WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 13, Issue 13, 585-603. Review Article ISSN 2277–7105

TUBERCULOSIS THERAPEUTICS REDEFINED: MERGING NANOMEDICINAL INNOVATIONS WITH TRADITIONAL PREVENTION TACTICS

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Article Received on
13 May 2024,

Revised on 03 June 2024,
Accepted on 24 June 2024

DOI: 10.20959/wjpr202413-33054

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ABSTRACT

Tuberculosis is a persistent infectious ailment instigated by the Mycobacterium tuberculosis bacterium, primarily impacting the lungs but with the capability to disseminate to other bodily organs. Despite worldwide initiatives, tuberculosis persists as a predominant cause of mortality globally, disproportionately affecting nations with low and middle incomes. Factors such as destitution, undernourishment, tobacco consumption, HIV/AIDS, and drug resistance contribute to the endurance of this disease. Natural substances have played a pivotal role in the pursuit of novel anti-tuberculosis medications, with the medicinal plant Azorella compacta exhibiting promising anti-mycobacterial properties. This review elucidates the global burden of tuberculosis, its risk factors, obstacles in treatment, and the potential of natural products like A. compacta in developing new therapeutic strategies to combat this deadly disease.

KEYWORDS: Tuberculosis, Mycobacterium tuberculosis, worldwide health, drug resistance, Azorella compacta, anti-mycobacterial activity.

1. INTRODUCTION

Tuberculosis is an infectious illness that can be transmitted from person to person through respiratory droplets expelled by coughing, sneezing, or other means. It is caused by the bacterium Mycobacterium tuberculosis, which primarily affects the lungs, leading to a

condition known as pulmonary tuberculosis. However, the bacteria can also spread to other parts of the body. The World Health Organization estimates that one-third of the global population is infected with M. tuberculosis.[1]

Tuberculosis exacerbates poverty levels in countries as it thrives in impoverished and underprivileged communities. The risk of contracting tuberculosis is significantly higher in these populations. Additionally, drug-resistant strains of M. tuberculosis are emerging, posing challenges in treatment due to their low cure rates and high mortality rates.

While the lungs are the primary target, M. tuberculosis can also affect various organs, including the kidneys, lymphatic system, central nervous system (causing meningitis), circulatory system (resulting in miliary tuberculosis), genitourinary system, joints, and bones.[1] The success or failure of tuberculosis treatment depends on several factors, such as patient compliance with the prescribed regimen, malnutrition, smoking, coexisting diseases like HIV, and inadequate supervision by healthcare professionals.

Over the past century and a half, tuberculosis has re-emerged as a leading cause of death worldwide, claiming nearly 3 million lives annually.[2] This deadly disease has infected over 33% of the global population. It is estimated that approximately 8.8 million new cases of tuberculosis occur each year, resulting in 52,000 human deaths per week or more than 7,000 deaths per day.[3]

Tuberculosis primarily affects adults in their most productive years, but all age groups are at risk. More than 80% of cases and deaths occur in low- and middle-income countries.[4] In 2022, the largest number of new TB cases occurred in the WHO's South-East Asian Region (46%), followed by the African Region (23%) and the Western Pacific (18%). Around 87% of new TB cases were reported in the 30 high-burden countries, with more than two-thirds of the global total in Bangladesh, China, Democratic Republic of the Congo, India, Indonesia, Nigeria, Pakistan, and the Philippines. Globally, about 50% of TB patients and their households face catastrophic total costs (direct medical expenses, non-medical expenses, and indirect costs like income losses) exceeding 20% of their total household income, far from the WHO's End TB Strategy target of zero. Individuals with compromised immune systems, such as those living with HIV, undernutrition, diabetes, or tobacco use, have a higher risk of developing tuberculosis. In 2022, there were 2.2 million new TB cases attributable to

undernutrition, 0.89 million to HIV infection, 0.73 million to alcohol use disorders, 0.70 million to smoking, and 0.37 million to diabetes.[4]

