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Insights into innovative therapeutics for drug-resistant tuberculosis: Host-directed therapy and autophagy inducing modified nanoparticles

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1. Introduction

Tuberculosis (TB) remains one of the deadliest communicable diseases caused by *Mycobacterium tuberculosis* (Mtb) since its discovery in the 1880s (Cambau and Drancourt, 2014; Singh et al., 2020). Over 1 billion mortalities have been recorded to date due to TB, and it was the leading cause of death from a single infectious agent before the COVID-19 pandemic, with an estimated 10.4 million new cases and an average of 1.7 million deaths yearly (Gagneux, 2018; Barberis et al., 2017; Scriba et al., 2020; Allué-Guardia et al., 2021; Organization, 2021). Further, about 25% of the world's population are latently ill or infected, providing a substantial pool for future cases of active TB (Gagneux, 2018). The World Health Organisation (WHO) reported that in 2019 an average of 10 million new cases were recorded, with 1.2 million cases being children and an estimated total of 1.4 million mortalities (Organization, 2019). Eight countries known for high TB burden accounted for 67% of the total cases logged in 2019. India was the leading country, followed by Indonesia, China, Philippines, Pakistan, Nigeria, Bangladesh, and South Africa (Organization, 2019). However, between 2020 and 2021, services aimed at eradicating TB were severely disrupted, and case recordings were significantly hindered by the Covid-19 pandemic (Crowther and Qualls, 2020; Pai et al., 2022; Organization, 2021). In 2020, WHO estimated that over 10 million individuals contracted TB, but only 5.8 million cases were diagnosed and recorded, a decline of 18% from 2019 (Pai et al., 2022; Organization, 2021). The decline spread across 16 countries, with Asian countries witnessing far more significant reductions in case reporting due to substantial Covid-19 outbreaks and healthcare service interruptions (Organization, 2021). As a result, there was an increase in TB mortality, with about 1.5 million deaths globally, the first increase in TB deaths since 2005 (Organization, 2021). Other adverse Covid-19 related drawbacks included a 15% drop in the number of people treated for drug-resistant TB and a 21% drop in people receiving TB infection prevention treatment (Organization, 2021; Pai et al., 2022).

TB mainly affects the lungs (pulmonary TB); however, it can spread to other neighbouring organs, which is known as extrapulmonary TB (EPTB) (Sunnetcioglu et al., 2015). EPTB results from the hematogenous spread of Mtb, with about 10% of all TB cases having pulmonary and EPTB (Narita and Spitters, 2017). Different factors contribute to high susceptibility to TB infection. These include compromised immune systems and defects in immune cells (macrophages and monocytes) due to various diseases or conditions such as human immunodeficiency virus (HIV), kidney disease, diabetes, substance abuse, and cancer (Kumari and Meena, 2014; Alavi-Naini et al., 2012). Other essential factors include malnutrition and smoking (tobacco). Various studies have demonstrated that more current smokers developed TB and successively died within the follow-up period than non-smokers (Alavi-Naini et al., 2012).

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The treatment of TB follows the standard guidelines outlined by the WHO, consisting of the multidrug therapy of first-line anti-TB drugs (acronym RIPE): rifampicin (RIF), isoniazid (INH), pyrazinamide (PZA), and ethambutol (EMB) (Organization, 2017). The recommended treatment plan comprises daily administration of all the first-line drugs (RIPE) in the first two months, followed by the daily administration of INH and RIF for four months (Organization, 2020). However, this treatment plan is often met with numerous challenges, such as poor patient compliance due to lengthy multidrug therapy (4–6 months), increased pill burden and drug-drug interaction from co-morbidities, which often leads to overlapping severe side effects (Dartois, 2014; Costa et al., 2016). This often leads to patient withdrawal before the course of treatment is completed, leading to treatment failure and subsequent development of drug-resistant TB (Dartois, 2014). The development of drug-resistant TB is a global threat in the fight against TB, and It is one of the significant contributors to the current anti-TB treatment regime failure (Mishra et al., 2020; Koch et al., 2018). MDR-TB is defined as TB that is resistant to RIF and INH, whilst extensively drug-resistant (XDR-TB) is defined as MDR-TB that is resistant to at least one of the injectable second-line drugs (amikacin, kanamycin and capreomycin) and any fluoroquinolone(Organization, 2017; Koch et al., 2018). Beside the development of drug-resistant TB, the difficulty of managing TB is that several anti-TB drugs fail to effectively reach the lungs and penetrate the alveolar macrophages (AMs) where the pathogen is hosted (Andrade et al., 2013; Pandey and Khuller, 2005). As a result, this enables the Mtb pathogen to remain viable within the host AMs for a more extended period following its adaptation to survive and evade the destructive environment of the host (Pieters, 2008). Treatment of drug-resistant TB makes use of the 2nd line anti-TB therapeutics with an extended treatment period (18–24 months) and with even more toxic severe side effects such as hepatotoxicity (liver damage), ototoxicity (loss of hearing and balance) and nephrotoxicity (kidney damage) (Shehzad et al., 2013; Ma et al., 2010; Niemi et al., 2003).

