Malaysian Journal of Microbiology, Vol 19(6) Special Issue 2023, pp. 786-804
DOI: http://dx.doi.org/10.21161/mjm.230010

Malaysian Journal of Microbiology
Published by Malaysian Society for Microbiology
(In SCOPUS since 2011)

Mycobacterium tuberculosis as a resilient foe in the mechanisms of colonisation, pathogenesis and host immune responses serves as a prerequisite for the development of potential mangrove plant-derived anti-TB drugs

Tamar Kansil[1], Zarina Amin[1], Nur Athirah Yusof[1], Zainul Amiruddin Zakaria[2] and Ruzaidi Azli Mohd Mokhtar[1]*

[1]Biotechnology Research Institute, Universiti Malaysia Sabah, Jalan UMS, 88400 Kota Kinabalu Sabah, Malaysia.
[2]Borneo Research for Algesia, Inflammation and Neurodegeneration (BRAIN) Group, Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Universiti Malaysia Sabah, Jalan UMS, 88400 Kota Kinabalu Sabah, Malaysia.
Email: ruzaidi@ums.edu.my

ABSTRACT

Mycobacterium tuberculosis (MTB) is a highly adaptive pathogen that emerged as a devastating and mortality-related disease agent. The limited efficacy of the *Mycobacterium bovis* BCG vaccine, antibiotics and intensive treatment to prevent mortality have piqued researchers' interest in host-pathogen interactions. Besides the emergence of multi-drug resistant TB as a drawback, the host immune responses could be successfully subverted and exploited by the MTB-host pathogenesis during the early stages of innate immunity. Factors contributing to mycobacterial pathogenesis are concomitant and multifactorial, including virulence factors such as adhesins, toxins and enzymes that drive the progression of MTB infection. Initially, alveolar macrophage (AM), which has been considered to restrain bacterial growth, facilitates the spread of disease through interactions with MTB. The progression to bacterial replication and systemic infection before the initiation of cell-mediated immunity (CMI) indicates a delay in the activation of adaptive immunity, which is crucial. The findings are supported by the bacterial multiplication and dissemination in the infected alveolar macrophage in animal models. On the other hand, mangrove plants have revealed a structural diversity and a plethora of compounds responsible for antibacterial, antifungal and antiviral activities. These may serve as potential bioactive compounds for anti-TB drugs. In this review, we discuss mycobacterial colonisation, tissue invasion and host inflammatory responses that lead to the pathogenesis of MTB, along with the potential bioactive compounds for alternative plant-derived anti-TB drugs. The mechanistic insights provide significant discoveries on the limitations of immunity, offering important strategies for developing immunomodulating drugs.

Keywords: Adaptive response, bioactive compounds, innate response, mangroves, *Mycobacterium tuberculosis*

INTRODUCTION

Tuberculosis (TB) is a contagious and potentially fatal disease caused by the human pathogen, *Mycobacterium tuberculosis* (MTB), primarily affecting the lungs. It can also spread to other areas of the body, such as the kidneys and spine, resulting in extrapulmonary tuberculosis. TB ranks among the top 10 most devastating infectious diseases worldwide, with 1.6 million reported cases and 6.4 million diagnoses in 2020, resulting in TB-related deaths (WHO, 2022). In Malaysia, tuberculosis is one of the two most highly contagious diseases, alongside dengue (MOH, 2020). The state of Sabah has the second-highest number of TB cases after Selangor, with 5,008 cases out of a total of 25,837 reported cases (MOH, 2020). TB imposes a significant economic burden on affected individuals, their families, and communities (Wingfield *et al.*, 2016). The heavy reliance on long duration of treatment with antibiotics, contributes to the high costs associated with managing TB. The increase in TB-related deaths in 2021 compared to 2020 can be attributed to limited access to TB diagnosis and treatment, as reported by the WHO (WHO, 2022). Furthermore, the misuse of antibiotics has resulted in the emergence of multidrug-resistant TB (MDR-TB), rendering TB drugs ineffective. In 2021, approximately 0.45 million new cases of MDR-TB or rifampicin-resistant TB (WHO, 2022). The standard treatment regimen for tuberculosis involves a six-month course of antibiotics, including rifampicin, isoniazid, ethambutol and pyrazinamide. However, these drugs may have the disadvantage of causing adverse side effects and the TB-causing bacteria can easily develop resistance against them. Noncompliance with medication during the first year of treatment increases the risk of relapse in TB patients, potentially leading to drug-resistant TB (Adaikkappan *et*

***Corresponding author**

ISSN (print): 1823-8262, ISSN (online): 2231-7538

al., 2012). The side effects of tuberculosis drugs and their modes of action are displayed in Table 1. Table 1 shows the tuberculosis drugs are categorised into two main groups: first-line and second-line anti-TB drugs. The first-line drugs such as isoniazid, rifampicin, pyrazinamide and ethambutol are generally more effective and have a better safety profile compared to second-line drugs. They are the preferred choice for treating drugs-sensitive TB. First-line anti-TB drugs are the preferred choice for treating drugs-sensitive TB due to their effectiveness and tolerability. The second-line drugs such as kanamycin and streptomycin are used when TB is resistant to first-line treatments or when the patient experiences adverse effects of intolerance to first-line drugs. Second-line drugs are reserved for drug-resistant TB cases and are often used when first-line treatments fail. However, they are associated with more side effects and are less effective, making them a less favourable option.

Researchers have shown increased interest in host-pathogen interactions due to the rising rates of rifampicin-resistant TB and multidrug resistant TB, aiming to improve the development of vaccine strategies. Figure 1 illustrates the mechanisms of current anti-TB drugs, which target different aspects of MTB pathogenesis, and it sheds light on the designations of vaccine strategies. Anti-tuberculosis drugs target MTB, the bacterium responsible for tuberculosis. Each drug has its own mechanism of action and their combined use in various drug regimens helps to treat TB effectively. Isoniazid, rifampicin and moxifloxacin primarily target processes involved in cell wall or DNA synthesis. Kanamycin and bedaquiline interfere with protein synthesis and energy production, respectively. Isoniazid and rifampicin are first-line drugs and are typically used in the initial phase of TB treatment. Second-line drugs like kanamycin, moxifloxacin and bedaquiline are used when first-line drugs fail or in cases of drug-resistant TB. The combination of these drugs in multi-drug regimens are essential to prevent drug resistance and effectively treat TB. The pathogenesis of MTB infection is complex, involving various factors such as endogenous and exogenous reinfection dynamics, lung parenchyma drainage, respiratory mechanics, local fibrosis processes and blood supply (Cardona, 2018). Macrophages and other immune cells play central roles in the invasion and dissemination of the pathogen (Queval, *et al.*, 2017; Martinot, 2018). MTB employs adaptation strategies to evade host immune clearance by manipulating the regulatory machinery of immunity. The interaction between alveolar macrophage and mycobacteria is the initial event that determines the pathogenic capacity. Understanding the interactions between host responses and the adaptive processes of MTB, including the utilisation of virulence factors for survival, is crucial for drug discovery.

A plant-based therapeutic holds promise as a safe and effective solution to combat the global burden of drug-resistant TB. Mangrove plants, known for their ability to thrive in challenging environments, have been found to possess remarkable compounds with medicinal significance, including antimicrobial activities that may have immunomodulating effects. Mangrove plants, belonging primarily to the families Rhizophoraceae, Acanthaceae, Lythraceae, Combretaceae and Arecaceae, are coastal shrubs that flourish in intertidal areas. They have adapted to biotic and abiotic stressors such as high salinity, sediment distribution, low-oxygen levels, and storm surges (Blankespoor *et al.*, 2017; Mitra *et al.*, 2021). These adaptations enable mangroves to produce bioactive compounds crucial for their survival, which have demonstrated antimicrobial, enzyme inhibitory, activators, antioxidant, anti-inflammatory, anticancer and antimycobacterial properties (Sulmartiwi *et al.*, 2018; Eswaraiah *et al.*, 2020; Sasidhar, 2020; Karthik *et al.*, 2023). Globally, approximately 15.2 million hectares of land are covered by mangroves, with the majority located in Southeast Asia (42%), followed by Africa (21%), North and Central America (15%), Oceania (12%) and South America (11%) (Leal and Spalding, 2022). In Malaysia, Sabah boasts the largest mangrove area, spanning 629,038 hectares, making it one of the countries with the highest distribution (58.6%) of mangroves (Omar

Table 1: The side effects and mode of actions of anti-tuberculosis drugs.

Synthetic drugs	Side effects	Mode of action	References
Isoniazid	Hepatitis nausea, vomiting, reduced appetite	Inhibit the reproduction of mycobacteria	Yew and Leung (2006)
Streptomycin	Hearing problem and ear imbalance (ototoxicity)	Suppress the protein synthesis of mycobacteria	Vianna *et al.* (2019); Goldberger (1988)
Rifampicin	Drug-induced hepatotoxicity	Suppress the enzyme activity RNA polymerase by inhibiting the transcription	Scharf *et al.* (2017); Tostmann *et al.* (2008)
Pyrazinamide	Hepatitis, swelling of joints, arthritis, yellowish of eyes	Release pyrazinoic acid and kill drug-tolerant mycobacteria	Kokesch-Himmelreich *et al.* (2022); Gopal *et al.* (2019); Tostmann *et al.* (2008)
Ethambutol	Reduced eye-sight, numbness and skin rash	Interrupt the synthesis of mycolic acid in the cell wall	Schubert *et al.* (2017); Yee *et al.* (2003)
Kanamycin	Loss of hearing, nephrotoxic	Suppress the synthesis of protein by binding to the bacterial 30S ribosomal subunit	Chulluncuy *et al.* (2016); Sowajassatakul *et al.* (2014)

 ISSN (print): 1823-8262, ISSN (online): 2231-7538

Malays. J. Microbiol. Vol 19(6) Special Issue 2023, pp. 786-804
DOI: http://dx.doi.org/10.21161/mjm.230010

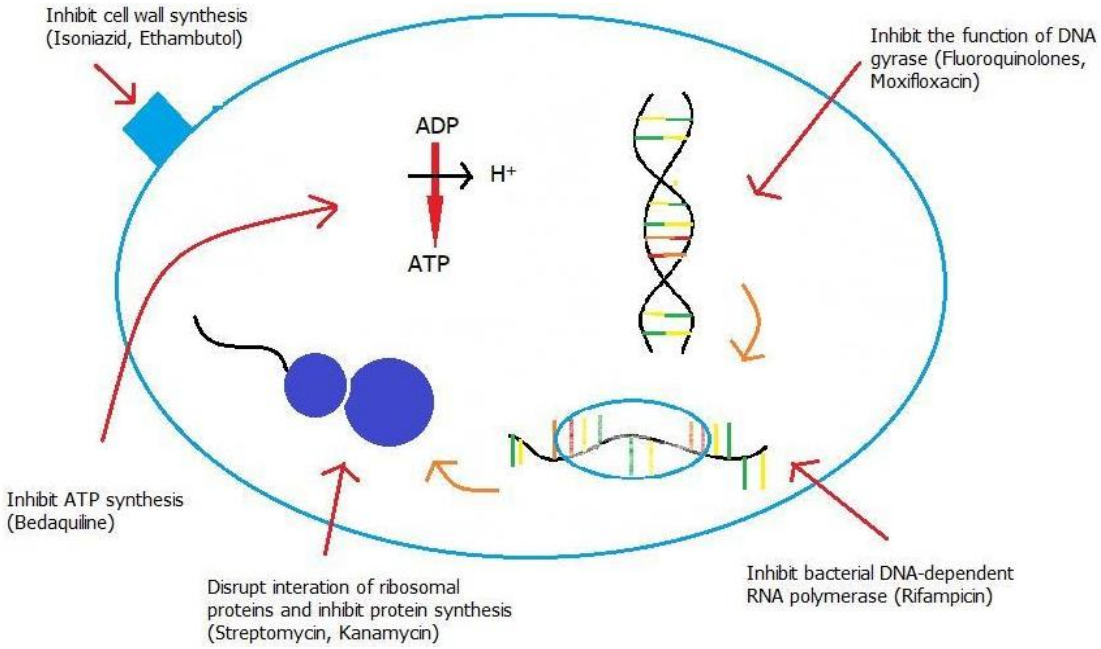

Figure 1: The mechanisms of anti-tuberculosis drugs.

and Misman, 2020). Table 2 displays the phytochemicals produced by mangroves, highlighting their pharmacological significance. Mangrove species are known for their various bioactivities and different species may exhibit distinct properties. *Avicennia marina* has been studied for its potential anticancer properties. It contains compounds such as flavonoids and tannins, which have antioxidant and anticancer properties. They may help in preventing or slowing the growth of cancer cells. *Rhizophora* species have been explored for their bioactive compounds. While there may be some potential anticancer compounds in *Rhizophora mucronata*, more research is needed to confirm their efficacy. Mangrove species such as *Ceriops decandra* has been traditionally used in some regions for the treatment of malignant ulcers. The bark and leaves contain bioactive compounds that may possess antimicrobial and wound-healing properties. While *Bruguierra gymnorrhiza* and *Avicennia marina* have been investigated for their antimicrobial properties which contain antibacterial and antifungal effects, likely due to the presence of secondary metabolites. *Avicennia alba* is known to contain antioxidants such as tannins, naphthoquinones and polyphenols, these compounds may help to protect cells from oxidative stress and reduce the risk of diseases related to oxidative damage. *Ceriops decandra* has been reported to possess antioxidant properties, likely attributed to its triterpenes and phenolic content, as antioxidants help neutralise harmful free radicals in the body. Other mangrove species such as *Excoecaria agallocha*, *Aegiceras corniculatum* and *Avicennia officinalis* have also been studied for their antimycobacterial properties, and its extracts have shown activity against tuberculosis-causing mycobacteria.