In the search for novel anti-tuberculosis drugs, natural products have played a crucial role in maintaining human health for thousands of years.[5] Azorella compacta Phill., commonly known as "llareta," is a green, compact, resinous cushion shrub of the Apiaceae family found in the high Andes of southern Peru, Bolivia, northeastern Chile, and northwestern Argentina. This medicinal plant has been traditionally used to treat various ailments, including colds, pain, diabetes, asthma, bronchitis, womb problems, gastric disorders, backache, wounds, and altitude sickness.[6] Previous research has reported on the anti-M. tuberculosis activity of several natural azorellanes and mulinanes, diterpenoids isolated from this medicinal plant.[7]

1.1 Transmission & risk factors for tuberculosis

While tuberculosis has the potential to impact any organ, the lungs typically serve as the primary entry point. The most prevalent method for the bacilli to be discharged into the air is through the aerosolization of pulmonary secretions from individuals with pulmonary tuberculosis, via actions such as coughing, sneezing, speaking, and singing. These aerosol droplets rapidly dehydrate, leaving behind minuscule droplet nuclei harboring a few bacilli. While larger droplets descend to the ground, smaller droplets ranging from 1 to 10 microliters remain suspended in the air for extended periods, contingent upon environmental conditions. Consequently, tuberculosis is fundamentally an infectious disease, with the majority of cases resulting from the inhalation of droplet nuclei.[8] Investigations have revealed that the infection rate among close contacts spans from 25% to 50%, even in severely overcrowded and substandard circumstances.[9]

1.2 Risk factors for tuberculosis

Numerous elements can influence the risk of tuberculosis development in individuals or populations, as well as the timing of tuberculosis "epidemic waves." Additional risk factors specific to certain populations may also play a role. Interestingly, among sailors who tested positive for purified protein derivative (PPD) but did not have active disease, no correlation was found. However, it has been observed that tall, slender naval personnel contracted tuberculosis more frequently than sailors with more average builds. Other factors linked to an increased risk of developing tuberculosis include diabetes mellitus, lymphoma, chronic debilitating illnesses, post-gastrectomy status, and cancer. Notably, human immunodeficiency

virus (HIV) infection is currently considered the strongest risk factor for tuberculosis development.[10]

1.3 Laboratory examination and diagnosis

Routine laboratory tests rarely provide definitive evidence for diagnosing tuberculosis. In cases of chronic tuberculosis, mild normochromic, normocytic anemia may occur. The white blood cell (WBC) count is typically within the normal range, and counts exceeding 20,000/microlitre suggest the presence of another infectious process. However, a leukemoid reaction can be observed in miliary tuberculosis but not in pulmonary tuberculosis.

Diagnostic testing for both latent tuberculosis infection (LTBI) and active disease has undergone minimal changes over the past century. Due to the limitations of available tests, there has been a long-standing need for improved diagnostic methods. Until recently, LTBI was diagnosed exclusively through the tuberculin skin test (TST), which suffers from poor sensitivity and specificity. Newer tests for LTBI offer the promise of enhanced diagnostic accuracy. Tools for diagnosing active tuberculosis disease include clinical suspicion, response to treatment, chest radiographs, acid-fast bacilli (AFB) staining, mycobacterial culture, and, more recently, nucleic acid amplification (NAA) assays.[11]

1.4 Chest radiography

The chest radiography is the single most useful study for suggesting the diagnosis of tuberculosis. The appearance of the radiograph differs in primary or reactivation tuberculosis.