In the last 40 years, only three anti-TB drugs with novel mechanisms of action have been approved to treat MDR-/XDR-TB: delamanid, bedaquiline, and pretomanid, respectively (Baranyai et al., 2020). Bedaquiline and delamanid have demonstrated an effective improved treatment outcome rate at the end of treatment and a shorter treatment period for drug-resistant TB. Nonetheless, there are concerns about the possibility of cardiotoxicity caused by drug-drug interactions (Baranyai et al., 2020; Conradie et al., 2017; Olugbosi et al., 2020). The Food and Drug Administration (FDA) recently approved a novel oral regimen containing bedaquiline, pretomanid, and linezolid (BPaL) for the treatment of XDR-TB and MDR-TB after undergoing intensive clinical trials (NIX-TB trial) (Baranyai et al., 2020). This novel regime therapy has shown high favourable effective outcomes against drug-resistant TB; however, linezolid toxicity was frequently observed (Bigelow et al., 2020; Baranyai et al., 2020). Studies conducted in South Africa demonstrated the favourable outcome of the BPaL regime after treatment therapy (six months) in many patients with MDR and XDR-TB; with some related toxic effects to the treatment observed (Conradie et al., 2017; Olugbosi et al., 2020; Conradie et al., 2020). Despite the positive results or outcomes demonstrated by the BPaL treatment regimen, WHO guidelines on drug-resistant TB treatment recommend that it be used only if all other options are ineffective (Organization, 2019).

To overcome these limitations and challenges posed by drug-resistant TB, new research fields are emerging, such as Host Directed Therapeutics (HDTs), autophagy manipulation and Nanotechnology. HDT aims to increase the success of TB treatment by providing immunomodulation to the host response to infection by interfering with the host's mechanisms required by an Mtb pathogen for progressive persistence and replication (Kaufmann et al., 2018; Young et al., 2020; Gina et al., 2019). HDT differs from the conventional treatment plan. It stimulates the immune response by enhancing host defence mechanisms against Mtb by targeting pathways perturbed by Mtb pathogen without interacting with the pathogen itself (Kaufmann et al., 2018; Kilinc et al., 2021; Gina et al., 2019). HDT can also be used to treat MDR/XDR TB that is resistant to commonly used antibiotics. Because Mtb bacillus is not subjected to direct selection pressure, host-targeting drugs are less likely to generate drug resistance (Kilinc et al., 2021). The combinations of HDT with conventional anti-TB regimens may reduce the duration of the treatment period, attain better treatment outcomes, lessen the chances of relapse and permit dose lowering of standard antibiotics, thus reducing toxicity without impacting efficacy (Zumla et al., 2015a; Kilinc et al., 2021). Furthermore, HDT may reduce risks associated with drug-drug interactions in patients with co-morbidities, such as antiretroviral drug interaction in TB-HIV patients (Zumla et al., 2015a; Kolloli and Subbian, 2017).