However, there is a scarcity of reported data on mangroves with mycobacterial properties, necessitating further studies to explore the potential of phytochemical contents of mangroves that can be tested *in vivo* for their anti-TB properties, thus filling the gaps in the existing literature. This review focuses on the study of host-pathogen interactions, including the adherence, colonisation and survival of mycobacteria within host cells, which require surface adhesions. The effectiveness of successive host immune responses depends on the capability of host defence mechanisms and the ability of tuberculosis to evade or manipulate host responses during the ingestion of mycobacteria by macrophages. Furthermore, this review also discusses some of the antimicrobial activities exhibited by mangroves.

Colonisation by tuberculosis

Tuberculosis is transmitted through infectious aerosols that enter the pulmonary alveoli and cause infection. Transmission occurs when healthy individuals inhale droplet nuclei, measuring approximately 1-5 µm, from infected people who have coughed, sneezed or spoken, through nasopharyngeal passages (Ryndak and Laal, 2019). These particles can remain in the air for several hours. The first line of defence encountered by MTB is the alveolar macrophage (AM) and the ability of the bacterium to infect the AM determines the outcome of the infection. The adherence of mycobacteria to host cells and their ability to evade the host's innate and adaptive immunity may facilitate mycobacterial colonisation. Several factors can influence the infective capacity, including the infectious inoculum and the size of aerosol particles, which are crucial for ensuring penetration into the

 ISSN (print): 1823-8262, ISSN (online): 2231-7538

Malays. J. Microbiol. Vol 19(6) Special Issue 2023, pp. 786-804
DOI: http://dx.doi.org/10.21161/mjm.230010

Table 2: The bioactivity of different types of mangrove species.

Mangrove species	Compound	Bioactivity	References
Acanthus ilicifolius	Benzoxaxoline	Anticancer	Das *et al.* (2015)
Avicennia officinalis	Triterpene, betulinic acid	Anticancer	Das *et al.* (2015)
Ceriops decandra	Quinine	Malignant ulcer	Govindasamy and Kannan (2012)
Avicennia marina	Tannins, triterpenes, flavonoids, phenolic	Anticancer	Cerri *et al.* (2022); Eldohaji *et al.* (2021); Esau *et al.* (2016)
Rhizophora mucronata	Alkaloids, flavonoids, steroids	Anticancer	Youssef *et al.* (2022)
Avicennia marina	2H-Pyran-3-ol, tetrahydro-2,2,6-trimethyl-6-(4-methyl-3-cyclohexen-1-yl, β-Sitosterol	Antimicrobial	Ibrahim *et al.* (2022)
Bruguiera gymnorrhiza, *Avicennia marina*	Saponin, tannin	Antimicrobial	Audah (2020)
Aegiceras corniculatum	Tannin, saponin, glycosides, phenolics, flavonoids	Antimicrobial	Janmanchi *et al.* (2017)
Rhizophora mucronata	Flavonoids, tannins	Antimicrobial	Mikchaell and Eddy (2018)
Avicennia rumphiana	Phenolic, tannin, flavonoids	Antioxidant	Sulmartiwi *et al.* (2018)
Avicennia alba, *Bruguiera gymnorrhiza*, *Ceriops decandra*	Phenolic, tannin, naphthoquinones, triterpenes	Antioxidant	Banerjee *et al.* (2008)
Avicennia officinalis	Phenolic compounds, flavonoids	Antioxidant	Nguyen *et al.* (2021)
Excoecaria agollacha, *Aegiceras corniculatum*, *Avicennia officinalis*	Alkaloids, flavonoids, phytosterols, tannins	Antituberculosis	Amudha *et al.* (2014)
Aegiceras corniculatum	Tannin, saponin, glycosides, phenolics, flavonoids	Antituberculosis	Janmanchi *et al.* (2017)

alveolus for the development of infection (Fennelly and Jones-Lopez, 2015). Recent investigations using rabbit models have shown that larger droplets cannot reach the alveolus (Plumlee, 2021). Additionally, pulmonary surfactant plays a role in preventing the destructions of alveoli by breaking down the lipophilic wall of mycobacteria, thereby facilitating the phagocytosis of alveolar macrophages (Chroneos *et al.*, 2009).

Adherence of M. tuberculosis to host mucosal epithelial cells

Inhaled bacilli encounter the primary innate defence system through mucociliary clearance before they can reach the alveolus in the lungs (Tena and Clara, 2012). The attachment of MTB to alveolar epithelial cells can be facilitated by adherence to mucins via nasopharyngeal colonisation and airway infections (Kinhikar *et al.*, 2006). Mucins, which are glycoproteins lining the mucosal surfaces of the upper respiratory tract (URT), not only act as lubricants for cilia movement but also contain antimicrobial agents (Janssen *et al.*, 2016). Mucus entrapment helps trap mycobacteria in the mucus layer, providing a favourable niche and nutrients for MTB to persist in the nasopharynx.

Adherence of M. tuberculosis to host alveolar macrophage

Each alveolar macrophage (AM) is tasked with clearing the air spaces of bacilli that have managed to evade the mechanical defences of the upper respiratory tract, such as the mucociliary system, within a single alveolus (Cardona, 2018). AMs recognize viable bacilli and phagocytize them. MTB secretes one of its essential factors, 6 kDa early secretory antigenic target (ESAT-6), to prevent the phagosome-lysosome mechanism from killing the mycobacteria, thus providing an opportunity for intracellular replication (Cardona, 2018; Ryndak and Laal, 2019). ESAT-6 plays roles in inhibiting phagosome maturation, de-acidification of the phagosome vacuole, escaping from the vacuole to the cytosol, and stimulating macrophage apoptosis (Awuh and Flo, 2017; Ryndak and Laal, 2019).

Upon entry into the cytoplasm after escaping from the phagosome-lysosome fusion (Mitchell *et al.*, 2017), the bacillus has the capacity to multiply, reaching concentrations of 32 and 64 bacilli (Lee *et al.*, 2006). This multiplication leads to the necrosis of alveolar macrophages (Behar *et al.*, 2010), causing the bacilli to become extracellular. The extracellular bacilli are then phagocytized by additional circulating alveolar macrophages from the interstitial space and neighbouring alveoli, which in turn produce more bacilli. Once the concentration of the bacilli reaches approximately 1000, it triggers the release of chemokines such as CCL2 (also

 ISSN (print): 1823-8262, ISSN (online): 2231-7538

known as monocyte chemoattractant protein-1, MCP-1), CXC chemokine ligand 10 (CXCL10) and tumor necrosis factor alpha (TNF-α), as well as cytokines such interferon-gamma (IFN-γ), interleukin-2 (IL-2) and interleukin-12 (IL-12) by the infected AMs, initiating an inflammatory response and allowing the entry of neutrophils and monocytes (Jang *et al.*, 2008; Deshmane *et al.*, 2009; Domingo-Gonzalez *et al.*, 2017; Cardona, 2018). Furthermore, it has been observed that alveolar macrophages are more conducive to MTB replication compared to interstitial macrophages (Huang *et al.*, 2018). This suggests that MTB requires a certain time frame for niche adaptation and survival before dissemination. Targeting these strategies could potentially prevent replication and the escape of bacilli from innate mechanisms. Numerous studies have demonstrated the significant role of cellular immunity in the elimination of bacilli and providing host protection against TB (Chackerian *et al.*, 2001; Ryndak and Laal, 2019). However, there is limited analysis on MTB replication and escape from the phagosome-lysosome union specifically in alveolar macrophage (Ryndak and Laal, 2019). These findings could help the delay in adaptive immunity, where cellular responses are initiated during the bacterial replication and systemic dissemination several weeks after infection (Ryndak and Laal, 2019).

Previous studies have demonstrated that granulomas, organised collections of macrophages and lymphocytes, play a role in limiting mycobacterial infection (Bold and Ernst, 2009). However, recent findings have raised the possibility that granulomas may contribute to the pathogenic capacity of MTB. A study utilising quantitative intravital microscopy in zebrafish infected with *Mycobacterium marinum* shed light on the process of granuloma formation, the consequences of infection and bacterial numbers (Davis and Ramakrishnan 2009). The study revealed the expansion of infected macrophages, increased bacterial numbers and the progression to secondary granulomas during the early innate immune phase (Davis and Ramakrishnan, 2009).

Adherence of M. tuberculosis to alveolar epithelial cell (AEC)

The alveolus consists of epithelial cells and its thin and delicate structure facilitates gas diffusion. This characteristic makes it susceptible to the entry of bacilli and other and other particles from the external air during alveolar expansion. Alveolar macrophages recognize these pathogens and initiate an inflammatory response. Additionally, surfactant aids in cleaning the alveolar space, which is continuously drained to the bronchioles and pharynx, ultimately being swallowed by the stomach through respiratory movements (Cardona, 2018). Droplet nuclei ranging from 1-5 µm in size can enter the alveolar sac, while larger droplet nuclei are trapped in the mucus of the upper respiratory tract (Tena and Clara, 2012). The innate immune system provides early protection to the lungs by maintaining the surface tension of the alveoli (Cardona, 2018). It can eliminate MTB infection before triggering an adaptive immune response. However, MTB is a highly adaptive pathogen that can evade host immune responses (Lerner *et al.*, 2015). Therefore, it is crucial to comprehend the physiological functions and metabolism reactions occurring in the alveolus, as alveolar epithelial cells (AEC) can provide a favourable environment for MTB replication and systemic dissemination (Ryndak and Laal, 2019).

The infection efforts of MTB are fundamentally based on bacterial-host interactions, with adherence serving as the initial step towards the invasion process. Adhesins, toxins and extracellular enzymes are binding components that mediate adhesion to alveolar epithelial cells. Adhesins, which are cell surface-exposed molecules expressed by pathogens, enable microbial adhesion to the host receptors of epithelial cells. Toxins are equally vital in assisting adhesins in cell destruction and exposing the host extracellular matrix, facilitating accessible penetration across barriers (Ryndak and Laal, 2019). Extracellular enzymes also function as adhesins, altering and modifying the cell membrane to enhance bacilli adherence to epithelial cells. The synergistic effect of these binding components could thereby increase AEC colonisation and systemic dissemination of the mycobacterium.

The expression of heparin-binding hemagglutinin adhesin (HBHA) is upregulated during MTB infection of alveolar epithelial cells, leading to increased adherence and invasion of these cells (Pethe *et al.*, 2001). It is noteworthy that HBHA is specifically expressed during infection of AEC, while Protein kinase D (PknD) is upregulated during infection of human brain microvascular endothelial cell (Nicholas *et al.*, 2012; Ryndak *et al.*, 2015; Abhishek *et al.*, 2018). This indicates that the pathogen employs different strategies to interact with specific host cell receptors for direct dissemination, independent of macrophages. Additionally, as previously mentioned regarding the prevention of phagosome-lysosome fusion, ESAT-6 acts as an adhesin that facilitates binding and damage to the basolateral Lm of AEC (Kinhikar *et al.*, 2010), enabling MTB dissemination through the alveolar wall (Ryndak and Laal, 2019).

In conclusion, the interaction between MTB and the host in the nasopharynx plays a significant role in the success of colonisation and facilitates the migration of the bacteria from the nasopharynx to the lungs and blood. However, the specific mechanism of nasopharynx colonisation by MTB is not well understood and require further research. Investigating the essential mechanisms and surface components utilised by MTB to evade mucociliary clearance in the URT could provide valuable insights. These findings could potentially be utilised in the development of targeted vaccine approaches for the prevention of MTB infection. Additionally, the adherence of MTB to alveolar macrophages and alveolar epithelial cells is crucial for the colonisation of the bacteria. This adherence allows the bacteria to cross the alveolar barriers and subsequently reach endothelial cells and the bloodstream.