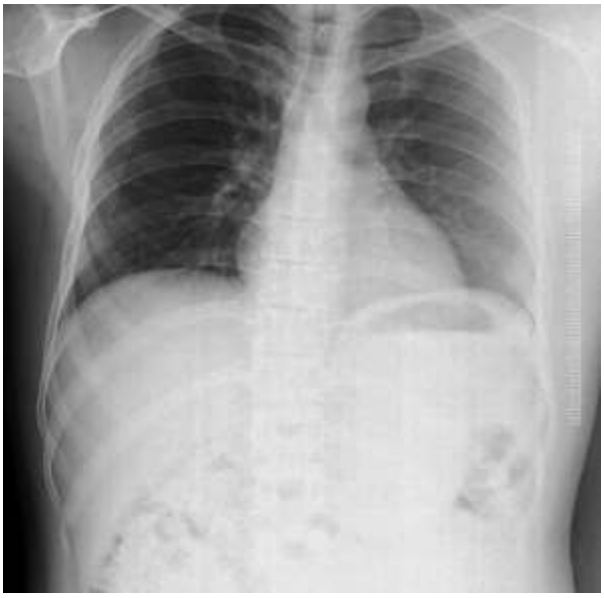

Figure 1: Primary tuberculosis in an adult.

1.5 Types of tuberculosis

There are mainly 3 types of tuberculosis

Miliary Tuberculosis: Miliary tuberculosis occurs when tubercle bacilli disseminate widely through the bloodstream. This form of the disease is characterized by numerous small lesions, resembling millet seeds, throughout the body. On X-rays, thousands of these tiny nodules can be observed in the lungs. Miliary tuberculosis is most prevalent in infants and young children during the primary infection but can manifest at any age when tubercle bacilli spread hematogenously from a lesion to other body parts. Common symptoms include anemia, leukopenia or leukocytosis, fever, weight loss, and can potentially lead to death. The diagnosis may be delayed, particularly in elderly adults, as miliary nodules on X-rays may appear late, leading to a potentially treatable disease becoming fatal.[12]

Childhood Tuberculosis: The most severe manifestation of tuberculosis in infants is hematogenous dissemination, resulting in miliary tuberculosis, renal tuberculosis, and involvement of other organs. In children, primary lesions may progress to tuberculous pneumonia, although cavities are uncommon. External pressure from lymph nodes in the hilum can obstruct a bronchus, causing atelectasis or erosion of the bronchial wall, leading to endobronchial disease and/or tuberculous pneumonia.[13]

Epituberculosis: A peculiar phenomenon known as epituberculosis tends to occur due to bronchial obstruction. While receiving tuberculosis chemotherapy, children may experience an enlargement of the pulmonary infiltrate for several months without systemic symptoms. In infants, bronchial obstruction typically occurs between the proximal and distal mucus-producing glands when lymph nodes block a bronchus. As the tuberculous glands heal, the obstruction is relieved, drainage stabilizes, and the pulmonary infiltrate resolves. Perifocal inflammation can also cause epituberculosis, although this is considered rare in infants.[14]

1.6 The four stages of pulmonary tuberculosis

The progression of pulmonary tuberculosis (TB) can be summarized in four distinct stages, reflecting the interaction between the Mycobacterium tuberculosis bacteria and the host's immune response.

Initial Macrophage Response: After inhalation, the TB bacteria reach the lungs' alveoli, where resident macrophages attempt to destroy them. If the macrophages fail, the bacteria

begin multiplying within them, leading to the destruction of these cells and the infection of nearby macrophages.

Symbiotic Stage: In the second week, if the initial macrophages cannot contain the bacteria, they proliferate rapidly within the non-activated macrophages. This exponential growth results in the formation of early lesions or tubercles, with a limited immune response allowing the bacteria to establish a strong foothold within the host.

Immune Control Stage: Around the third week, the host's immune system mounts a stronger response involving cell-mediated immunity and delayed-type hypersensitivity. This response leads to the containment of bacterial growth, creating a balance where the infection does not progress further. This stage is characterized by the formation of a granuloma or Ghon focus, where the infection is contained within a structured complex of immune cells.