Autophagy is a cellular process responsible for the lysosomal degradation of intracellular components, including invading pathogens such as Mtb (Goletti et al., 2013). The significant antimicrobial role of Autophagy against Mtb was first reported by Gutierrez et al. and Nakagawa et al. in 2004, respectively (Deretic, 2014). Mtb host cells (AMs) have mechanisms that induce autophagy to eliminate and decrease the bacterial loads within the infected host cell (Bento et al., 2015). Manipulation of autophagy activation in the infected host cell using various autophagy inducing compounds (AICs) has gained significant momentum as an alternate new treatment approach for treating TB (Maphasa et al., 2020). Treatment of drug-resistant TB with or without conventional TB antibiotics is one of the envisaged advantages of autophagy activation/manipulation (Paik et al., 2019; Maphasa et al., 2020). In addition, manipulation of autophagy activation further aids in controlling inflammation, contributing to a more efficient innate and adaptive immune response against Mtb bacilli (Bento et al., 2015; Goletti et al., 2013). Various novel innovations in anti-TB therapeutics have been envisaged based on manipulating autophagy activation, such as surface functionalised or modified nanoparticles (NPs) encapsulating conventional anti-TB therapeutics and other AICs capable of host-directed therapies. Some show significant success in clinical trials, increasing their possible implementation in the healthcare system (Bento et al., 2015). Given that HDT and autophagy manipulation are relatively new advances in the treatment of TB, there is minimal data published regarding the delivery of AICs or HDT adjuncts to the host and their treatment outcome and duration in the treatment of TB when combined with conventional treatment regimens (Maphasa et al., 2020). This dramatically enables a significant need to directly deliver HDT adjunct/AICs to their intended target sites to prevent undesired effects in other cells or organs (Paik et al., 2019).

NPs have provided significant advances as drug delivery systems in lung and respiratory infectious diseases for targeted drug delivery directly to their target sites (Andrade et al., 2013). They are designed to increase conventional drugs' efficacy by enhancing the absorption, stability, solubility, uptake by cells, and drug payload on targeted cells using minimum dosage whilst reducing immunotoxicology (Maretti et al., 2017; Zazo et al., 2016; Dobrovolskaia et al., 2016; Andrade et al., 2013; Andrade et al., 2011). Due to their highly desirable features, the nanoparticle can improve the efficacy of AICs or HDT adjuncts by directly transporting them to their target site (AMs); while protecting AICs from premature elimination, enhancing their absorption past biological barriers (Maphasa et al., 2020). Furthermore, some of the materials used in the fabrication of nanoparticles have an immunomodulatory effect on the host, and they can be further functionalized with AICs (Bekale et al., 2018). This review will summarise macrophages' role in Mtb uptake and response to early infection as a first-line defence innate immune response against invading pathogens. This review will also briefly examine the immunovasive and immunosuppressive processes that allow Mtb to survive in the host's hostile environment. In addition, the use of AICs to treat the host and nanoparticles for targeted distribution of AICs in the host will be discussed.

2. Recognition and uptake of mtb by macrophages

Macrophages are an essential component of the innate immune system. They play a crucial role in eliminating intracellular Mtb and initiating the innate and adaptive immune response through various bactericidal mechanisms (Liu et al., 2017; Hmama et al., 2015; Queval et al., 2017; Mortaz et al., 2015). However, AMs also serve as the primary host or reservoir for Mtb in initial and latency infection stages (Liu et al., 2017; Cadena et al., 2016). Mtb gains entry to macrophages via inhalation of tiny droplets from an infected individual, where it quickly reaches the lungs' alveolar spaces (Queval et al., 2017). The bacillus is then recognized and phagocytized by AMs upon its entry into alveolar spaces (Guirado et al., 2013). The AMs and other innate immune cells (neutrophils, natural killers and dendritic cells) contain different types of pattern recognition receptors (PRRs); these include C-type lectin receptors (CLRs), Toll-like receptors (TLRs) and Nod-like receptors (NLRs) (Liu et al., 2017). Upon Mtb infection, PRRs are stimulated by pathogen-associated molecular patterns (PAMPs) such as carbohydrates, lipoproteins and glycolipids expressed on the surface of Mtb (Mortaz et al., 2015; Liu et al., 2017). The stimulation of PRRs triggers various innate immune responses, including macrophage polarisation, phagocytosis, inflammation activation, autophagy (phagosome maturation, acidification and phagosome-lysosome fusion), production of reactive oxygen and nitrogen species (RONS), programmed cell death (apoptosis), and antigen processing (Mortaz et al., 2015; Liu et al., 2017; Atri et al., 2018).