 ISSN (print): 1823-8262, ISSN (online): 2231-7538

Malays. J. Microbiol. Vol 19(6) Special Issue 2023, pp. 786-804
DOI: http://dx.doi.org/10.21161/mjm.230010

Progression to tuberculosis disease

The progression from MTB infection to active tuberculosis is more likely and faster in immunosuppressed individuals. This can be attributed to the synthesis of virulence factors by the mycobacterial or the induction of alveolar macrophage necrosis (Cardona, 2018). The interplay between bacterial virulence and host resistance plays a crucial role in the pathogenesis of tuberculosis. Understanding the specific bacterial and host components involved allows for the identification of virulence factors, potential drug targets and components of the immune systems that are essential for the development of effective treatments. MTB is an obligatory aerobic pathogen that shows a preference for oxygen-rich areas of lung tissue. As mentioned earlier, infection occurs when droplets containing the bacteria are inhaled into the lungs and subsequently ingested by alveolar macrophage. This successful deposition of the tuberculosis infection in the pulmonary alveoli is a key step in the disease process. From there, the bacilli can disseminate to the lung apex, regional lymph nodes and other parts of the body.

Niche adaptation

Alveolar macrophages play a crucial role as the primary site of replication for MTB. Upon adherence of the mycobacteria to macrophages through adhesion molecules, the bacteria that have evaded initial elimination can persist and establish a latent infection. In some cases, the bacilli may actively replicate within the macrophages. Mycobacteria are highly adaptable pathogens that can manipulate host-pathogen interactions by secreting factors that affect both the host within the complex environment of macrophages, facilitating persistent infection. When internalised by phagocytes, the bacilli encounter various endocytic pathways, and they can employ different strategies to manipulate these pathways. This includes the ability to resist fusion with the phagolysosome and survive the acidic conditions encountered within these compartments (Cambier *et al.*, 2014). These observations suggest that MTB possesses specific virulence factors that confer acid resistance and allow the bacilli to survive within the host.

Furthermore, MTB has the ability to adapt to different sites within the host, which is a result of co-evolution and interaction with various host factors. This adaptability allows MTB to exist in multiple stages of TB, depending on the functionality of the host's immune system. These stages include the macrophage response, primary infection, latent infection and active tuberculosis, as shown in Figure 2, which depicts the clinical stages of tuberculosis. When MTB is inhaled into the lungs, it encounters the host's first line defence, which includes alveolar macrophages. Macrophages are the primary immune cells that respond to MTB infection. They engulf the bacteria and attempt to destroy them. MTB has developed mechanisms to resist macrophage killing, allowing it to survive and multiply within the macrophages. During primary infection, MTB establishes itself in the host's lungs. The infected macrophages transport the bacteria to regional lymph nodes, where they trigger an immune response. T lymphocytes are activated and recruited to the site of infection. This leads to the formation of granulomas, which are collections of immune cells that wall off the infected area. The host's immune system attempts to control the infection, leading to a balance between bacterial containment and bacterial replication. In many cases, the host's immune response is successful in containing the infection, leading to a state of latent tuberculosis. In latent tuberculosis infection, the host's immune system successfully controls the infection, preventing active disease. The bacteria remain dormant within granulomas, which can persist for years or even decades. However, they carry a risk of progressing to active tuberculosis if their immune system becomes compromised. Active tuberculosis occurs when the balance between the host immune response and bacterial replication is disrupted. This can happen when the immune system is weakened, allowing MTB to reactivate and cause disease. It is important to note that not everyone who is exposed to MTB will progress to active disease. Many individuals will remain in a latent infection state, and only a fraction of them will develop active tuberculosis if their immune system becomes compromised. It has been reported in a recent review that more than 90% of individuals infected with TB are able to control the infection, indicating that different levels of immune responses can influence the progression of the disease (Cambier *et al.*, 2014). However, in cases where the host's immune system is compromised, MTB can suppress both the innate and adaptive immune responses (Goldberg *et al.*, 2014). In healthy immunocompetent and bacterial determinants. This enables their survival individuals, bacilli within granulomas, which are aggregates of immune cells containing mycobacteria, can be contained for an extended period.

Indeed, bacilli that remain confined within granulomas can exhibit metabolic activity despite being dormant, highlighting the ability of MTB to adapt and balance within the highly stressful environment of the granuloma (Pienaar *et al.*, 2016; Chai *et al.*, 2018). This adaptation allows the bacilli to enhance their survivability and evade the immune response. Recent studies have linked the latent stage of MTB to adaptation in hypoxic environments, as indicated by the gene regulatory network involved in acclimation (Forrellad *et al.*, 2013; Chai *et al.*, 2018). It is important to note that in approximately 90% of individuals infected with TB, the growth of MTB is suppressed by the innate and adaptive immune responses, leading to the establishment of a latent infection (Rittershaus *et al.*, 2013; Bhavanam *et al.*, 2016). This represents one of the strategies employed by MTB to evade the host immune system, as the bacilli can remain dormant until reactivation occurs due to a compromised immune system (Dutta and Karakousis, 2014; Chai *et al.*, 2018). Furthermore, MTB possesses the ability to imitate the signalling pathways and cellular functions of the host, thereby gaining control over the

 ISSN (print): 1823-8262, ISSN (online): 2231-7538

Malays. J. Microbiol. Vol 19(6) Special Issue 2023, pp. 786-804
DOI: http://dx.doi.org/10.21161/mjm.230010

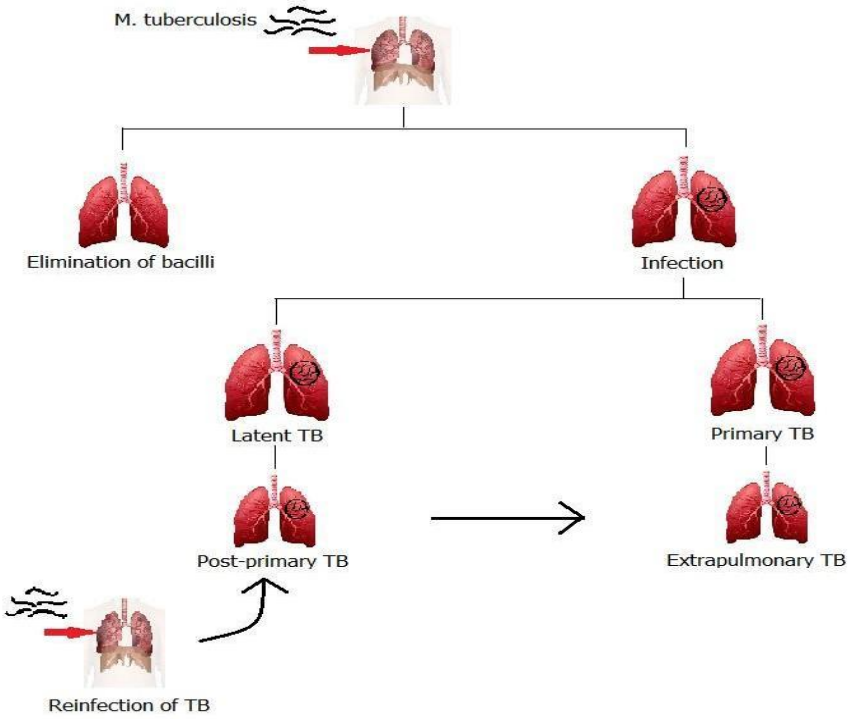

Figure 2: The clinical stages of tuberculosis in human lungs. Adapted from Bourguignon *et al.* (2023).

host's systems. Effector proteins such as MTB-encoded eukaryotic-like serine and MTB-encoded threonine phosphatases play a critical role in this imitation process and are essential for the survival of the mycobacteria (Forrellad *et al.*, 2013). In conclusion, the development of new drugs targeting the host-pathogen interactions specific for mycobacterial persistence has the potential to disrupt the imitation or modification efforts of MTB. By targeting these interactions, it may be possible to interrupt the survival strategies of the bacteria and improve treatment outcomes. Further exploration of the virulence factors of MTB will provide valuable insights into the pathogenesis of tuberculosis and inform the development of novel therapeutic approaches.

Invasion and dissemination

The chronology of the pathogenesis of human tuberculosis, which includes the initial stage of infection, the latent stage of infection, reactivation to post-primary infection and the dissemination stage, is largely influenced by the central roles of macrophages, granulomas and IFN-γ in systemic immunity (Nunes-Alves *et al.*, 2014; Queval *et al.*, 2017; Martinot, 2018). The ability of MTB to invade various epithelial cells and endothelial barriers may describe the penetration of tissues by MTB and thus its dissemination via bloodstream. Recent studies have suggested the ability of TB to invade various cells, including non-canonical immune cells, may result in TB dissemination to multiple organs (Randall *et al.*, 2015; Chai *et al.*, 2018). As discussed previously, TB adherence to the host cells favours the intracellular colonisation of mycobacteria and leads to the activation of pattern recognition receptors (PRRs) for phagocytosis, such as mannose receptors and DC-SIGN. To counteract the mechanisms, a few components of MTB, such as HBHA adhesin, are activated, which are responsible for the extrapulmonary dissemination of MTB (Pethe *et al.*, 2001). Additionally, Mce1 protein is one of the virulence-related proteins involved in the invasion of epithelial cells (Arruda *et al.*, 1993; Chai *et al.*, 2018) and Mce3C protein interrupts the β2 integrin-mediated signalling pathway for entry into macrophages (Zhang *et al.*, 2018).

There are a few types of common routes for bacilli dissemination, including the transmission of bacilli from venous capillaries to the left atrium and ventricle for systemic dissemination, the retransmission of bacilli backs into the lungs resulting from lymphadenitis, and the dissemination from the pharyngeal cavity to the mucous membrane via alveolar fluid, causing intestinal abdominal tuberculosis (ATB) (Cardona, 2018). In addition, bacilli tend to recolonize previous lesions with high vascularization and permeability, allowing for infection and multiplication of bacilli in the pulmonary venous capillaries (Osherov and Ben-Ami, 2016). The dissemination of bacilli is often related to a delay in the immune response (Cardona, 2018). Extrapulmonary infections have been implicated in 15% of the worldwide population, and their diagnosis and future treatments may be challenging (Behr *et al.*, 2018; Behr *et al.*, 2019; WHO, 2019; Moule and Cirillo, 2020). In cases of

 ISSN (print): 1823-8262, ISSN (online): 2231-7538

Malays. J. Microbiol. Vol 19(6) Special Issue 2023, pp. 786-804
DOI: http://dx.doi.org/10.21161/mjm.230010

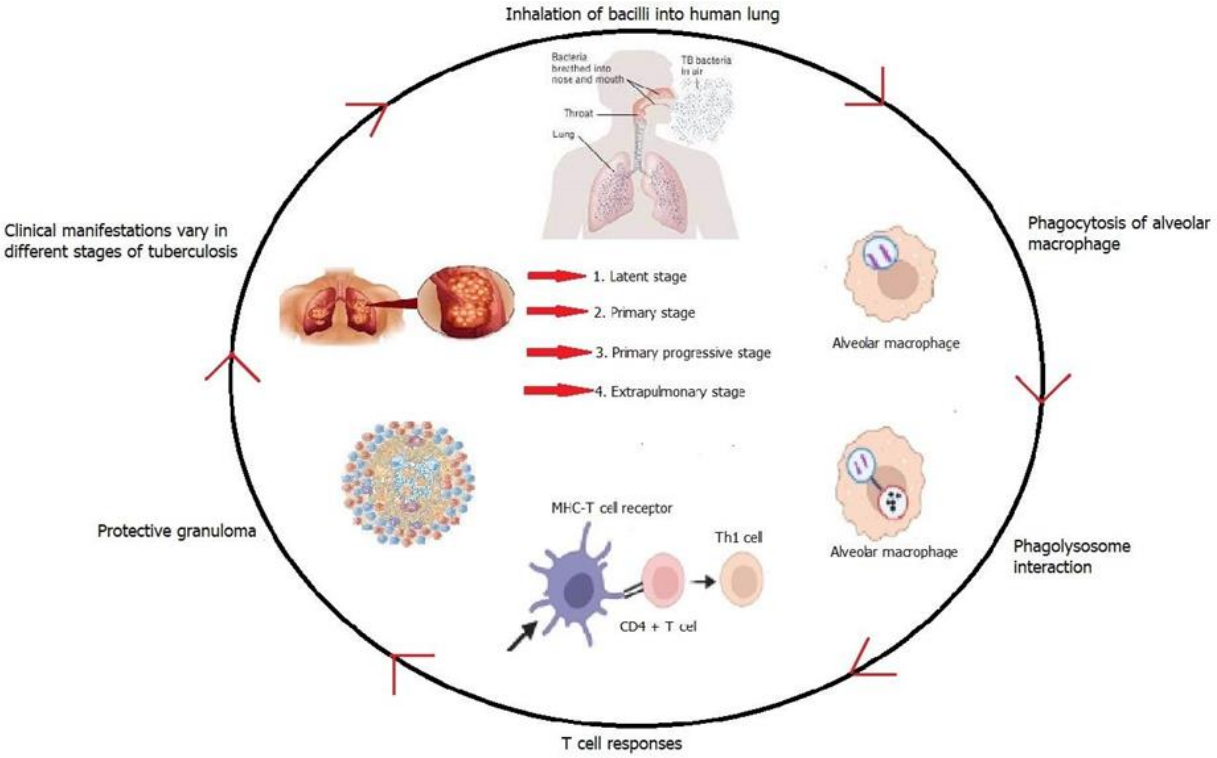

Figure 3: The pathophysiology of tuberculosis in the lungs of humans. Adapted from Yadav *et al.* (2021).

extrapulmonary infections, the absence of MTB in sputum can prevent detection through a regular sputum smear, primarily because the bacterium is not located within the pulmonary system (Zürcher *et al.*, 2019). Additionally, the wide range of additional symptoms such as swollen lymph nodes, pleural effusion, meningitis, bone and joint, gastrointestinal TB and skin TB, depending on the specific site of infection in extrapulmonary infections may complicate the current MTB treatment (Moule and Cirillo, 2020). Factors such as delayed diagnosis, complex diagnostic procedures, specialised treatment which require longer duration, risk of drug resistance, morbidity and complication and coexisting conditions can complicate the current MTB treatment in extrapulmonary tuberculosis (Moule and Cirillo, 2020). The pathophysiology of tuberculosis is illustrated in Figure 3, demonstrating the varying clinical manifestations in different stages of the disease.