Liquefaction and Cavitation Stage: In about 5% of cases, especially when the host's immune system weakens, the contained infection reactivates. The center of the granuloma liquefies, providing a nutrient-rich environment for rapid extracellular bacterial multiplication. This leads to extensive tissue damage and cavitation in the lungs, where large numbers of bacteria can be released into the airways, making the individual highly contagious. This stage often manifests with severe clinical symptoms and is crucial for the transmission of TB.

1.7 Treatment of tuberculosis

1.7.1 Drug-sensitive tuberculosis

The evidence for the recommended regimen for drug-sensitive tuberculosis, involving isoniazid and rifampicin for 6 months, along with pyrazinamide and ethambutol for the initial 2 months, was established decades ago. Despite being called a "short course," the regimen's duration remains a drawback, with patient default rates increasing linearly after 4 weeks and ranging from 7% to 53.6% in a systematic review.[19] Directly observed therapy (DOT) was widely implemented by tuberculosis control programs as a strategy to improve adherence and reduce default, despite lacking strong evidence of effectiveness.

1.7.2 Drug resistant TB

Regarding drug-resistant tuberculosis, the classification of antituberculosis drugs and their combinations is rapidly evolving due to new clinical trial data and meta-analyses.[20-21] The WHO's updated classification [22] guides physicians in constructing an effective drug-resistant

treatment regimen, using a minimum of four active drugs tailored to the patient's specific needs. The regimen recommends two core drugs (a later-generation fluoroquinolone and an injectable aminoglycoside) and the addition of other core drugs (e.g., ethionamide or prothionamide, cycloserine or terizidone, linezolid, and clofazimine). If further drugs are required due to resistance or intolerance, non-core drugs like bedaquiline (especially if the patient is quinolone-resistant) or delamanid should be added (combination of these two drugs is not recommended). Non-core drugs, such as para-aminosalicylic acid and carbapenems with clavulanate, are reserved for patients with extensively drug-resistant (XDR) tuberculosis with limited therapeutic options. Pyrazinamide and ethambutol might be added but should not be counted as active drugs in the regimen.[22-23]

1.8 New approaches for treating pulmonary tuberculosis

1.8.1 Nanotechnology-Based Therapy

In recent years, there has been a growing interest in exploring the potential of nanotechnology-based therapies for drug delivery. These approaches aim to encapsulate drug molecules within nanoparticles, rather than administering antibiotics or other drugs in their free form.[24] The use of nanoparticles as drug carriers offers an alternative mode of delivering therapeutic agents.

1.8.2 Nanoparticles and Tuberculosis

Nanoparticle-based drug delivery systems offer several advantages for the treatment of tuberculosis compared to conventional drug administration

1. High consistency and longer duration of action
2. High carrier capacity, allowing the encapsulation of multiple drugs in the nanoparticle matrix
3. Reduced side effects compared to conventional drugs
4. Increased bioavailability due to slow, sustained, and controlled drug release
5. Viable for various routes of administration, such as oral delivery and inhalation
6. Minimal side effects and improved patient compliance

Nanoparticles can be taken up by the body through various mechanisms

1. Transcytosis through M-cells
2. Intracellular uptake and transport via epithelial cells in the intestinal mucosa
3. Uptake by Peyer's patches

4. Oral administration of nanoparticles is possible due to the stability and sustained drug release from the nanoparticle system.[25] Reported that drug levels were maintained above the minimum inhibitory concentration (MIC90) in mice for 6 to 9 days in the plasma after a single oral administration of drug-loaded poly (lactic-co-glycolic acid) nanoparticles (PLGNPs), whereas free drugs were eliminated from the plasma within 12-24 hours following oral administration. It took 46 doses of free drugs to achieve the same exposure as a single dose of the nanoparticle formulation. Similar findings regarding pharmacokinetics, biodistribution, and chemotherapeutic effectiveness were observed in larger animal models, such as guinea pigs.[26]
5. In tuberculosis treatment, the World Health Organization (WHO) recommended adding ethambutol to the intensive phase of chemotherapy to enhance the rate of sputum conversion, as this drug is known to boost the rate of sputum conversion.[27] While free drugs were not detected in the plasma after 12 hours of intravenous or oral administration, anti-tuberculosis drug-loaded PLG nanoparticles were administered to Mycobacterium tuberculosis-infected mice every 10th day, in contrast to daily administration of free drugs. This approach further demonstrates the value of nanomedicine in tuberculosis treatment.[28]

