as tuberculosis (TB) in 2014. Among them, there were 140,000 children, 480,000 women, and 890,000 men. TB and HIV are presently the two biggest causes of mortality worldwide (WHO, 2015)

Out of the estimated 480,000 instances of MDR (multidrug-resistant) tuberculosis (TB), only around 123,000 were identified and treated worldwide in 2014. By 2030, all countries must simultaneously reduce tuberculosis (TB) fatalities to 90% and new cases to 80% in order to meet the goals for sustainable development (SDGs) (Javad *et al.*, 2020).

2017 had 1.3 million deaths from tuberculosis. 9,029 fresh infections of tuberculosis, also known as TB, were recorded in the US in 2018 (WHO, 2009). Rifampicin, the most successful first-line therapy, is thought to have contributed to over five hundred thousand new cases of tuberculosis in 2019, among whom 78% had multidrug resistance. WHO statistics from 2020 showed that India accounted for twenty-seven percent of infections caused by MDR or rifampicin-resistant (RR) TB (Lonnroth *et al.*, 2008).

According to recent data, more than 8 million people worldwide contracted tuberculosis in 2023, the most since WHO started keeping track of cases in 1995. Notably, with an estimated 1.25 million deaths in 2023, TB has overtaken COVID-19 as the most common infectious disease killer. With notable cases in India, Indonesia, China, the Philippines, and Pakistan, the disease is still common, particularly in Southeast Asia, Africa, and the Western Pacific. HIV, alcoholism, smoking, diabetes, and undernutrition are all contributing factors. Drug-resistant tuberculosis remains a serious public health concern. It is concerning that MDR-TB is disproportionately prevalent in places like China and India. These nations have high rates of drug-resistant tuberculosis, which are made worse by things like HIV prevalence, undernutrition, and restricted access to medical care. Targeted interventions are needed to address MDR-TB in these areas, such as better diagnostic facilities, easier access to efficient treatments, and all-encompassing public health plans. These high-burden areas must be given priority in MDR-TB efforts in order to meet international health goals and attain global TB control.

4. Factors Responsible For Disease Transmission

TB is closely associated with a number of socioeconomic problems, such as social inequality, drug and alcohol abuse, malnourishment, and tobacco use. Alcohol usage is significantly correlated with the progression of the illness because it compromises immunity. Actually, it alters cell signaling pathways and interferes with the functioning of B and T cells (Lonnroth *et al.*, 2008). Poor treatment is the primary cause of MDR-TB's global expansion (Caminero *et al.*, 2008).

The major causes of TB include inadequate compliance, poor disease management, or close interaction between an infected and an uninfected individual (Cox *et al.*, 2010). Patients who co-morbidly with HIV/AIDS may have high drug resistance. One contributing element to the MDR-TB pandemic is HIV infections (Well *et al.*, 2007). Children around the age limit of five and those who are HIV positive are particularly susceptible to the disease (Fox *et al.*, 2013).

While MTB is the main cause of TB in humans, infection with M. bovis can also induce TB in cattle, which may result in zoonotic TB in humans. Ingestion of tainted and unpasteurized milk and other dairy products, as well as close contact with sick animals, are among the primary ways that bovine tuberculosis, also known as TB, spreads (WHO, 2014).All patients with TB should undergo drug susceptibility testing to reduce the likelihood of acquiring antibiotic resistance. Patients with a history of TB treatment are more likely to develop multidrug-resistant tuberculosis; recent estimates show that 3.5% of new cases and 20.5% of cases that were previously treated have multidrug-resistant tuberculosis. Additional indicators of risk for multidrug resistant TB include younger age, younger household contacts of known sick individuals, and maybe the kind of tuberculosis strain (Caminero *et al.*, 2010; Faustini *et al.*, 2006).

5. Identification

Multidrug-resistant TB is diagnosed when resistance to both rifampicin and isoniazid is observed in the pathogenic microorganism in a laboratory sample, usually sputum. The quantity and quality of the sputum sample may have an effect on test performance (Peter *et al.*, 2013).

Multidrug resistance has been detected using an increasing number of innovative diagnostic techniques in recent years that can identify either genotypic resistance (based on genetic markers) or phenotypic resistance (based on growth-based resistance) (James Millard *et al.*, 2015).