Immune responses to tuberculosis

Innate immune responses: Roles of macrophages in phagocytosis and other initial host defences

The crucial phenomenon for the survival of host defences lies in the ability of macrophages and antigen-specific T cells to contain the persistent growth of bacilli and achieve complete clearance of MTB. The interaction between macrophages and antigen-specific T cells plays a critical role in determining the subsequent rate of host immune responses or evasion of MTB. Persistent bacilli can remain within the phagosomes of infected macrophages for extended periods, providing an opportunity for intracellular replication. The successive recognition of MTB components by macrophages and dendritic cells through toll-like receptors (TLRs) stimulates the activation of innate immunity and, in turn, the development of antigen-specific adaptive immunity. This adaptive immune response is initiated by the efficient presentation of MTB antigens by dendritic cells to $CD4^+$ T cells, along with the expression of costimulatory signals and cytokines.

More macrophages are recruited from the bloodstream following infection to control the bacilli in the lung. As discussed earlier, alveolar macrophages could provide a favourable niche for MTB replication by manipulating the microbicidal functions, leading to disease progression. Therefore, macrophages are not responsive to IFN-γ. However, infected macrophages could undergo early death with MTB or apoptosis, which is one of the strategies of host defence to suppress the intracellular replication of MTB (Amaral *et al.*, 2016). Macrophages responses to the bacilli depend on the type of cellular receptors that are normally expressed on cells such as macrophages, dendritic cells, NK cells and lymphocytes. Different receptors may result in varying levels of engagement between macrophages and the mycobacteria (Van Crevel *et al.*, 2002; Hernandez-Pando *et al.*, 2009). Increased engagement between macrophages and mycobacteria enhances the

 ISSN (print): 1823-8262, ISSN (online): 2231-7538

macrophages' capability to kill and digest the mycobacteria through the fusion of bacteria-containing phagosomes and lysosomes.

Phagocytosed antigens are presented to $CD4^+$ T lymphocytes by the major histocompatibility complex (MHC) class II for host protection. IFN-γ and IL-12, T cell-mediated cytokines, promote the attraction and activation of macrophages and the recruitment of additional lymphocytes to the site of infection for complete destruction of the infected cells (Hernandez-Pando *et al.*, 2009; Kulchavenya, 2013). These cytokines are vital in containing the growth of the bacilli, as evidenced by studies in human and mouse MTB infections, and by the increased susceptibility to mycobacterial infections in animals deficient in interferon gamma and interleukin 12 (Hernandez-Pando *et al.*, 2009). This condition may be associated with one of the determinant factors for TB disease, which is genetic control, along with environmental factors. According to Kang *et al.* (2011), mutations in the gene for IFN-γ producing Th1 cells in humans and mice likely contribute to susceptibility to mycobacterial infections. Additionally, different clinical manifestations of TB in individuals may exhibit diverse macrophage responses, which are likely associated with polymorphisms in genes. This variation may result in different gene profiles in innate immunity that could lead to susceptibility to mycobacterial infections in humans (Kulchavenya, 2013).

Studies have been conducted to explore the functions of macrophages in humans, including the phagocytosis of mycobacteria, stimulation of antimicrobial responses and responsiveness to interferon gamma (Sia *et al.*, 2015). Dendritic cells and monocyte-derived macrophages are immune cells involved in phagocytosis following the initial interaction between alveolar macrophages and MTB. The uptake of MTB is facilitated by different macrophage receptors on phagocytic cells, allowing for easy binding and invasion of mycobacteria into the host macrophages, indicating the early stages of infection. Opsonizations with complement factors such as C3 enhance the recognition of a wide range of antigens or mycobacterial ligands by macrophages, promoting phagocytosis and cell lysis (Van Crevel *et al.*, 2002). The absence of complement receptor CR3 in humans leads to an approximate 70-80% reduction in receptor-mediated phagocytosis of MTB by macrophages (Van Crevel *et al.*, 2002). Several receptors are involved in the opsonization process, including CR1, CR3, and CR4 (Van Crevel *et al.*, 2002); collectins such as surfactant proteins A and mannose-binding lectin; C-type lectins such as mannose receptor, DC-SIGN and DECTIN-1; and toll-like receptors such as TLR-2, TLR-4 and TLR-9 (Sia *et al.*, 2015). The binding of these receptors to non opsonized or opsonized MTB is crucial for the recognition and uptake of mycobacterial glycolipids, lipoproteins, and carbohydrates (Philips and Ernst, 2012; Sia *et al.*, 2015).

It is important to note that receptor-mediated phagocytosis *in vivo* continues to progress and may differ from what has been demonstrated *in vitro*. Therefore, further *in vivo* studies are necessary to unravel the mechanisms involved in the uptake of MTB by macrophages and its implications for immune activation. These studies could provide insights into preventing bacterial replication within macrophages during early infection and persistent bacterial infections within granulomas during chronic infection.

Neutrophils

Polymorphonuclear neutrophils, as part of the innate immune system, play a crucial role in combating invading bacilli during early TB infections through oxidative killing. They excel in phagocytosis and the release of reactive oxygen species (ROS), which possess antimicrobial properties, from their granules via the respiratory burst mechanism. Neutrophils are the most abundant type of white blood cells in the lungs of individuals infected with TB, and they can be observed in bronchoalveolar lavage (BAL) fluid of patients with pulmonary TB (Eum *et al.*, 2010; Sia *et al.*, 2015) as well as in murine models of pulmonary (Hilda *et al.*, 2020). A study conducted by Martineau *et al.* (2007), revealed an inverse relationship between the number of neutrophils functions, including chemotaxis, phagocytosis, the release of reactive oxidative compounds and activation of other immune responses, could increase susceptibility to TB infection due to immunological dysfunction (Kruger *et al.*, 2015; Hilda *et al.*, 2020). It should be noted that the mechanism of action of neutrophils demonstrates a higher level of phagocytosis and oxidative respiration compared to macrophages (Nordenfelt and Tapper, 2011). However, contradictory findings have been reported in other studies, which indicate a reduced capability of neutrophils in phagocytosis and oxidative burst response against TB infections (Hilda and Das, 2018; Gideon *et al.*, 2019). Exploring the roles of neutrophils in the context of bacilli could provide valuable insights into their functions that are yet to be fully explored.

Dendritic cells

Bone marrow-derived dendritic cells play a crucial role in bridging the gap between innate and adaptive immune responses. They are responsible for antigen presentation, activation of T cells and secretion of cytokines, all of which are essential for the initiation of T cell responses. Studies in mouse models, have demonstrated the presence of a significant number of MTB-infected dendritic cells, indicating their important role in presenting MTB antigens to T cells (Wolf *et al.*, 2008). The receptor DC-SIGN is prominently expressed on dendritic cells and facilitates efficient migration of these cells by binding to MTB ManLAM (Tailleux *et al.*, 2003; Sia *et al.*, 2015). However, dendritic cells have also been implicated in eliciting negative responses that allow MTB to evade host adaptive immunity. MTB can exploit the function of dendritic cells, leading to impaired maturation, inhibition of cytokine secretion and reduced production of stimulatory cells for antigen-specific T cells (Sia *et al.*, 2015; Balboa *et al.*, 2016). This can result in uncontrolled lymphocyte

 ISSN (print): 1823-8262, ISSN (online): 2231-7538

Malays. J. Microbiol. Vol 19(6) Special Issue 2023, pp. 786-804
DOI: http://dx.doi.org/10.21161/mjm.230010

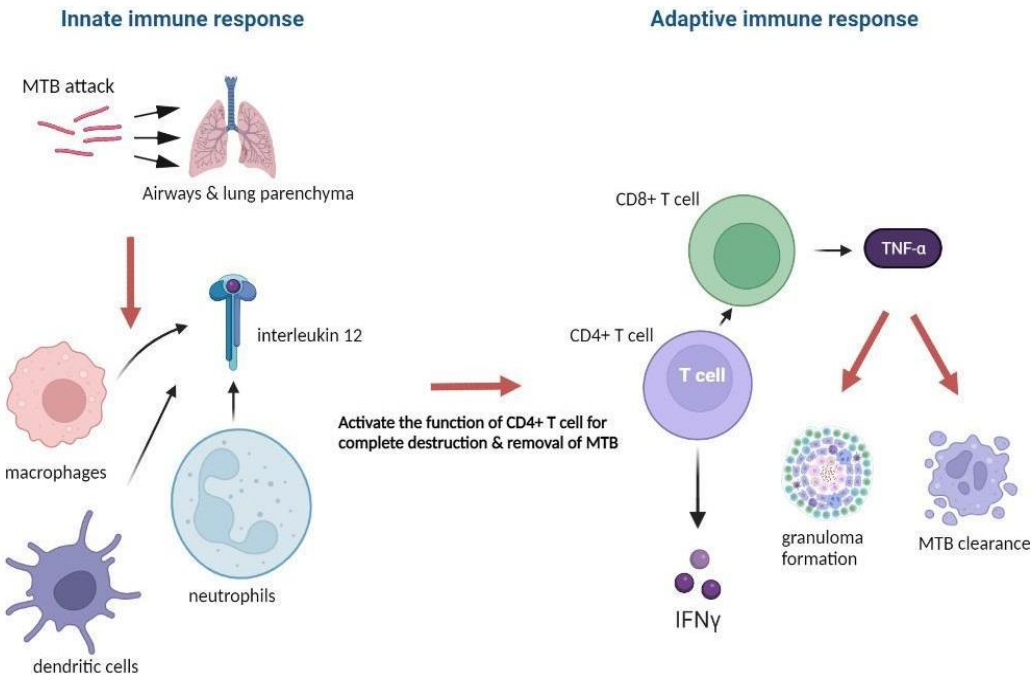

Figure 4: The general mechanism of the innate and adaptive immune responses to tuberculosis in humans.

production (lymphoproliferation) and irrelevant production of T cells at different stages of infection (Sia *et al.*, 2015), potentially leading to MTB persistence in the host. Other reviews have suggested that the presence of MTB-infected DC (MTB-DC) tends to promote the production of Th2 and Th17 responses over Th1 responses (Balboa *et al.*, 2016). Furthermore, the binding of MTB ManLAM and DC-SIGN inhibits the production of IL-12, which is an important cytokine for promoting Th1 responses (Sia *et al.*, 2015). These factors may contribute to the persistence of MTB in the host. Another factor that could influence the immune response is the reduced availability of antigens due to the slow growth of mycobacteria. This limited antigen availability may hamper the initiation of adaptive immune responses, potentially leading to poor responses of mycobacteria-specific T cells (Sia *et al.*, 2015). Similar to neutrophils, the precise contribution of DCs in the context of MTB infection is still not fully understood. Further research is necessary to investigate the specific functions of dendritic cells in the presentation of MTB antigens during the early stages of adaptive immune responses. These studies are crucial for establishing a comprehensive understanding of the consequences arising from the interaction between dendritic cells and MTB.

Adaptive immunity: Initiation of the cellular immune response

Innate and adaptive immunity exhibit a mutualistic relationship in effectively providing successive protection. The interaction between TB-infected macrophages and T lymphocytes predominantly contributes to the destruction and elimination of bacilli, underscoring the significance of cellular immunity in the host defence system against tuberculosis. The mechanisms involved in the innate immune response against MTB play a crucial role in initiating the adaptive immune response, encompassing antigen presentation, activation of synergistic combinations of secondary signalling pathways or co-stimulation, and the production of cytokines. In addition to macrophages, dendritic cells also serve as primary cells that play a pivotal role in bridging innate and adaptive immunity, as the initiation of adaptive immunity relies on the ability of dendritic cells to present the antigens to T cells. To effectively control the infection, host defences must surpass a certain threshold of mycobacterial numbers to successfully eradicate mycobacteria, which depends on the intrinsic relationship between the microbicidal capacity of macrophages and the engulfed MTB.