1.8.3 Ligand-conjugated oral-ATD nanomedicine

Polymeric nanoparticles can act as bio-adhesives in the gastrointestinal tract. The poly(lactic-co-glycolic acid) (PLG) nanomedicine was further improved by the addition of a bio-adhesive ligand. Lectins, which are mucosal ligands, have been shown to enhance the adhesion of nanoparticles to the mucosal surface, thereby increasing drug absorption and bioavailability.[29] Wheat germ agglutinin (WGA) receptors are distributed on the intestinal and alveolar epithelium, making WGA useful for both oral and aerosol drug delivery.[30] The covalent attachment of WGA to PLG nanoparticles has been demonstrated to improve the efficacy of anti-tuberculosis drugs.[31] Upon oral or aerosol administration of WGA-coated PLG nanoparticles in mice, prolonged plasma levels were observed: 6-7 days for rifampicin (RIF), and 13-14 days for isoniazid (INH) and pyrazinamide (PYZ), compared to uncoated PLG nanoparticles (4-6 days for RIF and 8-9 days for INH and PYZ). Three oral or nebulized doses of these lectin-coated nanoparticles every 14 days (versus 45 daily doses of free drugs) resulted in complete bacterial clearance. All three drugs were present in the lungs, liver, and spleen for 15 days.[31] Additionally, WGA has extensive applications in drug delivery due to its low immunogenicity.[32]

1.8.4 Intravenous Delivery of ATD Nanomedicine

There are three injectable routes for drug delivery: intravenous, subcutaneous, and intramuscular. Intravenous administration results in immediate availability of all drug molecules, increasing bioavailability. The subcutaneous and intramuscular routes also provide similar bioavailability compared to the intravenous route.[33] A single subcutaneous injection of poly (lactic-co-glycolic acid) (PLG) nanoparticles loaded with rifampicin (RMP), isoniazid (INH), and pyrazinamide (PZA) resulted in sustained therapeutic drug levels in the plasma for 32 days and in the lungs or spleen for 36 days. This treatment produced complete sterilization of organs in Mycobacterium tuberculosis-infected mice and demonstrated better therapeutic efficacy compared to daily oral administration of free drugs (35 doses).[30] This highlights the superior efficacy of nanoparticles over microparticles. Microparticles with a diameter greater than 1 μm cannot be administered intravenously; however, nanoparticles are small enough to pass through the vascular system.[34]

1.8.5 Liposome-based Drug Delivery System

Liposomes are miniature closed vesicles consisting of a phospholipid bilayer enclosing an aqueous interior. When administered, these carriers are promptly recognized by phagocytic cells and cleared from the bloodstream. To avoid rapid removal and extend their circulation time, liposomes are typically modified with polyethylene glycol (PEGylated) and stabilized. Researchers have explored the incorporation of the antibiotic gentamicin into liposomes and evaluated its antimicrobial activity compared to the free drug in a mouse model of disseminated Mycobacterium avium complex infection.

1.8.6 Novel Drug Delivery System

In recent years, a number of novel colloidal drug delivery systems incorporating anti-tuberculosis drugs have been developed to combat the global endemic of tuberculosis. These systems aim to deliver drugs to specific sites in a controlled manner, reducing dosing frequency to achieve maximum patient compliance with therapy. These advancements in novel drug delivery systems offer a promising alternative to address the problems of therapeutic treatment failure due to patient non-adherence to therapy.