Macrophages are classified into two types: classically activated macrophages (M1) and alternatively activated macrophages (M2). The physiological environment governs the functional response and polarisation of AMs into M1 or M2 during different stages of acute bacterial infection (Yao et al., 2019; Murray, 2017; Atri et al., 2018). Macrophage polarization (Fig. 1) is associated with both resolving inflammation, wherein the tissue heals after infection, and non-resolving inflammation, whereby the pathogen prolongs inflammation (Italiani et al., 2014). M1/M2 macrophages have different essential activities to eliminate pathogens, repair inflammation, and maintain homeostasis, and this polarization can happen at any point during the inflammatory process (Italiani et al., 2014). However, research has revealed that the regulated biological polarisation process and its induction routes are complex interlacing network systems that remain unclear rather than a simple process. (Yao et al., 2019; Atri et al., 2018). To assure a protective function during Mtb infection, macrophages are polarized toward the M1 phenotype, which has significant bactericidal activity during the early phases of infection (Atri et al., 2018).

Briefly, M1 macrophages are activated by intracellular bacterial stimuli such as lipoproteins or tumour necrosis factor (TNF-α) and Interferon-gamma (IFN-γ) cytokines, as shown in Fig. 1 (Roszer, 2015). Activation of M1 macrophages results in the secretion of pro-inflammatory cytokines, chemokines, and nitric oxide (NO) production (Fig. 1); this activates the Th1 response, facilitates complement-mediated phagocytosis, promotes type I inflammation, and assists in bacterial killing (Liu et al., 2017; Yao et al., 2019; Roszer, 2015). As a result, M1 macrophages are often found in an inflammatory milieu dominated by TLRs, TNF-α and IFN-γ signalling (Atri et al., 2018). M2 macrophages, in contrast to classically activated M1 macrophages, exhibit modulator activity, negatively regulate pro-inflammatory cytokines and increase the synthesis of anti-inflammatory mediators. (Jaguin et al., 2013; Atri et al., 2018). Various interleukin cytokines activate M2 macrophages (IL-3, IL-10, and IL-13), tumour growth factor-beta (TGF-β) and macrophage colony-stimulating factor (MCSF) (Roszer, 2015; Liu et al., 2017). Activation of M2 macrophages results in anti-inflammatory cytokines, increased phagocytic capacity, microbial defence, clearing of apoptotic cells and tissue repair (Roszer, 2015; Tarique et al., 2015).

3. Mtb defence mechanisms against the host immune response (autophagy)

Autophagy is a homeostatic and inducible process in which cytoplasmic components, such as organelles and intracellular pathogens, are collected in autophagosomes and delivered to the lysosome for