$CD4^+$ T cells, a part of adaptive T cell-mediated immunity, help suppress the intracellular replication of the bacilli by activating macrophages and halting the growth of MTB. Other T cell subsets, such as $CD8^+$ T cells, gamma delta T cells and CD1-restricted T cells, also contribute to the immune response against tuberculosis. The combined effects of these T cells broaden the range of mycobacterial antigens accessible to the host through antigen-presenting cells (APCs) (Boom *et al.*, 2003), significantly contributing to the control of persistent bacilli (Kawamura, 2006; Kulchavenya, 2013). During the early stages of TB infection, some bacilli employ versatile strategies to escape phagosomes and multiply. The proliferation of escaped bacilli leads to disruption in macrophages and the recruitment of blood-derived

 ISSN (print): 1823-8262, ISSN (online): 2231-7538

macrophages to the lung (Van Crevel *et al.*, 2002; Campillo-Navarro *et al.*, 2015) without causing severe tissue damage. However, blood-derived macrophages can ingest the bacilli but cannot eliminate them, resulting in a continuous influx of blood monocytes into the lung and increased inflammatory signals (Campillo-Navarro *et al.*, 2015). The accumulation of immune cells triggers synergistic mechanisms between macrophages and dendritic cells in engulfing the bacilli. This inflammatory environment promotes the migration of dendritic cells from the lungs to the lymph nodes, where they activate the proliferation of $CD4^+$ T cells and $CD8^+$ T cells at the site of infection (Tian *et al.*, 2005). Consequently, MTB antigen-specific T cells activate infected macrophages to destroy intracellular mycobacteria and prevent their growth.

The activation of infected macrophages by antigen-specific T cells occurs through the release of a large number of cytokines, such as IFN-γ, which are characteristic of Th1 cell function. Following antigen presentation by APCs, the release of IFN-γ by activated $CD4^+$ T cells contributes to the protective effect. These cytokines enhance the microbicidal capacity of infected macrophages, enabling them to kill the mycobacteria and halt the logarithmic growth of bacilli. In a murine study, Th2 clones, another subset of T cell, were induced by interleukin 4 (IL-4) and were also found in high concentrations in tuberculosis patients (Van Crevel *et al.*, 2002). Th2-inducing cytokines are known to limit the activation of macrophages (Campillo-Navarro *et al.*, 2015) and inhibit the in *vitro* production of IFN-γ (Van Crevel *et al.*, 2002). Unlike Th2 cells, Th1-inducing IL-12 helps to protect the host against tuberculosis, as evidenced by the high susceptibility to MTB in IFN-γ gene knockout mice (Cooper *et al.*, 1993) and the occurrence of recurrent mycobacterial infections in individuals with IFN-γ receptor deficiency (Iho *et al.*, 1999).

In addition to its role in promoting the destruction of bacilli through macrophage activation, IFN-γ also helps induce the $CD8^+$ T cell-mediated response, which is responsible for the apoptosis of infected cells (Serbina *et al.*, 2001; Hernandez-Pando *et al.*, 2009). This suggests the relative importance of $CD8^+$ T cell-mediated apoptosis in controlling intracellular replication by containing the pathogen within apoptotic bodies (Kulchavenya, 2013). Mice with $CD8^+$ T cell deficiency are more susceptible to MTB compared to animals with intact $CD8^+$ T cell function (Hernandez-Pando *et al.*, 2009). The mechanisms underlying $CD8^+$ T cell responses involving cytolytic functions appear to reduce the number of intracellular bacteria, possibly related to the presence of granular exocytosis in $CD8^+$ T granules (Hernandez-Pando *et al.*, 2009).

Evasion of host immune responses and granuloma formation

One way MTB evades immune responses is through evolutionary mechanisms that inhibit phagosome maturation, preventing the destruction of ingested bacilli by phagosome-lysosome fusion. This promotes the survival and proliferation of MTB (Campillo-Navarro *et al.*, 2015). The release of the ESX system by MTB can block phagosome maturation through nucleoside diphosphate kinase (Npk) following primary infection (Mihret, 2012). SecA2, another virulence factor of MTB, subverts phagosome maturation to facilitate intracellular growth (Sullivan *et al.*, 2012). However, the synergistic effect of IFN-γ and TNF-α helps control the intracellular growth of bacilli by increasing the expression of inducible nitric oxide synthase (iNOS) and promote bacilli killing in macrophages (Scanga *et al.*, 2001; Kanabalan *et al.*, 2021).

The progressive accumulation of cells, including mature macrophages, scattered neutrophils, dendritic cells, natural killer cells and surrounded by lymphocytes ($CD4^+$ T, $CD8^+$ T cells, B cells) and fibroblasts, could be exploited by the bacterium to evade the immune response, replicate, and spread (Bozzano *et al.*, 2014). This organised aggregation of cells is known as a granuloma. Mycobacteria have the ability to survive within granulomas (Ulrichs *et al.*, 2004). Initially, granulomas were seen as evidence of concentrated efforts to destroy MTB (Longo *et al.*, 2012). However, the roles of granulomas in either protecting the host or promoting infection remain unresolved.

In the early granuloma, adaptive responses are delayed and the immune defence relies solely on innate responses mediated by neutrophils, macrophages and dendritic cells (Vivier *et al.*, 2011). This delay in adaptive responses may be attributed to the inefficient presentation of MTB antigens by dendritic cells to $CD4^+$ T cells in the early granuloma (Egen *et al.*, 2011). Consequently, it favours increased macrophage accumulation, disease replication and systemic spread of MTB. At this stage, mycobacteria are well-established and protected within the granuloma, and the activation of Ag-specific $CD4^+$ T cells may have minimal antimycobacterial effects (Gallegos *et al.*, 2008). Following the initiation of the adaptive response, bacterial concentrations increase by 100-fold causing further local delay in the adaptive response within the lung. This delay is attributed to the influx of Ag-specific $CD4^+$ regulatory T cells and the inhibition of neutrophil apoptosis by MTB (Gallegos *et al.*, 2008). Further studies should focus on targeting the innate immune mechanisms that predominate in the early phase of MTB infection to effectively launch the subsequent adaptive phase.

Generally, the development of cell-mediated immunity occurs within 2 to 6 weeks after infection, characterised by the influx of lymphocytes and activated macrophages into the lesions, leading to the formation of granulomas (Alamelu, 2004). The dead macrophages within the granulomas form caseum, where the bacilli are restrained and may remain indefinitely Reactivation of the bacilli can also occur, leading to post-primary tuberculosis. As discussed earlier, the pathogenesis of tuberculosis involved not only the ability of MTB to exploit interactions between pattern recognition receptors (PRRs) in host macrophages and MTB virulence factors but also the

 ISSN (print): 1823-8262, ISSN (online): 2231-7538

Malays. J. Microbiol. Vol 19(6) Special Issue 2023, pp. 786-804
DOI: http://dx.doi.org/10.21161/mjm.230010

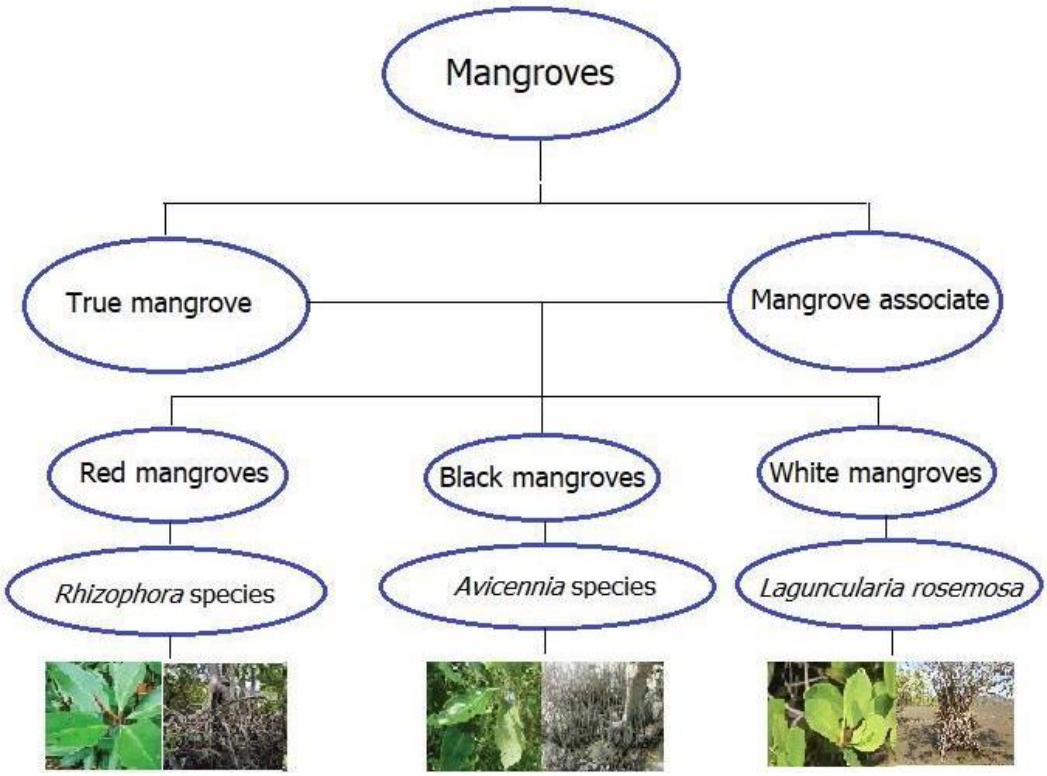

Figure 5: The classification of mangroves in the world. Adapted from Bibi *et al.* (2019) and Othman (2018).

manipulation of the granuloma response to maintain dynamic equilibrium following primary infection (Miggiano *et al.*, 2020; Kanabalan *et al.*, 2021). The mobility of macrophages may correspond to the control of bacterial growth (Bold and Ernst, 2009). Macrophages are highly mobile in the early granuloma (Davis *et al.*, 2002) but less mobile in the mature granuloma (Egen *et al.*, 2008), suggesting differences in the stage of TB infection. Figure 4 illustrates the general mechanism of the innate and adaptive immune responses to tuberculosis in humans.

Antimycobacterial activity of mangrove plants as potential immunomodulator

Mangroves are assemblages of halophytic woody plants that thrive in estuarine or brackish habitats in tropical and subtropical regions. It is noteworthy that around 75% of the world's tropical coastline is covered by mangroves (Kathiresan, 2000; Bandaranayake, 2002). The term 'mangrove' refers to an intertidal wetland ecosystem that forms through a unique association of animals and plants, flourishing abundantly in coastal areas and river estuaries across low-lying tropical and subtropical latitudes (Bandaranayake, 2002). Mangrove forests rank among the most productive tropical ecosystems globally, offering significant potential for beneficial use of plant species. These ecosystems face constant stress, which prompts the production of certain compounds crucial for their survival (Richards and Friess, 2016). Figure 5 illustrates the classification of mangroves. Mangrove ecosystems are characterised by a unique group of salt-tolerant trees and shrubs that thrive in intertidal zones along coastlines. Mangrove species can be classified into two main categories, including true mangroves and mangrove associates. True mangroves are plant species that are specially adapted to thrive in the harsh conditions of coastal mangrove ecosystems. They are obligate inhabitants of mangrove environments and are typically found within the intertidal zone, where they are regularly inundated by saltwater. Some common true mangroves include *Rhizophora* spp., *Avicennia* spp. and *Bruguiera* spp. While mangrove associates are plant species that are found in proximity to mangrove ecosystems but are not obligate inhabitants of these environments. They can tolerate the presence of saltwater but are not as specialised for intertidal life as true mangroves. Examples of mangrove associates include certain types of palms, ferns or terrestrial shrubs and can be considered as mangrove associates because they can grow in mangrove-adjacent habitats but are not fully adapted to the intertidal environment. Besides, some mangrove associates can also include *Rhizophora* spp., *Avicennia* spp. and *Bruguiera* spp. As they are found in proximity to mangrove ecosystems.

For centuries, extracts from mangrove plants have been widely utilised as a popular method for treating various health disorders. With a rich history in folklore medicine, these extracts have demonstrated inhibitory

 ISSN (print): 1823-8262, ISSN (online): 2231-7538

activity against human, animal and plant pathogens. Mangroves and their associated species contain biologically active compounds with antiviral, antibacterial and antifungal properties (Bandaranayake, 2002; Das *et al.*, 2015). Numerous studies have described the effects of mangrove extracts on microorganisms such as *Shigella* sp., *Staphylococcus* sp., *Escherichia coli*, *Proteus* sp. and *Pseudomonas* sp., particularly in the field of pharmacology (Arivuselvan *et al.*, 2011; Abdel-Aziz *et al.*, 2016). Additionally, mangrove extracts have shown potential as sources of mosquito larvicides, antifungal agents, and compounds with anti-diabetic properties (Das *et al.*, 2015).