1.8.7 Liposomes

Liposomes are vesicular systems consisting of an aqueous compartment surrounded by lipid layers. Due to their lipoidal nature, these systems have excellent biodegradability and biocompatibility, and can incorporate both hydrophilic and hydrophobic drug moieties.

Liposomes can naturally target macrophages, which are the host cells for tuberculosis, and their surfaces can be decorated with various ligands to impart functions such as stimuli responsiveness, targeting, and incorporation of diagnostic agents for specific site targeting.[35] Researchers have formulated novel PEGylated liposomal systems to incorporate the principal anti-tuberculosis drugs along with small interfering RNA (siRNA) to inhibit transforming growth factor-beta1. They encapsulated rifampicin, isoniazid, and pyrazinamide and administered them to guinea pigs. They found that after inhalation, rifampicin and isoniazid remained in the blood for 24-48 hours, whereas in macrophages, they lasted for 5 days.

1.8.7 Niosomes

Niosomes are nanocarrier systems resembling the structure of liposomes and mainly composed of cholesterol and non-ionic surfactants with or without phospholipids. The self-assembled niosomes are arranged in such a way that hydrophobic tails form the bilayer facing each other, while hydrophilic heads form the core and the outer surface of the vesicle.[36] Moreover, niosomes are easy to prepare, have economical production costs, are easy to handle, and do not require special storage conditions. Researchers have prepared extended-release niosomes for the targeted delivery of levofloxacin to the lungs. The niosomes were prepared by the thin-film hydration and sonication method using the surfactant (Span 60) and cholesterol at different ratios. The drug entrapment efficiency of the niosomes was found to be 98%. The formulation followed zero-order drug release kinetics and a non-Fickian diffusion mechanism.[8]

Chowdhury et al. prepared a niosomal formulation of rifampicin and ofloxacin for the treatment of drug-resistant tuberculosis.[28] These controlled-release niosomes were able to retard the drug release for up to 15 days, following a non-Fickian diffusion mechanism. The size of the niosomes was found to be between 100–300 nm, with good entrapment efficiency of 81.76%. They concluded that the controlled-release niosomes containing anti-tubercular drugs are a promising approach for the treatment of tuberculosis.

1.9 BCG vaccination

The Bacillus Calmette-Guérin (BCG) vaccine is an attenuated strain of Mycobacterium bovis derived through serial passage. Mycobacterium bovis was first isolated in 1908 by Albert Calmette and Camille Guéri at the Pasteur Institute in Lille, France.[32] From 1908 to 1921, they serially passaged the strain, obtaining a low-virulence strain that they found protected against virulent Mycobacterium tuberculosis, and named it BCG.[37] Trained immunity is a

concept that refers to the long-term functional reprogramming of innate immune cells, triggered by exogenous or endogenous insults, leading to increased effector function upon secondary stimulation after returning to an inactive state.[38] Trained immunity differs from classical immunological memory in several ways. First, it involves myeloid cells, natural killer cells, and germline-encoded recognition and effector molecules (e.g., pattern recognition receptors, cytokines) rather than those involved in classical memory. Second, the increased responsiveness to secondary stimuli is not specific to a particular pathogen. Finally, trained immunity relies on changes in the functional state of innate immune cells that persist for weeks to months, rather than years, after the initial stimulus is eliminated.[39]

The BCG vaccine is included in the childhood vaccination programs of many countries. However, controlled trials have shown varying estimates of its efficacy in preventing pulmonary tuberculosis, the major burden of tuberculosis disease, ranging from 0% in the Chingleput trial in South India to 80% in the UK Medical Research Council (MRC) trial.[40-44] Consistently high estimates of efficacy have been reported for infant BCG vaccination against severe primary progressive disease.[45-47]