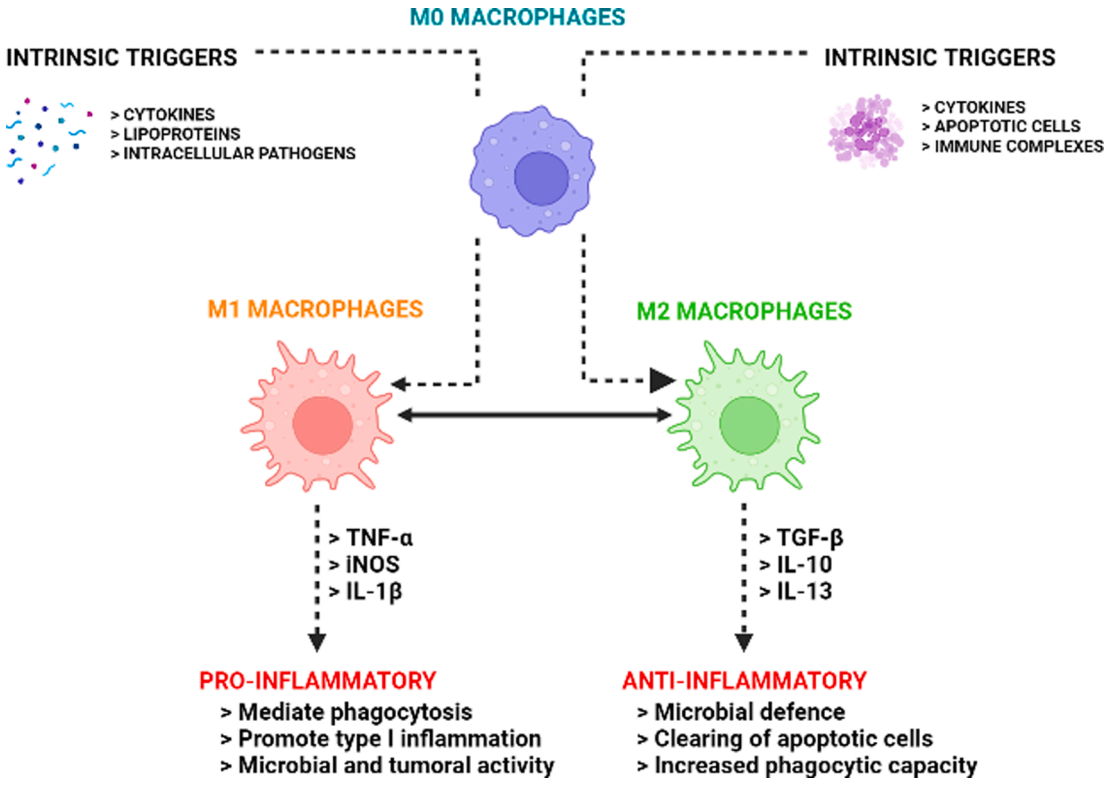

Fig. 1. Summarises macrophage polarisation to produce distinct functional phenotypes as a reaction to specific microenvironmental stimuli and signals.

degradation in macrophages (Fig. 2) (Gutierrez et al., 2004). Through autophagy, macrophages have demonstrated an effective antimicrobial response against Mtb infection. However, Mtb has adopted supreme strategies to evade, disrupt and manipulate the antimicrobial mechanisms of macrophages (Queval et al., 2017; Upadhyay et al., 2018; Chai et al., 2020). Mtb gains control of the host by disrupting autophagy, which includes the following vital steps, phagosome maturation, acidification and phagosome-lysosome fusion; and further by disrupting the production of reactive oxygen species (ROS), apoptosis and antigen presentation (Queval et al., 2017; Hmama et al., 2015). Disruption of these vital mechanisms alters the macrophages' ability to recognize and neutralize Mtb infection effectively and subsequently enables the survival and advanced replication of the Mtb within the host (Hmama et al., 2015).

3.1. Disruption of phagolysosome maturation and acidification

Once phagocytosed by AMs, Mtb is enclosed within phagosomes, the organelles responsible for routine clearance of pathogens (Chai et al., 2020). The phagosomes rapidly undergo a maturation process, a vital cellular process where phagosomes interact and fuse with lysosomes and endosomes, resulting in the exchange of endocytic solute materials and membrane components between them (Sturgill-Koszycki et al., 1994; Hmama et al., 2015). The maturation process is subsequently followed by a production of RONS intermediates, resulting in microbicidal and degrading characteristics being acquired by the phagolysosomes (Queval et al., 2017; Sturgill-Koszycki et al., 1994; Hmama et al., 2015).

3.1.1. Inhibition of phagolysosome maturation and fusion

The maturation process of phagosomes from early to late stages is primarily regulated by Rab GTPase proteins (Queval et al., 2017; Prashar et al., 2017). Rab GTPase proteins also contribute to the endosomal organelle identity and further facilitate many fusion events during the maturation process (Prashar et al., 2017). Studies have shown that Mtb actively inhibits the accumulation of Rab GTPase proteins by secreting bacterial macromolecules such as ATP1/2, secretory acid phosphatase (SapM), tyrosine phosphatase (PtpA), early secretory antigen target-6 (ESAT-6) and culture filtrate protein, resulting in decreased intracellular pH and subsequently suppressing the phagosome maturation (Zhai et al., 2019; Maphasa et al., 2020; Chai et al., 2018). Cytokine IFN-α has also been found to inhibit phagosome maturation by inducing the production of IL-10 in a signal transducer and activator of transcription-1 dependent manner (Ma et al., 2014). The induced release of IL-10 reduces the excess IL-1β resulting in the suppression of caspase1-dependent IL-1β maturation of pleural fluid mononuclear cells (Ma et al., 2014; Maphasa et al., 2020).