These findings align with other studies highlighting the advantages of natural products as templates for the development of safe, highly therapeutic and cost-effective drugs (Newman and Cragg, 2007). Mangrove plants have shown antimicrobial activity against MTB (Amudha *et al.*, 2014), but research on the antimycobacterial properties of mangroves is still in the early stages and yet to be fully explored. Further studies are needed to investigate the bioactive compounds within mangroves that contribute to their ability to combat microbial infections, including pathogenic tuberculosis. Given the extensive distribution of mangroves worldwide and their therapeutic potential, it is crucial to unravel their therapeutic value. Mangroves are renowned for their ability to thrive in saline and brackish water environments, due to their intertwining roots system. It is likely that their efficient nutrient retention mechanism plays a significant role in their survival. The adaptations of mangrove plants to stressful conditions stimulates the production of secondary metabolites that contribute to their viability, often exhibiting antimicrobial properties. Carrière *et al.* (1997) have long suggested the potential of mangroves as inhibitors against tuberculosis. Various metabolites, such as flavonoids, carotenoids and alkaloids, have demonstrated the potential of mangroves as sources of novel agrochemicals, medicinal compounds and biologically active compounds (Carrière *et al.*, 1997; Bandaranayake, 2002).

The study conducted by Amudha *et al.* (2014) demonstrated that methanolic extracts of mangrove species such as *Excoecaria agallocha*, *Aegiceras corniculatum* and *Asparagus officinalis* exhibited the significant inhibitory effects against MTB strains. These extracts showed high inhibitory percentages, with 88.95% inhibition against the MTB strain H37Rv, 70.02% against clinical isolates of multi-drug resistant TB strains and 85.54% against drug-susceptible TB strains at concentration of 500 µg/mL. This study is one of the pioneering investigations into the antimycobacterial activity of mangrove plants, highlighting the urgent need to explore the potential of mangroves as a source of new drugs to combat the rising prevalence of drug-resistant TB strains. Earlier studies on the antimycobacterial properties of mangroves were limited due to the scarcity of information available on the benefits of mangrove species and the challenges associated with screening methods, particularly the safety concerns related to handling airborne-transmitted infectious pathogens. However, there is a gradual increase in research focusing on the antimycobacterial properties of various plant species and the potential of mangroves as valuable sources of drugs should not be overlooked. This review emphasises the medicinal properties of certain mangrove species and highlights their potential antimycobacterial activity, which could enhance the host immune response against tuberculosis.

The observed activities against tuberculosis displayed by potent mangrove species are likely attributed to the presence of bioactive compounds in the extracts, such as tannins and flavonoids (Amudha *et al.*, 2014; Janmanchi *et al.*, 2017). In the case of *Aegiceras corniculatom*, the bioactive compounds responsible for the antimycobacterial activity against tuberculosis strains could include saponins, glycosides and phenolics (Janmanchi *et al.*, 2017). It is not surprising that mangrove species like *E. agollacha*, which exhibit antimycobacterial activity, have been traditionally used in medicinal practices for treating conditions such as flatulence, leprosy, inflammation, sores and stings. These species have also been tested for their antiviral and antibacterial properties (Premanathan *et al.*, 1999; Kathiresan, 2000; Bandaranayake, 2002; Amudha *et al.*, 2014). The presence of high concentrations of intracellular active compounds in mangrove species may contribute to their various medicinal properties, including their anti-TB activity.

Besides, *Aegiceras corniculatom* has shown slightly higher antibacterial activity against Gram-negative bacteria (*E. coli*) compared to the Gram-positive bacterium *B. subtilis*, with percentage deaths of 79.86% and 47.19%, respectively (Janmanchi *et al.*, 2017). However, the extracts exhibited significant antimycobacterial activity at a minimum inhibitory concentration (MIC) of 19.53 µg/mL, whereas the MIC for *E. coli* and *B. subtilis* was 5 mg/mL. This suggests selective inhibition against MTB, providing a platform for identifying active fractions for the development of novel drugs (Janmanchi *et al.*, 2017). Recent studies have suggested that the presence of large quantities of phenolic content in mangroves could contribute to their activity against MTB, specifically by targeting the dihydrofolate reductase (DHFR) enzyme and bacterial type II fatty acid synthase (Kim *et al.*, 2014; Raju *et al.*, 2015; Janmanchi *et al.*, 2017). These enzymes play crucial roles in DNA synthesis and lipid metabolism of MTB, respectively. This indicates the potential of polyphenols to disrupt cell survival and replication mechanisms of MTB by targeting multiple pathways and virulence factors associated with its pathogenesis.

Exploring the combination of potential phytochemicals present in mangroves as antitubercular agents, along with targeting different virulence factors, can enhance host immune responses. Additionally, future *in vivo* studies will help uncover the mechanisms of interaction between MTB and host cells, leading to therapeutic interventions that can shorten the current lengthy treatment duration. Although natural products lack the high-purity compound

 ISSN (print): 1823-8262, ISSN (online): 2231-7538

libraries of synthetic drugs, a few natural products with antitubercular activities have been identified and recent research has focused on screening mangrove plants for their potential against tuberculosis.

CONCLUSION

This review provides a comprehensive overview of the current research on mangroves as a potential treatment for tuberculosis. The inclusion of both *in vitro* and *in vivo* studies adds depth to the analysis. The evidence-based analysis, including the mangroves species that showed anti-tuberculosis activity, was emphasised in this review. This is important for evaluating the efficacy of mangrove-derived compounds as potential tuberculosis treatments, providing insights into the specific compounds and their mechanisms of action. This review acknowledges the limitations of the existing research, including the limited number of clinical trials available, potential toxicity concerns and the challenges of extracting the active compounds from mangroves. Ecological and sustainable considerations of using mangroves in drug discovery should also be considered. Additionally, it is crucial to investigate and understand related studies involved in the interactions between host immune responses and MTB virulence factors, which maintain a dynamic equilibrium between the host and pathogen. Understanding the immune evasion strategies employed by MTB is also essential for the development of treatment for tuberculosis.

ACKNOWLEDGEMENTS

This review was supported by the External Collaboration Research Grant Scheme (GKP-0021-2018) and UMS Postgraduate Research Grant (UMSgreat) (GUG0287-2/2018).

CONFLICTS OF INTEREST

The authors have declared that there is no conflict of interest.

REFERENCES

Abdel-Aziz, S. M., Mouafi, F. E., Moustafa, Y. A. and Abdelwahed, N. A. (2016). Medicinal importance of mangrove plants. *In*: Microbes in Food and Health. Garg, N., Abdel-Aziz, S. and Aeron, A. (eds.). Springer, Cham. **pp. 77-96.**

Abhishek, S., Saikia, U. N., Gupta, A., Bansal, R., Gupta, V., Singh, N. *et al.* (2018). Transcriptional profile of *Mycobacterium tuberculosis* in an *in vitro* model of intraocular tuberculosis. *Frontiers in Cellular and Infection Microbiology* **8, 330.**

Adaikkappan, P., Kannapiran, M. and Anthonisamy, A. (2012). Antimycobacterial activity of *Withania somnifera* and *Pueraria tuberosa* against *Mycobacterium tuberculosis* $H_{37}Rv$. *Journal of Academia and Industrial Research* **1(4), 153-156.**

Alamelu, D., Khodade, P. S., Shah, P. M. and Aggarwal, S. K. (2004). Investigations on atomic and oxide ion formation of plutonium and uranium in thermal ionization mass spectrometry (TIMS) for determination of ^{238}Pu. *International Journal of Mass Spectrometry* **239(1), 51-56.**

Amaral, E. P., Lasunskaia, E. B. and D'Império-Lima, M. R. (2016). Innate immunity in tuberculosis: How the sensing of mycobacteria and tissue damage modulates macrophage death. *Microbes and Infection* **18(1), 11-20.**

Amudha, Prabuseenivasan and Kumar, V. (2014). Antimycobacterial activity of certain mangrove plants against multi-drug resistant *Mycobacterium tuberculosis*. *Asian Journal of Medical Sciences* **5(3), 54-57.**

Arivuselvan, N., Silambarasan, D., Govindan, T. and Kathiresan, K. (2011). Antibacterial activity of mangrove leaf and bark extracts against human pathogens. *Advances in Biological Research* **5(5), 251-254.**

Arruda, S., Bomfim, G., Knights, R., Huima-Byron, T. and Riley, L. W. (1993). Cloning of an *M. tuberculosis* DNA fragment associated with entry and survival inside cells. *Science* **261(5127), 1454-1457.**

Audah, A. K., Batubara, R., Julkipli, J., Wijaya, E., Kurniawaty, E. and Batubara, I. (2020). Antibacterial screening of mangrove extract library showed potential activity against *Escherichia coli* and *Staphylococcus aureus*. *Journal of Tropical Life Science* **10(2), 105-111.**

Awuh, J. A. and Flo, T. H. (2017). Molecular basis of mycobacterial survival in macrophages. *Cellular and Molecular Life Sciences* **74(9), 1625-1648.**

Balboa, L., Kviatcovsky, D., Schierloh, P., García, M., de la Barrera, S. and del Carmen Sasiain, M. (2016). Monocyte-derived dendritic cells early exposed to *Mycobacterium tuberculosis* induce an enhanced T helper 17 response and transfer mycobacterial antigens. *International Journal of Medical Microbiology* **306(7), 541-553.**

Bandaranayake, W. M. (2002). Bioactivities, bioactive compounds and chemical constituents of mangrove plants. *Wetlands Ecology and Management* **10(6), 421-452.**

Banerjee, D., Chakrabarti, S., Hazra, A. K., Banerjee, S., Ray, J. and Mukherjee, B. (2008). Antioxidant activity and total phenolics of some mangroves in Sundarbans. *African Journal of Biotechnology* **7(6), 805-810.**

Behar, S. M., Divangahi, M. and Remold, H. G. (2010). Evasion of innate immunity by *Mycobacterium tuberculosis*: Is death an exit strategy? *Nature Reviews Microbiology* **8(9), 668-674.**

Behr, M. A., Edelstein, P. H. and Ramakrishnan, L. (2018). Revisiting the timetable of tuberculosis. *BMJ* **362, k2738.**

Behr, M. A., Edelstein, P. H. and Ramakrishnan, L. (2019). Is *Mycobacterium tuberculosis* infection lifelong? *BMJ* **367, l5770.**

Bhavanam, S., Rayat, G. R., Keelan, M., Kunimoto, D. and Drews, S. J. (2016). Understanding the pathophysiology of the human TB lung granuloma using *in vitro* granuloma models. *Future Microbiology* **11(8), 1073-1089.**

Bibi, N. S., Fawzi, M. M., Gokhan, Z., Rajesh, J., Nadeem, N., Kannan, R. R. R. *et al.* (2019). Ethnopharmacology, phytochemistry, and global distribution of mangroves – A comprehensive review. *Marine Drugs* **17(4), 231.**

Blankespoor, B., Dasgupta, S. and Lange, G. (2017). Mangroves as a protection from storm surges in a changing climate. *Ambio* **46(4), 478-491.**

Bold, T. D. and Ernst, J. D. (2009). Who benefits from granulomas, mycobacteria or host? *Cell* **136(1), 17-19.**

Boom, W. H., Canaday, D. H., Fulton, S. A., Gehring, A. J., Rojas, R. E. and Torres, M. (2003). Human immunity to *M. tuberculosis*: T cell subsets and antigen processing. *Tuberculosis* **83(1-3), 98-106.**

Bourguignon, T., Godinez-Leon, J. A. and Gref, R. (2023). Nanosized drug delivery systems to fight tuberculosis. *Pharmaceutics* **15(2), 393.**

Bozzano, F., Marras, F. and De Maria, A. (2014). Immunology of tuberculosis. *Mediterranean Journal of Hematology and Infectious Diseases* **6(1), e2014027.**

Cambier, C. J., Falkow, S. and Ramakrishnan, L. (2014). Host evasion and exploitation schemes of *Mycobacterium tuberculosis*. *Cell* **159(7), 1497-1509.**

Campillo-Navarro, M., Wong-Baeza, I., Serafn-López, J., Hernández-Pando, R., Estrada-Parra, S., Estrada-García, I. *et al.* (2015). Regulation of the immune response by *Mycobacterium tuberculosis* Beijing genotype. *In*: Tuberculosis – Expanding Knowledge. Ribón, W. (ed.). IntechOpen Limited, London, UK.