- **Indirect phenotypic drug susceptibility testing:** Phenotypic, or culture-based, methods have been employed in the past for this. Phenotypic testing employs indirect methods of drug susceptibility testing. An isolate has to be grown before it can be inserted into either liquid or solid media to allow this to happen. The findings are not accessible for several months, which is a major delay (James Millard *et al.*, 2015).
- **Resistance to drugs due to direct phenotypic susceptibility:** For phenotype direct susceptibility to drug testing, a sputum sample is inoculated. This process avoids the need for subculturing and yields an instantaneous response. Samples are put into drug-containing medium at precisely essential concentrations; growth indicates phenotypic resistance, whether it is visible as a change in color or as microscopic growth (Martin *et al.*, 2008; Moore *et al.*, 2006). These methods are non-commercial, fast, and cheap (WHO, 2011).
- **Drug susceptibility testing based on genotype**: These approaches frequently use polymerase chain reaction techniques to detect genetic changes that confer drug resistance. Molecular techniques for drug susceptibility testing (DST) produce findings far faster than culture-based techniques. Molecular testing may uncover mutations with modest resistance levels that are clinically significant but are missed by culture-based testing (Kwonjune *et al.*, 2015). Molecular beacon assays and line probe hybridization tests are the two forms of genotypic assays that have been authorized by the World Health Organization.
    - **Assay for molecular beacons:** The WHO has authorized the use of the biochemical beacon assay called Xpert MTB/RIF (Cepheid, Sunnyvale, California) as a preliminary diagnostic test (WHO, 2013). This test detects Mycobacterium tuberculosis and rifampicin resistance using an instantaneous polymerase chain reaction. The fact that it is able to be finished on-site in two hours is a significant advantage. Further testing of the drug susceptibilities for additional first-

and second-line drugs is still necessary, even after rifampicin resistance has been established. Typically, phenotypic (culture-based) approaches are used for this purpose (Zetola *et al.*, 2014). The test's greater expense in comparison to phenotypic testing is another drawback, particularly if isoniazid susceptibility investigation is not included (Choi *et al.*, 2013; Find Diagnostics, 2013).

- **The line probe test:** This assay is available in two main commercial versions: the INNO-LipA Rif. TB, which looks for rifampicin resistance. This is the term Genotype MTBDR plus, which looks for mutations in the rpoB gene to identify both rifampicin and isoniazid resistance (Hillemann *et al.* 2007). The WHO has not yet authorized it, but it is used for drug susceptibility testing to find the fluoroquinolone, aminoglycoside, and ethambutol in cultured isolates or smear-positive sputum samples (Raizada *et al.*, 2014; Barnard *et al.*, 2012). Treatment Since the majority of second-line TB drugs are toxic and ineffective, treating MDR-TB is difficult. Treatment for MDR-TB often lasts between 18 and 24 months because second-line TB drugs don't sterilize well (Mitnick *et al.*, 2003; Shin *et al.*, 2006). Anti-TB drugs have historically been categorized as first- and second-line therapies. Ethambutol, isoniazid, pyrazinamide, rifampicin, and streptomycin are the primary first-line medicines. Recently, a lot of investigation has been done on developing innovative anti-TB drugs to better therapy for tuberculosis. The first anti-TB drugs in almost 40 years are now available in two freshly formulated formulations. Bedaquiline received conditional clearance from the U.S. FDA in December of 2012 for the treatment of MDR-TB. In November 2013, the European Medicines Agency authorized delamanid subject to specific requirements. Three new TB drugs are now being studied in late-stage clinical studies (Kwonjune *et al.*, 2015).

6. Drug Regimen

One of the most important steps in creating an MDR-TB regimen is getting a complete history of prior TB treatment. This is particularly important for those who have received many rounds of therapy with initial or second-line antituberculosis drugs. Any medicine that was a part of a regime that did not result in the patient's recovery, even while a recent DST indicates that the patient's strain is still vulnerable, should be considered unlikely to have remained effective (Kwonjune *et al.*, 2015).

Taking at least five drugs for 18 to 24 months is the current standard of care for multidrug-resistant TB; these therapies are less tolerated and more harmful than isoniazid or rifampicin. Countries with assured access to high-quality drug sensitivity testing for second-line drugs are likely to offer "individualized" treatment plans that take into account each patient's unique resistance pattern. In the absence of this capacity, countries will probably provide "standardized" regimens, which are substantially the same for each patient and are based on historical patterns of medication use and resistance in that particular location (WHO, 2011).