1.10 Advantages and Disadvantages

A major advantage of a vaccination program is that it has low financial costs. The vaccine administration does not require repeated visits, and preliminary tuberculin testing is unnecessary. Although vaccination does not appear to be beneficial for individuals already infected, it does not seem to cause harm. In developing countries or areas of developed countries with a high risk of infection, vaccination programs among infants and young children could contribute substantially to tuberculosis control over time.[48] Most vaccines produce localized ulcerations that are limited in extent and duration, and more serious complications are very uncommon. The only significant disadvantage of vaccination is the production of sensitivity to tuberculin. In areas with a high risk of infection, most individuals will become tuberculin reactors over time, and the premature production of tuberculin sensitivity by vaccination is rarely consequential. However, in areas with a low risk of infection, interference with the diagnostic value of the tuberculin test constitutes an additional contraindication to BCG vaccination. A reasonable definition of low risk might be an annual infection rate of less than 1%, as this will make early recognition of new infections and their preventive treatment impossible. While many individuals in these areas may have been

vaccinated with BCG, the only safe assumption is that all reactors have been infected with virulent tubercle bacilli and are candidates for preventive therapy.[48]

1.11 Isoniazid preventive therapy

Preventive therapy involves the oral administration of isoniazid. It can be a useful tool, particularly when the risk of infection is low, and the infected population is relatively small. During the 1950s in the United States, children with primary tuberculosis were considered to require chemotherapy only if they were clinically ill. When isoniazid was added to the treatment arsenal of streptomycin, para-aminosalicylic acid (PAS), and promizole, Dr. Edith Lincoln observed that children hospitalized at Bellevue Hospital in New York City did not develop complications of primary tuberculosis when their medication included isoniazid. At her suggestion, the United States Public Health Service organized a multi-clinic controlled trial among 2,750 children with asymptomatic primary tuberculosis or a recent tuberculin conversion. Preventive therapy with isoniazid proved remarkably effective, producing a 94% reduction in tuberculous complications during a year of preventive treatment and a 70% reduction over the subsequent 9-year period.[8]

1.12 Benefits and risks

Isoniazid is one of the least toxic antituberculosis drugs, with most reactions being mild and transient. The primary concern is hepatitis, which is rare in those under the age of 20 but increases with age, peaking at 2% to 3% in the 50 to 64 age group.[49] Deaths due to isoniazid-associated hepatitis have occurred, especially among individuals who continued taking the drug after symptoms of hepatitis appeared. The risk of infected individuals developing tuberculosis if preventive therapy is not given must be weighed against the risk of hepatitis if it is administered. For tuberculin reactors with no additional risk factors, a sensitivity analysis suggests that the balance favors preventive treatment most strongly among children and young adults. For individuals with additional risk factors, the benefit-risk ratio increases at all ages. A committee convened by the American Thoracic Society recommended certain screening procedures before starting preventive therapy.[50] The presence of active tuberculosis should be ruled out, and individuals who have already had an adequate course of chemotherapy, those with previous serious side effects from isoniazid, and those with current acute liver disease should be excluded. Conditions that do not contraindicate preventive therapy but require special medical assessment include interactions with other medications, daily alcohol use, previous minor side effects from isoniazid, chronic

liver disease, and pregnancy. Patients need to be motivated to take their medication faithfully and must be warned to promptly report symptoms that might indicate its discontinuation.

1.13 Preventive therapy for people exposed to drug-resistant M tuberculosis

Isoniazid is the only preventive drug that has been extensively tested and accepted in broad trials. There is no proven alternative when there is clear evidence of infection with an isoniazid-resistant strain of tubercle bacilli. Rifampin emerges as a viable option because it can be taken orally and is well-known for its efficacy in clinical regimens.[51] Early animal and human trials suggest that rifampin will be as effective as or more effective than isoniazid, with better tolerance and less hepatotoxic reactions. However, rifampin causes a red-orange discoloration in body fluids like urine, saliva, and tears, and has interactions with various other medications like methadone and oral contraceptives. These side effects should not be a concern if patients are informed about the need for preventive treatment and the drug's action. Rifampin should be prescribed at the same dosage used for disease treatment, 10 to 20 mg/kg of body weight up to a maximum dose of 600 mg taken once daily, for the same duration as isoniazid.[51] Although there may be concerns about the emergence of resistant organisms when rifampin is given alone, it is reassuring that isoniazid resistance has not been demonstrated when isoniazid was used alone in preventive treatment.[52]