Cardona, P. (2018). Pathogenesis of tuberculosis and other mycobacteriosis. *Infectious Diseases and Clinical Microbiology* **36(1), 38-46.**

Carrière, C., Riska, P. F., Zimhony, O., Kriakov, J., Bardarov, S., Burns, J. *et al.* (1997). Conditionally replicating luciferase reporter phages: Improved sensitivity for rapid detection and assessment of drug susceptibility of *Mycobacterium tuberculosis*. *Journal of Clinical Microbiology* **35(12), 3232-3239.**

Cerri, F., Giustra, M., Anadol, Y., Tomaino, G., Galli, P., Labra, M. *et al.* (2022). Natural products from mangroves: An overview of the anticancer potential of *Avicennia marina*. *Pharmaceutics* **14(12), 2793.**

Chackerian, A. A., Perera, T. V. and Behar, S. M. (2001). Gamma interferon-producing CD4+ T lymphocytes in the lung correlate with resistance to infection with *Mycobacterium tuberculosis*. *Infection and Immunity* **69(4), 2666-2674.**

Chai, Q., Zhang, Y. and Liu, C. H. (2018). *Mycobacterium tuberculosis*: An adaptable pathogen associated with multiple human diseases. *Frontiers in Cellular and Infection Microbiology* **8, 158.**

Chroneos, Z. C., Midde, K., Sever-Chroneos, Z. and Jagannath, C. (2009). Pulmonary surfactant and tuberculosis. *Tuberculosis* **89, S10-S14.**

Chulluncuy, R., Espiche, C., Nakamoto, J. A., Fabbretti, A. and Milón, P. (2016). Conformational response of 30S-bound IF3 to A-Site binders streptomycin and kanamycin. *Antibiotics* **5(4), 38.**

Cooper, A. M., Dalton, D. K., Stewart, T. A., Griffin, J. P., Russell, D. G. and Orme, I. M. (1993). Disseminated tuberculosis in interferon gamma gene-disrupted mice. *The Journal of Experimental Medicine* **178(6), 2243-2247.**

Das, G., Gouda, S., Mohanta, Y. K. and Patra, J. K. (2015). Mangrove plants: A potential source for anticancer drugs. *Indian Journal of Geo-Marine Sciences* **44(5), 666-672.**

Davis, J. M. and Ramakrishnan, L. (2009). The role of the granuloma in expansion and dissemination of early tuberculous infection. *Cell* **136(1), 37-49.**

Davis, J. M., Clay, H., Lewis, J. L., Ghori, N., Herbomel, P. and Ramakrishnan, L. (2002). Real-time visualization of mycobacterium-macrophage interactions leading to initiation of granuloma formation in zebrafish embryos. *Immunity* **17(6), 693-702.**

Deshmane, S. L., Kremlev, S., Amini, S. and Sawaya, B. E. (2009). Monocyte chemoattractant protein-1 (MCP-1): An overview. *Journal of Interferon and Cytokine Research* **29(6), 313-326.**

Domingo-Gonzalez, R., Prince, O., Cooper, A. and Khader, S. A. (2017). Cytokines and chemokines in *Mycobacterium tuberculosis* infection. *In*: Tuberculosis and the Tubercle Bacillus. Jacobs, W. R., McShane, H., Mizrahi, V. and Orme, I. M. (eds.), John Wiley & Sons, United States. **pp. 33-72.**

Dutta, N. K. and Karakousis, P. C. (2014). Latent tuberculosis infection: Myths, models, and molecular mechanisms. *Microbiology and Molecular Biology Reviews* **78(3), 343-371.**

Egen, J. G., Rothfuchs, A. G., Feng, C. G., Horwitz, M. A., Sher, A. and Germain, R. N. (2011). Intravital imaging reveals limited antigen presentation and T cell effector function in mycobacterial granulomas. *Immunity* **34(5), 807-819.**

Egen, J. G., Rothfuchs, A. G., Feng, C. G., Winter, N., Sher, A. and Germain, R. N. (2008). Macrophage and T cell dynamics during the development and disintegration of mycobacterial granulomas. *Immunity* **28(2), 271-284.**

Eldohaji, L. M., Fayed, B., Hamoda, A. M., Ershaid, M., Abdin, S., Alhamidi, T. B. *et al.* (2021). Potential targeting of Hep3B liver cancer cells by lupeol isolated from *Avicennia marina*. *Archiv der Pharmazie* **354(9), e2100120.**

Esau, L., Sagar, S., Bajic, V. B. and Kaur, M. (2016). Autophagy inhibition enhances the mitochondrial-mediated apoptosis induced by mangrove (*Avicennia marina*) extract in human breast cancer cells. *European Journal of Medicinal Plants* **5(3), 304-317.**

Eswaraiah, G., Peele, K. A., Krupanidhi, S., Kumar, R. B. and Venkateswarulu, T. C. (2020). Studies on phytochemical, antioxidant, antimicrobial analysis and separation of bioactive leads of leaf extract from the selected mangroves. *Journal of King Saud University-Science* **32(1), 842-847.**

Eum, S. Y., Kong, J. H., Hong, M. S., Lee, Y. J., Kim, J. H., Hwang, S. H. *et al.* (2010). Neutrophils are the predominant infected phagocytic cells in the airways of patients with active pulmonary TB. *Chest* **137(1), 122-128.**

Fennelly, K. P. and Jones-López, E. C. (2015). Quantity and quality of inhaled dose predicts immunopathology in tuberculosis. *Frontiers in Immunology* **6, 313.**

Forrellad, M. A., Klepp, L. I., Gioffré, A., Sabio y García, J., Morbidoni, H. R., Santangelo, M. D. L. P. *et al.* (2013). Virulence factors of the *Mycobacterium tuberculosis* complex. *Virulence* **4(1), 3-66.**

Gallegos, A. M., Pamer, E. G. and Glickman, M. S. (2008). Delayed protection by ESAT-6-specific effector CD4+ T cells after airborne *M. tuberculosis* infection. *Journal of Experimental Medicine* **205(10), 2359-2368.**

Gideon, H. P., Phuah, J., Junecko, B. A. and Mattila, J. T. (2019). Neutrophils express pro-and anti-inflammatory cytokines in granulomas from *Mycobacterium tuberculosis*-infected cynomolgus macaques. *Mucosal Immunology* **12(6), 1370-1381.**

Goldberg, M. F., Saini, N. K. and Porcelli, S. A. (2014). Evasion of innate and adaptive immunity by *Mycobacterium tuberculosis*. *Microbiology Spectrum* **2(5), MGM2-0005-2013.**

Goldberger, M. J. (1988). Antituberculosis agents. *The Medical Cinics of North America* **72(3), 661-668.**

Gopal, P., Grüber, G., Dartois, V. and Dick, T. (2019). Pharmacological and molecular mechanisms behind the sterilizing activity of pyrazinamide. *Trends in Pharmacological Sciences* **40(12), 930-940.**

Govindasamy, C. and Kannan, R. (2012). Pharmacognosy of mangrove plants in the system of unani medicine. *Asian Pacific Journal of Tropical Disease* **2, S38-S41.**

Hernandez-Pando, R., Orozco, H. and Aguilar, D. (2009). Factors that deregulate the protective immune response in tuberculosis. *Archivum immunologiae et Therapiae Experimentalis* **57(5), 355-367.**

Hilda, J. N. and Das, S. (2018). Neutrophil CD64, TLR2 and TLR4 expression increases but phagocytic potential decreases during tuberculosis. *Tuberculosis* **111, 135-142.**

Hilda, J. N., Das, S., Tripathy, S. P. and Hanna, L. E. (2020). Role of neutrophils in tuberculosis: A bird's eye view. *Innate Immunity* **26(4), 240-247.**

Huang, L., Nazarova, E. V., Tan, S., Liu, Y. and Russell, D. G. (2018). Growth of *Mycobacterium tuberculosis in vivo* segregates with host macrophage metabolism and ontogeny. *Journal of Experimental Medicine* **215(4), 1135-1152.**

Ibrahim, H. A., Abdel-Latif, H. H. and Zaghloul, E. H. (2022). Phytochemical composition of *Avicennia marina* leaf extract, its antioxidant, antimicrobial potentials and inhibitory properties on *Pseudomonas fluorescens* biofilm. *The Egyptian Journal of Aquatic Research* **48(1), 29-35.**

Iho, S., Yamamoto, T., Takahashi, T. and Yamamoto, S. (1999). Oligodeoxynucleotides containing palindrome sequences with internal 5′-CpG-3′ act directly on human NK and activated T cells to induce IFN-γ production *in vitro*. *Journal of Immunology* **163(7), 3642-3652.**

Jang, S., Uzelac, A. and Salgame, P. (2008). Distinct chemokine and cytokine gene expression pattern of murine dendritic cells and macrophages in response to *Mycobacterium tuberculosis* infection. *Journal of Leukocyte Biology* **84(5), 1264-1270.**

Janmanchi, H., Raju, A., Degani, M. S., Ray, M. K. and Rajan, M. G. R. (2017). Antituberculosis, antibacterial and antioxidant activities of *Aegiceras corniculatum*, a mangrove plant and effect of various extraction processes on its phytoconstituents and bioactivity. *South African Journal of Botany* **113, 421-427.**

Janssen, W. J., Stefanski, A. L., Bochner, B. S. and Evans, C. M. (2016). Control of lung defence by mucins and macrophages: Ancient defence mechanisms with modern functions. *European Respiratory Journal* **48(4), 1201-1214.**

Kanabalan, R. D., Lee, L. J., Lee, T. Y., Chong, P. P., Hassan, L., Ismail, R. *et al.* (2021). Human tuberculosis and *Mycobacterium tuberculosis* complex: A review on genetic diversity, pathogenesis and omics approaches in host biomarkers discovery. *Microbiological Research* **246, 126674.**

Kang, D. D., Lin, Y., Moreno, J., Randall, T. D. and Khader, S. A. (2011). Profiling early lung immune responses in the mouse model of tuberculosis. *PLoS ONE* **6(1), e16161.**

Karthik, Y., Kalyani, M. I., Krishnappa, S., Devappa, R., Goud, C. A., Ramakrishna, K. *et al.* (2023). Antiproliferative activity of antimicrobial peptides and bioactive compounds from the mangrove *Glutamicibacter mysorens*. *Frontiers in Microbiology* **14, 1096826.**

Kathiresan, K. (2000). A review of studies on Pichavaram mangrove, southeast India. *Hydrobiologia* **430, 185-205.**

Kawamura, I. (2006). Protective immunity against *Mycobacterium tuberculosis*. *Kekkaku* **81, 687-691.**

Kim, H. S., Quon, M. J. and Kim, J. A. (2014). New insights into the mechanisms of polyphenols beyond antioxidant properties; Lessons from the green tea polyphenol, epigallocatechin 3-gallate. *Redox Biology* **2, 187-195.**

Kinhikar, A. G., Vargas, D., Li, H., Mahaffey, S. B., Hinds, L., Belisle, J. T. *et al.* (2006). *Mycobacterium tuberculosis* malate synthase is a laminin-binding adhesin. *Molecular Microbiology* **60(4), 999-1013.**

Kinhikar, A. G., Verma, I., Chandra, D., Singh, K. K., Weldingh, K., Andersen, P. *et al.* (2010). Potential role for ESAT6 in dissemination of *M. tuberculosis* via

human lung epithelial cells. *Molecular Microbiology* **75(1), 92-106.**

Kokesch-Himmelreich, J., Treu, A., Race, A. M., Walter, K., Hölscher, C. and Römpp, A. (2022). Do anti-tuberculosis drugs reach their target? High-resolution matrix-assisted laser desorption/ionization mass spectrometry imaging provides information on drug penetration into necrotic granulomas. *Analytical Chemistry* **94(14), 5483-5492.**

Kruger, P., Saffarzadeh, M., Weber, A. N., Rieber, N., Radsak, M., von Bernuth, H. *et al.* (2015). Neutrophils: Between host defence, immune modulation, and tissue injury. *PLoS Pathogens* **11(3), e1004651.**

Kulchavenya, E. (2013). Innate and acquired response on tuberculosis. *Journal of Clinical and Cellular Immunology* **S13, 005.**

Leal, M. and Spalding, M. D. (2022). The State of the World's Mangroves 2022. Global Mangrove Alliance, Washington.

Lee, J., Remold, H. G., Ieong, M. H. and Kornfeld, H. (2006). Macrophage apoptosis in response to high intracellular burden of *Mycobacterium tuberculosis* is mediated by a novel caspase-independent pathway. *Journal of Immunology* **176(7), 4267-4274.**

Lerner, T. R., Borel, S. and Gutierrez, M. G. (2015). The innate immune response in human tuberculosis. *Cellular Microbiology* **17(9), 1277-1285.**

Longo, D., Fauci, A., Kasper, D., Hauser, S., Jameson, J. and Loscalzo, J. (2012). Harrison's Principles of Internal Medicine. McGraw-Hill, United States.