The individualized treatment plan is based on the DST or any drugs considered sensitive. More drugs are added until five appropriate meds are identified. A minimum of five can be used if the regimen contains few bactericidal drugs or if it is unclear how sensitive a specific therapy is.

- If the isolate is sensitive, use any first-line oral drug (pyrazinamide, isoniazid, rifampicin, or ethambutol).
- If the isolate is sensitive, use an injectable, like aminoglycosides or capreomycin. Injectable medications are used for longer than six months following culture conversion since they are usually among only two bactericidal elements of a treatment plan.
- If the isolate is susceptible to quinolones but sensitive to medications of a lower generation, use a higher-generation quinolone. Quinolines have been used in randomized controlled studies.
- Add as many second-line bacteriostatic medications to the five-drug regimen as needed. When it comes to second-line medications, ethionamide and cycloserine are usually the first choices because of their shown effectiveness, affordability, side-effect profile, in-vitro and in-vivo evidence, and historical usage in TB. P-aminosalicylic acid is frequently used in the treatment of patients with higher-grade resistance.
- Alternative drugs If the regimen does not contain five adequate prescriptions, think about adding more treatments, including clofazimine and amoxicillin or clavulanate. This will depend on several factors, such as the clinical state of the patient and the kind, severity, and extent of the illness (Frieden *et al.*, 1995).

For MDR-TB patients with few other treatment options, the WHO (World Health Organization) and the US Centers for the Prevention and Control of Diseases (CDC) have released interim recommendations allowing bedaquiline to be administered. Bedaquiline can be used to treat strains that are resistant to fluoroquinolones or XDR. Bedaquiline may also be used in situations when an injectable medicine poses a risk or when there is a lack of response to any second-line injectable treatment. Bedaquiline must be administered as part of an arrangement that can closely monitor any side effects (CDC, 2020).

Table 1: Drug Usage Guidelines

Drug Category	Drug Names	Usage Guidelinesx
First-Line Oral Drugs	Pyrazinamide, Isoniazid, Rifampicin, Ethambutol	Used if isolate is sensitive
Injectable Drugs	Aminoglycosides, Capreomycin	Used for at least 6 months post-culture conversion
Quinolones	Higher-generation quinolones	Used if resistance to lower-generation quinolones is detected
Second-Line Bacteriostatic Drugs	Ethionamide, Cycloserine, P-Amino Salicylic Acid	Added as necessary; chosen based on effectiveness, affordability, and side-effect profile
Alternative Drugs	Clofazimine, Amoxicillin/ Clavulanate	Used if five effective drugs are not available, depending on disease severity
Emerging Treatment (WHO-Approved)	Bedaquiline	Used for XDR-TB, fluoroquinolone-resistant strains, or when injectables pose risks; must be administered under strict monitoring

7. Controlling Adverse Consequences

Second-line anti-TB drugs dramatically increase adverse effects in comparison to first-line anti-TB drugs. Inadequate management of adverse effects is a major cause of MDR-TB treatment discontinuation. It is important to inform the patient undergoing treatment of any possible side effects even before they begin therapy. Throughout treatment, patients should have routine checkups with a physician.

- Gastrointestinal distress is a typical adverse effect of MDR-TB treatment, triggered by ethionamide and PAS.
- Nephrotoxicity is a documented adverse reaction to aminoglycosides and capreomycin. Patients who have become older and have previous episodes of renal sickness require more regular monitoring, particularly during the initial phases of treatment.
- Hypothyroidism can result from extended contact with PAS or ethionamide prothionamide. After the third consecutive month of MDR-TB therapy, all patients should have a test for hypothyroidism because the symptoms are not well-defined.
- Cycloserine may cause neurotoxic side effects, such as psychosis or depression.
- Ototoxicity from the injectables may damage cranial nerve VIII. This might result in hearing loss or buzzing in the ears, among other vestibular symptoms. Stopping treatment is frequently necessary to reverse hearing loss (Kwonjune *et al.*, 2015).

Nonetheless, patients treated with the subsequent generations of quinolone, prothionamide, or ethionamide; four or more strong pharmaceuticals during the intense phase; and three or more strong medicinal products during the continuation phase appear to have better outcomes, according to the evidence that is currently available (Ahuja *et al.*, 2012).