Exposure to tuberculosis cases involving organisms resistant to both isoniazid and rifampin is becoming more common, particularly among impoverished populations.[53] The treatment of individuals exposed to such cases should be largely based on clinical and epidemiologic judgment. Those with healthy immune systems and a low risk of infection from these multidrug-resistant strains should follow the standard tuberculosis contact guidelines. Multidrug preventive therapy should be considered if they have a moderate to high likelihood of being infected with multidrug-resistant M. tuberculosis and have a high risk of developing tuberculosis due to immunosuppression, risk factors for HIV infection, or other conditions known to increase the risk of active disease. This should include at least two antituberculosis drugs based on the resistance history of the strain from the suspected source case and the patient's ability to tolerate these drugs. Possible regimens include ofloxacin and pyrazinamide or ethambutol and pyrazinamide. The drugs should be administered for 12 months at standard dosages used in disease treatment.[53]

2. CONCLUSION

The prevalence of tuberculosis remains disturbingly high globally, with millions contracting this infectious disease each year, facing potential life-threatening consequences. While antibiotic treatments are available, they are challenged by issues such as patient non-adherence, toxic side effects, and the continuous emergence of drug-resistant bacterial strains. There is an urgent need to explore and develop innovative therapeutic approaches that can address these limitations and enhance overall treatment outcomes.

Recent research has highlighted the promising potential of nanotechnology-based drug delivery systems for more effective tuberculosis management. By encapsulating anti-tubercular drugs within nanoparticulate carriers, these formulations offer unique advantages, including controlled and sustained drug release, targeted delivery to infection sites like the lungs, reduced systemic toxicity, and improved bioavailability. Preliminary studies involving nanoparticle platforms such as liposomes, polymeric nanoparticles, and niosomes have shown encouraging results in preclinical animal models.

Complementing these novel therapeutic approaches, preventive measures like the BCG vaccine and isoniazid prophylactic therapy continue to play a crucial role, particularly in high-risk populations. However, ongoing efforts are required to further optimize these preventive regimens, striking a balance between maximizing effectiveness and minimizing potential adverse effects.

A comprehensive, multi-faceted strategy, integrating cutting-edge nanomedicines with existing preventive measures, holds immense potential to revolutionize tuberculosis management globally. Accelerating research and development efforts in this domain should be a top priority for the global public health community, as it offers a promising path to finally overcome this ancient and persistent scourge. With sustained scientific advancements, more effective treatment and prevention strategies for tuberculosis are well within reach, providing hope for millions worldwide affected by this devastating disease.

ACKNOWLEDGEMENT

All authors are grateful to Teerthanker Mahaveer College of Pharmacy for providing the facility.

AUTHORS CONTRIBUTION

MA: Methodology, Writing – Original Draft; IK: Methodology, Writing – Original Draft; MF: Conceptualization, Resources, Writing - Review & Editing, Supervision. HH: Conceptualization, Writing - Review & Editing, Supervision; AM: Conceptualization, Writing - Review & Editing, Supervision; ST: Conceptualization, Writing - Review & Editing, Supervision. AS: Conceptualization, Review & Editing, Supervision. JS: Conceptualization, Review & Editing, Supervision.

CONFLICT OF INTEREST

None.

FUNDING/SPONSORSHIP

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

ETHICAL COMMITTEE APPROVAL

As a narrative review, this study is not subject to ethical approval.

DECLARATION OF COMPETING INTEREST

None of the authors received payments or services, either directly or indirectly from a third party in support of any aspect of this work. All authors read and approved the final manuscript.

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