Mtb further inhibits the formation of lysosomes by enhancing the expression of the coronin-1 protein (Zhai et al., 2019; Schuller et al., 2001). Coronin-1 is a tryptophan aspartate rich coat protein recruited to phagosomes containing active bacilli but rapidly released from phagosomes containing inactive Mtb (Maphasa et al., 2020; Schuller et al., 2001). Coronin-1 activates calcium-calcineurin signal on the phagosome surface, blocking the fusion of lysosomes and Mtb phagosomes (Queval et al., 2017; Hmama et al., 2015). Mtb further secretes protein kinase G (PKnG), which aids in the inhibition of lysosome maturation by down-regulating adrenoleukodystrophy (ALD) and GlpK and upregulating the expression of Ag85A and Ag85C, resulting in enhanced Mtb infectivity, metabolism, growth rate and drug resistance (Walburger et al., 2004; Zhai et al., 2019; Maphasa et al., 2020). PKng further inhibits the fusion of the lysosomes with phagosomes by enhancing a transduction signal in the host cell (Zhai et al., 2019; Maphasa et al., 2020). The phagolysosome fusion is also inhibited via the calmodulin-dependent production of phosphatidylinositol-3-phosphate (PI3P), lower biosynthesis and trafficking of the toxin lipoarabinomannan (LAM) following Mtb infection (Vergne et al., 2003; Maphasa et al., 2020; Queval et al., 2017).

3.1.2. Inhibition of phagolysosome acidification

Phagosome acidification is essential for intracellular bacterial clearance. The RONS production and optimal activity of lysosome digestive enzymes require an acidic intracellular environment (Queval et al., 2017; Sun-Wada et al., 2009); hence, inhibition of phagosome acidification is crucial for the survival of Mtb within macrophages. The phagosome pH is hastily dropped by the high activity of a vesicular proton-pump ATPase (H+ V-ATPase) from neutral to pH ~ 4.5 as the maturation process progresses (Russell et al., 2009; Hmama et al., 2015). H+ V-ATPase pump is a protein complex that controls

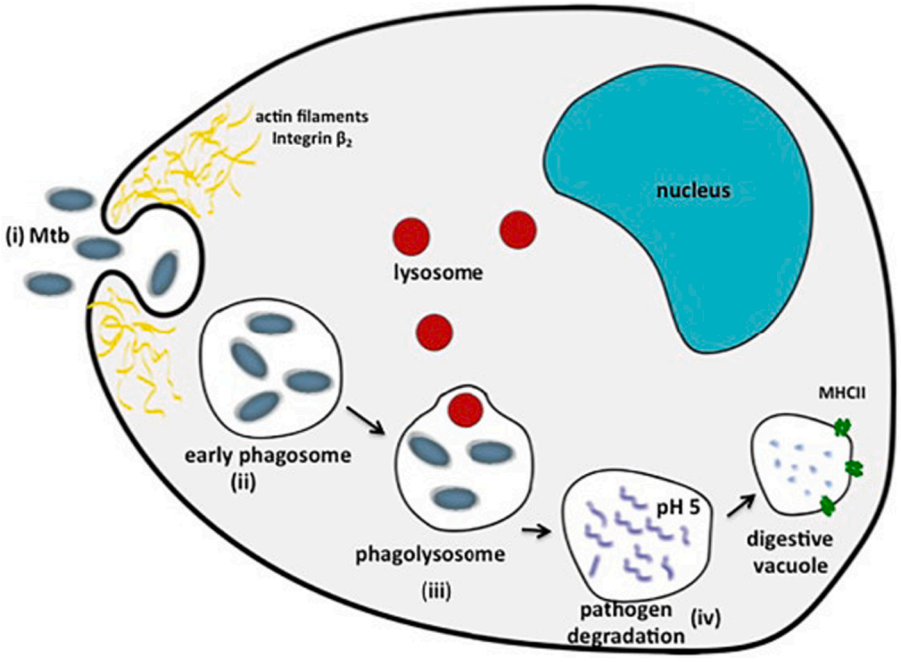

Fig. 2. Normal process of autophagy where Mtb is digested and cleared. However, Mtb evades this response by blocking maturation (ii), phagolysosome fusion (iii), acidification of the phagosomes (iv) and antigen presentation (Reprinted from Carranza and Chavez-Galan, 2019 with permission).

phagosome acidification by transporting protons across membranes (Hmama et al., 2015). However, Mtb inhibits the assembly of the H+ V-ATPase complex and its subsequent fusion with the phagosome membrane to stabilize the phagosome pH between 6.2 and 6.5 (Queval et al., 2017; Sturgill-Koszycki et al., 1994); thus enabling Mtb to persist and progress within an intracellular environment.