8. Emerging Treatment

There are currently new antituberculosis drugs available for the very first time in over forty years. Delamanid and bedaquiline are two examples of such drugs that may be used compassionately to treat both highly drug-resistant TB and multidrug-resistant tuberculosis, which is incurable. Furthermore, there's a fresh emphasis on how well linezolid and clofazamine work. A few studies in phase III are currently in progress.

In a randomized supervised research, a nine-month therapy that has demonstrated encouraging results in Bangladesh and other West African nations is presently formally being investigated (VanDeun *et al.*, 2010).

The effectiveness of innovative treatment plans for multidrug-resistant tuberculosis (MDR-TB) has been investigated in recent clinical trials. An all-oral 6-month regimen was evaluated in the NExT study, which showed encouraging results. Additionally, the STREAM stage 2 trial compared different standardized regimens, providing insights into optimizing MDR-TB treatment. The field of MDR-TB management is constantly changing as a result of these studies.

9. Alternative Approaches to Cure TB

9.1. Traditional Indian Medical Systems

India has one of the most well-known traditional medical systems in the world. Optimal benefits are these systems' main advantage. Ayurveda, Yoga, Unani, the Siddha & Homeopathy (AYUSH) are the six globally acknowledged medicinal systems that India has to offer.

A. Ayurvedic Medicine

In conventional medicine, PTB (pulmonary tuberculosis) is called "Yakshma." After then, it became a prefix throughout Ayurveda and became known as "Rajayakshma" in mythology.

Ayurvedic tuberculosis therapy was first introduced in 1933 with the establishment of the Patipukur TB hospital in Kolkata. Kaviraj Gananath Sen, an Ayurvedic scientist, took the initiative on this one (Sailaja *et al.*, 2000). Ayurvedic rasayanas such as ashwagandha and shilajeet therapy have the potential to modify a patient's immune profile (Debnath *et al.*, 2012). An investigation on the immunology profiling and ashwagandha, an herb commonly used in the practice of Ayurveda, was conducted based on the existing ingredients (Davis *et al.*, 2002).

B. Herbal Remedies

Homeopathy is a distinct, natural, all-encompassing medical approach that promotes the body's natural healing mechanisms, eliminating the need for pharmaceutical medications or their sometimes negative side effects (Davis *et al.*, 2002). Homeopathy lacks a comprehensive strategy for treatment since homeopathic waters are insufficient to treat TB. A new study suggests that antibiotics could be used in combination with homeopathic therapy to maximize their benefits while maintaining the antibiotic's site of action.

C. Siddha

The Siddha system, often known as the mother medicine of the Tamilians, is the oldest healthcare system in India. The term "Siddha" is derived from the Sanskrit word "Siddhi," signifying achievement. Treatment with a Siddha is mentioned in manuscripts on palm leaves. Ashtasthanapareeksha is detected under the medicine of Siddha protocol (test of eight sites). This method includes exams of the tongue (Naa), color (Niram), voice (Mozhi), face (Vizhi), stool (Malam), urine (Moothiram), touch (Sparisam), and pulse (Naadi) (Mubarak *et al.*, 2012). The core concept of Siddh is defined as:

- **Illness Prevention:** These efforts to avoid sickness are summarized as follows:
    - Fill your glass with hot water.
    - Eat two meals a day.
    - Combine melted ghee with dissolved buttermilk.
    - Make enough milk and dairy products.
- **Intervention:** Concepts of habitat and season When one awakens (KaalaiEzhuthal): 4:00 AM till 5:00 AM is when people are awake.
    - Exercise: When we don't get the necessary amount of exercise, our bodies become disease sites, much as iron corrodes away when it's not used.
    - Bath: It is recommended to add gingelly oil, ghee, or a particular therapeutic oil. Then, cleansing is usually done with panchakarpam, an herbal bath powder. Participating in this activity all year round is said to protect against illness.
    - Diet: Eating a certain dish together with its disagreeable flavor might have harmful effects due to dietary incompatibilities. Milk and fish, for example, should never be kept in storage (Suvetha *et al.*, 2016).