Martineau, A. R., Newton, S. M., Wilkinson, K. A., Kampmann, B., Hall, B. M., Nawroly, N. *et al.* (2007). Neutrophil-mediated innate immune resistance to mycobacteria. *The Journal of Clinical Investigation* **117(7), 1988-1994.**

Martinot, A. J. (2018). Microbial offense vs host defense: Who controls the TB granuloma? *Veterinary Pathology* **55(1), 14-26.**

Miggiano, R., Rizzi, M. and Ferraris, D. M. (2020). *Mycobacterium tuberculosis* pathogenesis, infection prevention and treatment. *Pathogens* **9(5), 385.**

Mihret, A. (2012). The role of dendritic cells in *Mycobacterium tuberculosis* infection. *Virulence* **3(7), 654-659.**

Mikchaell, A. P. P. and Eddy, S. (2018). Antibacterial compounds activity of mangrove leaf extract *Rhizophora mucronata* on *Aeromonas hydrophyla*. *Russian Journal of Agricultural and Socio-Economic Sciences* **73(1), 187-193.**

Mitchell, G., Chen, C. and Portnoy, D. A. (2017). Strategies used by bacteria to grow in macrophages. *In*: Myeloid Cells in Health and Disease: A Synthesis. Gordon, S. (ed.). American Society for Microbiology, Washington. **pp. 701-725.**

Mitra, S., Naskar, N. and Chaudhuri, P. (2021). A review on potential bioactive phytochemicals for novel therapeutic applications with special emphasis on mangrove species. *Phytomedicine Plus* **1(4), 100107.**

MOH, Ministry of Health Malaysia. (2020). Malaysian Health at a Glance 2018. Ministry of Health Malaysia, Putrajaya, Malaysia.

Moule, M. G. and Cirillo, J. D. (2020). *Mycobacterium tuberculosis* dissemination plays a critical role in pathogenesis. Fro*ntiers in Cellular and Infection Microbiology* **10, 65.**

Newman, D. J. and Cragg, G. M. (2007). Natural products as sources of new drugs over the last 25 years. *Journal of Natural Products* **70(3), 461-477.**

Nguyen, N. T., Duong, N. T., Nguyen, K. H., Bui, N. T., Pham, T. T., Nguyen, K. T. *et al.* (2021). Effect of extraction solvent on total phenol, flavonoid content, and antioxidant activity of *Avicennia officinalis*. *Biointerface Research in Applied Chemistry* **12(2), 2678-2690.**

Nicholas, A. B., Bishai, W. R. and Jain, S. K. (2012). Role of *Mycobacterium tuberculosis pknD* in the pathogenesis of central nervous system tuberculosis. *BMC Microbiology* **12, 7.**

Nordenfelt, P. and Tapper, H. (2011). Phagosome dynamics during phagocytosis by neutrophils. *Journal of Leukocyte Biology* **90(2), 271-284.**

Nunes-Alves, C., Booty, M. G., Carpenter, S. M., Jayaraman, P., Rothchild, A. C. and Behar, S. M. (2014). In search of a new paradigm for protective immunity to TB. *Nature Reviews Microbiology* **12(4), 289-299.**

Omar, H. and Misman, M. A. (2020). Extents and distribution of mangroves in Malaysia. *In*: Status of mangroves in Malaysia. Omar, H., Mubarak, H. and Parlan, I. (eds.). Forest Research Institute Malaysia, Selangor, Malaysia. **pp. 1-42.**

Osherov, N. and Ben-Ami, R. (2016). Modulation of host angiogenesis as a microbial survival strategy and therapeutic target. *PLoS Pathogens* **12(4), e1005479.**

Othman, R. (2018). Identification and characterization of Pteroplinthite Mangrove Forests. *Journal of Architecture, Planning and Construction Management* **8(1), 55-63.**

Pethe, K., Alonso, S., Biet, F., Delogu, G., Brennan, M. J., Locht, C. *et al.* (2001). The heparin-binding haemagglutinin of *M. tuberculosis* is required for extrapulmonary dissemination. *Nature* **412(6843), 190-194.**

Philips, J. A. and Ernst, J. D. (2012). Tuberculosis pathogenesis and immunity. *Annual Review of Pathology* **7, 353-384.**

Pienaar, E., Matern, W. M., Linderman, J. J., Bader, J. S. and Kirschner, D. E. (2016). Multiscale model of *Mycobacterium tuberculosis* infection maps metabolite and gene perturbations to granuloma sterilization predictions. *Infection and Immunity* **84(5), 1650-1669.**

Plumlee, C. R., Duffy, F. J., Gern, B. H., Delahaye, J. L., Cohen, S. B., Stoltzfus, C. R. *et al.* (2021). Ultra-low dose aerosol infection of mice with *Mycobacterium tuberculosis* more closely models human tuberculosis. *Cell Host and Microbe* **29(1), 68-82. e5.**

Premanathan, M., Arakaki, R., Izumi, H., Kathiresan, K., Nakano, M., Yamamoto, N. *et al.* (1999). Antiviral

properties of a mangrove plant, *Rhizophora apiculata* Blume, against human immunodeficiency virus. *Antiviral Research* **44(2), 113-122.**

Queval, C. J., Brosch, R. and Simeone, R. (2017). The macrophage: A disputed fortress in the battle against *Mycobacterium tuberculosis*. *Frontiers in Microbiology* **8, 2284.**

Raju, A., Degani, M. S., Khambete, M. P., Ray, M. K. and Rajan, M. G. R. (2015). Antifolate activity of plant polyphenols against *Mycobacterium tuberculosis*. *Phytotherapy Research* **29(10), 1646-1651.**

Randall, P. J., Hsu, N. J., Quesniaux, V., Ryffel, B. and Jacobs, M. (2015). *Mycobacterium tuberculosis* infection of the 'non-classical immune cell'. *Immunology and Cell Biology* **93(9), 789-795.**

Richards, D. R. and Friess, D. A. (2016). Rates and drivers of mangrove deforestation in Southeast Asia, 2000-2012. *Proceedings of the National Academy of Sciences* **113(2), 344-349.**

Rittershaus, E. S., Baek, S. H. and Sassetti, C. M. (2013). The normalcy of dormancy: Common themes in microbial quiescence. *Cell Host and Microbe* **13(6), 643-651.**

Ryndak, M. B. and Laal, S. (2019). *Mycobacterium tuberculosis* primary infection and dissemination: A critical role for alveolar epithelial cells. *Frontiers in Cellular and Infection Microbiology* **9, 299.**

Ryndak, M. B., Singh, K. K., Peng, Z. and Laal, S. (2015). Transcriptional profile of *Mycobacterium tuberculosis* replicating in type II alveolar epithelial cells. *PLoS ONE* **10(4), e0123745.**

Sasidhar, K. (2020). Mangrove medicinal plants and its chemistry: A review. *International Journal of Multidisciplinary Educational Research* **10, 16-21.**

Scanga, C. A., Mohan, V. P., Tanaka, K., Alland, D., Flynn, J. L. and Chan, J. (2001). The inducible nitric oxide synthase locus confers protection against aerogenic challenge of both clinical and laboratory strains of *Mycobacterium tuberculosis* in mice. *Infection and Immunity* **69(12), 7711-7717.**

Scharf, N. T., Molodtsov, V., Kontos, A., Murakami, K. S. and Garcia, G. A. (2017). Novel chemical scaffolds for inhibition of rifamycin-resistant RNA polymerase discovered from high-throughput screening. *SLAS Discovery* **22(3), 287-297.**

Schubert, K., Sieger, B., Meyer, F., Giacomelli, G., Böhm, K., Rieblinger, A. *et al.* (2017). The antituberculosis drug ethambutol selectively blocks apical growth in CMN group bacteria. *mBio* **8(1), e02213-16.**

Serbina, N. V., Lazarevic, V. and Flynn, J. L. (2001). CD4+ T cells are required for the development of cytotoxic CD8+ T cells during *Mycobacterium tuberculosis* infection. *Journal of Immunology* **167(12), 6991-7000.**

Sia, J. K., Georgieva, M. and Rengarajan, J. (2015). Innate immune defenses in human tuberculosis: An overview of the interactions between *Mycobacterium tuberculosis* and innate immune cells. *Journal of Immunology Research* **2015, Article ID 747543.**

Sowajassatakul, A., Prammananan, T., Chaiprasert, A. and Phunpruch, S. (2014). Molecular characterization of amikacin, kanamycin and capreomycin resistance in M/XDR-TB strains isolated in Thailand. *BMC Microbiology* **14, 165.**

Sullivan, J. T., Young, E. F., McCann, J. R. and Braunstein, M. (2012). The *Mycobacterium tuberculosis* SecA2 system subverts phagosome maturation to promote growth in macrophages. *Infection and Immunity* **80(3), 996-1006.**

Sulmartiwi, L., Pujiastuti, D. Y., Tjahjaningsih, W. and Jariyah. (2018). Potential of mangrove *Avicennia rumphiana* extract as an antioxidant agent using multilevel extraction. *IOP Conference Series: Earth and Environmental Science* **137, 012075.**

Tailleux, L., Schwartz, O., Herrmann, J., Pivert, E., Jackson, M., Amara, A. *et al.* (2003). DC-SIGN is the major *Mycobacterium tuberculosis* receptor on human dendritic cells. *Journal of Experimental Medicine* **197(1), 121-127.**

Tena, A. F. and Clarà, P. C. (2012). Deposition of inhaled particles in the lungs. *Archivos de Bronconeumología* **48(7), 240-246.**

Tian, T., Woodworth, J., Sköld, M. and Behar, S. M. (2005). *In vivo* depletion of CD11c+ cells delays the CD4+ T cell response to *Mycobacterium tuberculosis* and exacerbates the outcome of infection. *Journal of Immunology* **175(5), 3268-3272.**

Tostmann, A., Boeree, M. J., Aarnoutse, R. E., de Lange, W. C., van der Ven, A. J. and Dekhuijzen, R. (2008). Antituberculosis drug-induced hepatotoxicity: Concise up-to-date review. *Journal of Gastroenterology and Hepatology* **23(2), 192-202.**

Ulrichs, T., Kosmiadi, G. A., Trusov, V., Jörg, S., Pradl, L., Titukhina, M. *et al.* (2004). Human tuberculous granulomas induce peripheral lymphoid follicle-like structures to orchestrate local host defence in the lung. *The Journal of Pathology* **204(2), 217-228.**

van Crevel, R., Ottenhoff, T. H. and van der Meer, J. W. (2002). Innate immunity to *Mycobacterium tuberculosis*. *Clinical Microbiology Reviews* **15(2), 294-309.**

Vianna, J. F., Bezerra, K. S., Oliveira, J. I., Albuquerque, E. L. and Fulco, U. L. (2019). Binding energies of the drugs capreomycin and streptomycin in complex with tuberculosis bacterial ribosome subunits. *Physical Chemistry Chemical Physics* **21(35), 19192-19200.**

Vivier, E., Raulet, D. H., Moretta, A., Caligiuri, M. A., Zitvogel, L., Lanier, L. L. *et al.* (2011). Innate or adaptive immunity? The example of natural killer cells. *Science* **331(6013), 44-49.**

Wingfield, T., Tovar, M. A., Huff, D., Boccia, D., Montoya, R., Ramos, E. *et al.* (2016). The economic effects of supporting tuberculosis-affected households in Peru. *European Respiratory Journal* **48(5), 1396-1410.**

WHO, World Health Organization. (2019). Global tuberculosis report 2019. World Health Organization, Geneva.

 ISSN (print): 1823-8262, ISSN (online): 2231-7538

WHO, World Health Organization. (2022). Global tuberculosis report 2022. World Health Organization, Geneva.

Wolf, A. J., Desvignes, L., Linas, B., Banaiee, N., Tamura, T., Takatsu, K. *et al.* (2008). Initiation of the adaptive immune response to *Mycobacterium tuberculosis* depends on antigen production in the local lymph node, not the lungs. *The Journal of Experimental Medicine* **205(1), 105-115.**

Yadav, R. K., Kaphle, H. P., Yadav, D. K., Marahatta, S. B., Shah, N. P., Baral, S. *et al.* (2021). Health related quality of life and associated factors with medication adherence among tuberculosis patients in selected districts of Gandaki Province of Nepal. *Journal of Clinical Tuberculosis and Other Mycobacterial Diseases* **23, 100235.**

Yee, D., Valiquette, C., Pelletier, M., Parisien, I., Rocher, I. and Menzies, D. (2003). Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. *American Journal of Respiratory and Critical Care Medicine* **167(11), 1472-1477.**

Yew, W. W. and Leung, C. C. (2006). Antituberculosis drugs and hepatotoxicity. *Respirology* **11(6), 699-707.**

Youssef, A. M., Maaty, D. A. and Al-Saraireh, Y. M. (2022). Phytochemistry and anticancer effects of mangrove (*Rhizophora mucronata* Lam.) leaves and stems extract against different cancer cell lines. *Pharmaceuticals* **16(1), 4.**

Zhang, Y., Li, J., Li, B., Wang, J. and Liu, C. H. (2018). *Mycobacterium tuberculosis* Mce3C promotes mycobacteria entry into macrophages through activation of β2 integrin-mediated signalling pathway. *Cellular Microbiology* **20(2), e12800.**

Zürcher, K., Ballif, M., Kiertiburanakul, S., Chenal, H., Yotebieng, M., Grinsztejn, B. *et al.* (2019). Diagnosis and clinical outcomes of extrapulmonary tuberculosis in antiretroviral therapy programmes in low-and middle-income countries: A multicohort study. *Journal of the International AIDS Society* **22(9), e25392.**

 ISSN (print): 1823-8262, ISSN (online): 2231-7538