D. Unani

The Unani healthcare system holds that illnesses are the result of naturally occurring processes that are out of our control (Kitab *et al.*, 1991). The role of a Unani physician is to assist the body's natural healing processes. Hippocrates, the first physician, introduced and accepted the central tenet of the Unani medical system (Syed *et al.*, 2002). In the Unani medical system, pulmonary tuberculosis is known as tap-e-diq, humma-e-diq, or tadarrun-e-revi. The lungs develop an ulcer known as "sil" as a result of TB (Jamil *et al.*, 2005). Goat and milk from donkeys are used in the Unani method of treating TB (Sil), along with a high-protein diet that includes bird meat (Razi *et al.*, 1991).

E. Yoga & Naturopathy

Utilizing the force of nature, naturopathy is a medical system that is recognized as an approach to thought, science, and art (Smith MJ *et al.*, 2002). A holistic approach to infection diagnosis and treatment is often recommended by yoga. Despite the fact that there are many different diseases among the sick population, the primary objective of medicine is to radically improve people's quality of life. Data on yoga and naturopathy were not attempted to be provided, as they are mostly non-drug therapies (Sharma P *et al.*).

9.2. Traditional Knowledge on Plants Used Against Tuberculosis

People have been using medicinal plants for millennia to cure a wide range of ailments, including TB. For many years, indigenous people have been treating tuberculosis (TB) with infusions that are macerations, tinctures, and extracts of medicinal plant components, such as roots, leaves, stems, bark, flowers, and fruits. Research on ethnobotany and ethnopharmacology has validated their extensive use in treating TB; nevertheless, the majority of these substances still require their safe and effective dosages to be established (Sharifi-Rad *et al.*, 2020). Medical theory states that shared contaminated food and utensils are the most typical route for TB to spread. Weight loss, breathing difficulties, coughing, and wheezing are all recognized signs of TB in the ancient medical system of Africa.

The disease TB is correctly termed Rajayakshma in the ancient Indian medicinal system known as Ayurveda. This illness, which spreads like bird flu from person to another (Jayana), in addition to ascites and marasmus, has a very bad prognosis. Tissue emaciation or decrease (Dhatukshaya) in pathophysiology is associated with metabolic dysfunction (Dhatwagninasana): immunosuppression results from the loss of generative adipose, muscle, fluid, and blood (Debnath *et al*., 2012).

9.2.1. Medicinal Herbs Used in Traditional African Medicine to Treat TB

In Africa, TB is treated with 222 plant species, which are divided into 71 families. Having twenty species each, Compositae (or Asteraceae) and Leguminosae (or Fabaceae) are the plant families having the most species that are used to cure TB. The most often utilized plant components are, in general, the leaves, whole roots, and stem bark (Tabuti *et al*., 2010). With a minimum inhibitory concentration (MIC) that varied from 1000 to 3000 µg/mL, A. sativum extract inhibited both the MDR and non-MDR strains of M. tuberculosis isolates. The bacterial pilosa leaf extract made of ethanol was effective against M. tuberculosis at 100 µg/mL (Gautam *et al*., 2007).

9.2.2. The Medicinal Plants Utilized in Asian Traditional Medicine

Ayurveda, to treat tuberculosis: 44 families of plants and 84 species of plants have been discovered. Leguminosae (or Fabaceae, 8 species), Lamiaceae (6 species), and Compositae (4 species) are the families with the highest presence. With five instances, Adhatoda vasica is among the most commonly reported species. Adhatodavasica oil, which is extracted from leaves, roots, and flowers, successfully stopped M. tuberculosis B19-4 from growing at a concentration of 4 µg/mL (Gautam *et al*., 2012).

9.2.3. Plants with Medicinal Properties Used in Traditional American and South Pacific Medicine to Treat TB

In American traditional medicine, which often incorporates knowledge from Asia and Africa, 52 plant species, belonging to 27 families, were found as cures for TB and its related symptoms. The three plant families containing the highest representation are Lamiaceae, 12 species of Compositae, and 5 species of Leguminosae (or Fabaceae) (Ahmed HM *et al*., 2016).

9.2.4. Organic Remedies for XDR- and MDR-TB

Medicinal herbs have been utilized for treating many kinds of illnesses, including infectious disorders, from the beginning of time. They have also shown to be reliable providers of ideas for developing cutting-edge medications. Actually, throughout the past 25 years, the FDA in the United States has evaluated and approved close to 50% of new medications that are made using natural components (Newman *et al*., 2007; Kinghorn *et al*., 2011; Cragg *et al*., 2013; Atanasov *et al*., 2015). In order to treat tuberculosis (TB), 350 species of plants from different countries are used, and many naturally occurring chemicals have been isolated and identified (Camacho Corona *et al*., 2008; Samad, 2008).

System	Description	TB Treatment Approach	Notable Remedies
Ayurveda	One of the oldest holistic healing systems, emphasizing balance in the body.	Pulmonary tuberculosis (PTB) is known as "Rajayakshma." AyurvedicRasayanas, such as Ashwagandha and Shilajeet, help modulate the immune system.	Ashwagandha, Shilajeet
Homeopathy	A distinct, natural medical system that stimulates the body's healing response.	Lacks a comprehensive TB treatment but can be used as a complementary therapy alongside antibiotics.	Homeopathic dilutions (limited efficacy for TB)
Siddha	An ancient Tamil medical system focusing on disease prevention and holistic well-being.	Uses eight-site examination (Ashtasthanapareeksha) for diagnosis. Recommends dietary practices, herbal baths, and lifestyle modifications to prevent illness.	Herbal bath powders (Panchakarpam), Gingelly oil, Dietary interventions
Unani	Based on Hippocratic principles, emphasizing the body's natural healing ability.	TB is termed "Sil." Treatment includes dietary modifications and animal-based remedies.	Goat milk, Donkey milk, High-protein diet (bird meat)
Yoga & Naturopathy	Uses natural forces and holistic practices to maintain health.	Emphasizes lifestyle changes and non-drug therapies to improve quality of life in TB patients.	Breathing exercises, Detox therapies

10. Diet Management

Malnutrition and TB are serious problems in most impoverished countries worldwide. It is important to consider the frequent interactions between these two difficulties (Rubin *et al*., 1995).

Before antituberculosis chemotherapy was developed, a diet rich in calories, fats, proteins, mineral substances, and vitamins was considered an essential, if not a necessary, part of the treatment for TB (Gupta *et al*., 2009).

Compared to healthy controls, those with active pulmonary TB had much lower nutritional status, according to several research studies done in the nations of Indonesia, England, India, and Japan (Karyadi *et al*., 2000).

Micronutrient deficiencies are considered to be the most prevalent cause of infection-related morbidity, including TB, and secondary immunodeficiency (Gupta *et al*., 2009).

- **Zinc:** Zinc insufficiency affects the host defenses in several ways. At least in animal models, the results include lower tuberculin reactivity, lower circulating T-cells, and reduced phagocytosis (Karyadi *et al*., 2000). It was shown that when there was a zinc deficiency, macrophage in vitro cellular death was reduced and was promptly recovered with zinc supplementation (Shankar *et al*., 1998).
- **Vitamin A:** The metabolism of vitamin A requires zinc. Studies conducted on people and animals have shown that a zinc deficiency reduces plasma retinal concentration and prevents the production of retinal binding proteins (Brown *et al*., 1976). Taking zinc supplements therefore appears to benefit the antioxidant vitamin A metabolic rate, which is important for TB. Enough zinc may help shield membranes from damage caused by free radicals that cause inflammation (Taylor *et al*., 1991). Studies have shown how important vitamin A is for immunocompetence in tuberculosis in humans. In developed human macrophages, vitamin A has been shown to inhibit the growth of harmful bacilli (Crowle *et al*., 1989). Additionally, lymphocyte proliferation and the maintenance of epithelial tissues depend on vitamin A. Vitamin A is necessary for the synthesis of antibodies as well as macrophage activity and the healthy function of T & B lymphocytes (Semba *et al*., 1998).
- **Vitamin D:** Vitamin D affects the activity of macrophages, which are an essential part of the host's resistance to TB. Vitamin D levels in tuberculosis patients have been reported to be abnormal (Bellamy *et al*., 1999). Vitamin D is a potent modulator of both adaptive and innate immunity due to its impact on T cells, dendritic cells, and macrophage activity (Coussens *et al*., 2014; Aranow *et al*., 2011). Vitamin D treatment for active DS-TB had a negligible effect on immunologic and clinical outcomes. Notwithstanding evidence demonstrating that certain polymorphisms in the vitamin D receptor (VDR) are linked to sputum conversion time in individuals suffering from both drug-resistant tuberculosis (DR-TB) and drug-sensitive tuberculosis (DS-TB) (Xia *et al*., 2014; Jolliffe *et al*., 2018; Roth *et al*., 2004; Magee *et al*., 2017). A few studies have shown that adjunctive vitamin D appears to significantly accelerate mucous transformation among subgroups of patients receiving medication for active multidrug-resistant TB (Tukvadze *et al*., 2015; Ganmaa *et al*., 2017). Vitamin D has been demonstrated to have antimycobacterial properties as well as the ability to repair circulating immunologic signals that have been compromised by DS-TB therapy (Coussens *et al*., 2012). When treating MDR-TB, a daily dose of vitamin D may also improve immunological responses. A lack of vitamin D has been associated with an increased risk of contracting TB (Zeng *et al*., 2015 & Aibana *et al*., 2019) and of becoming ill with active tuberculosis (Huang *et al*., 2017 & Aibana *et al*., 2019), indicating that vitamin D deficiency is more likely to be a risk factor than an adverse consequence of tuberculosis (Martineau *et al*., 2007 & Larcombe *et al*., 2012).
- **Vitamin E:** Numerous studies have demonstrated that vitamin E concentrations in TB patients are much lower than in healthy controls. Studies have linked TB to a vitamin C deficiency (Rwangabwoba *et al*., 1998 & Panasiuk *et al*., 1991). In Ethiopian TB patients, levels of antioxidant vitamins C, E, and A were dramatically reduced, and a high substance concentration was associated with a poor clinical outcome (Madebo *et al*., 2003).
- **Iron:** Anemia is frequent in patients with pulmonary TB (Karyadi *et al*., 2000). According to a study conducted in Ghana, 50% of people with pulmonary TB had significantly lower hemoglobin levels than healthy matched controls. An iron deficiency might be another reason (Lawn *et al*., 2000).
- **Calcium:** Several investigations have connected vitamin C deficiency with tuberculosis (Rwangabwoba *et al*., 1998; Panasiuk *et al*., 1991). Antioxidant vitamins C, E, and A were much less prevalent in Ethiopian tuberculosis patients, and a high malonaldehyde level was linked to a severe clinical outcome (Madebo *et al*., 2003).
- **Iron: Anemia**
- **Polyunsaturated fatty acids:** It was determined that whereas (n-6-) fatty acid supplements have no effect on resistance to M. tuberculosis, (n-3-) fatty acid supplements can (Mayatepek *et al*., 1994).

- **Cholesterol:** Patients with tuberculosis frequently have hypocholesterolemia, which is linked to mortality in cases of miliary tuberculosis (Pervez-Guzman *et al.*, 2005).
- **Nutritional needs of children with tuberculosis:** Numerous research studies have come to the conclusion that all children who exhibit malnourishment or stunting need to have their tuberculosis risk assessed. It might be challenging to meet a child's dietary needs because of their small stomachs and lack of appetite (Gopalan *et al.*, 1957).
- **Nutritional treatment of tuberculosis:** Patients with tuberculosis may benefit from nutritional supplements. Minerals and vitamins can be very helpful in the treatment of tuberculosis. In a trial with 110 new instances of active tuberculosis, participants either received injectable vitamin B6 or tuberculosis chemotherapy in addition to it (Volosevich *et al.*, 1982 & Karyadi *et al.*, 2002). During the first two months of treatment, zinc and vitamin A supplements increased the antituberculosis medication's effectiveness. Patients with TB may be able to recuperate more rapidly by supplementing with diet. Moreover, enhancing the population's nutritional status might be an effective strategy against TB in impoverished countries (Gupta *et al.*, 2009).

11. Conclusion

Multidrug-resistant tuberculosis remains a significant public health threat, requiring urgent and comprehensive action. Addressing this challenge necessitates the prioritization of rapid and accurate diagnostic tools to ensure early detection and appropriate treatment initiation. Strengthening treatment regimens with newer, more effective anti-TB drugs, while ensuring adherence through patient-centered care, is essential to improving outcomes and reducing transmission. Additionally, robust public health policies must focus on infection control, surveillance, and the integration of community-based programs to enhance treatment accessibility and adherence. Global and national efforts should emphasize investment in research, capacity building, and cross-sector collaborations to curb the spread of MDR-TB. A multifaceted approach integrating diagnostics, optimized therapy, and strong public health frameworks is crucial in mitigating the impact of multidrug-resistant tuberculosis and preventing further resistance development.

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Authorship Contribution

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