3.2. Disruption of reactive oxygen species production

Reactive oxygen species (ROS) are essential signalling molecules involved in many cellular processes, including the clearance of intracellular pathogens in macrophages (Lammas et al., 1997). The activation of phagocytosis, a first-line innate defence mechanism, induces ROS generation; the phagocytic process is triggered by the detection of PAMPs by particular receptors present on the surface of phagocytic cells such as TLRs, Fc-gamma receptors (FcγR), β-glucan receptor or complement receptors (Pauwels et al., 2017; Liu et al., 2017). TLR signalling is activated during phagocytosis, resulting in the recruitment of the microtubule-associated 1A/1B-light chain-3 autophagy protein (LC3) to the phagosome, which speeds phagosome maturation and improves microbial elimination and antigen presentation (Pauwels et al., 2017; Yang et al., 2012). The recruitment of the autophagy protein LC3 to phagosomes distinguishes a type of phagocytosis known as 'LC3-associated phagocytosis' (LAP) (Mehta et al., 2014); LAP is required for effective control of IFN production and clearance of dead cells (Martinez et al., 2011). TLR and FcγR signalling also cause the phagocyte NADPH oxidase 2 (NOX2) to assemble in the phagosome membrane, resulting in the generation of ROS, including superoxide by the transfer of electrons from cytosolic NADPH to oxygen in the phagosome lumen (Bedard and Krause, 2007; Maphasa et al., 2020).

ROS produced during this process are extremely powerful and may actively kill intracellular microorganisms, including Mtb pathogens (Bedard and Krause, 2007; Yang et al., 2012); furthermore, NOX2-derived ROS generation is essential for driving the LAP process (Martinez et al., 2015). However, Mtb has gained the ability to deactivate NOX2-derived ROS via the secretion of various molecules such as Mtb nucleoside diphosphate kinase (Ndk) and Eis protein (Sun et al., 2013; Shin et al., 2010). Ndk binds to and deactivates Rac1 GTPase, a vital recruiter of NOX2 in the phagosomes, hence impairing the mediated production of ROS (Sun et al., 2013). Impaired ROS-mediated production alters LAP-associated proteins further, resulting in a deficiency in the effective engulfment and digesting of apoptotic cells (Martinez et al., 2016). The Eis protein by Mtb further improves its intracellular survival by reducing macrophage inflammatory responses, apoptosis, and autophagy by blocking ROS generation (Shin et al., 2010). In addition, the Eis protein has been found in the cytoplasm of infected macrophages and sera taken from individuals with pulmonary TB, thus signifying that Eis is produced during Mtb infection in humans (Dahl et al., 2001; Samuel et al., 2007).

3.3. Disruption of apoptosis and Mtb antigen presentation

Apoptosis is a regulated cell death process vital for removing damaged cells in multicellular organisms (Green, 2011). Damaged cells are confined within a membrane-bound structure known as apoptotic bodies, which expresses phosphatidyl serine signals leading to the recognition and removal of these cells by phagocytic cells (Behar et al., 2011). Hence, apoptosis is vital for the efficient removal of intracellular Mtb by eliminating the favourable intracellular niche for replicating and initiating effective antigen cross-presentation for the effective immune response against Mtb (Schaible et al., 2003; Hmama et al., 2015). Mtb has developed strategic mechanistic approaches to actively evade or disrupt macrophage apoptosis, thus enabling Mtb to survive within the host and spread to other neighbouring cells (Martin et al., 2014). Mtb contains apoptosis inhibitory genes such as secA2, nuoG, Ndk and PtpA (Hmama et al., 2015). Some studies have demonstrated that infecting SecA2 and nuoG with knockout strains results in a proapoptotic phenotype (Hinchey et al., 2007; Velmurugan et al., 2007; Sun et al., 2013).

SecA2 serve as the primary transporter of superoxide dismutase (SodA) out of the bacterial cell resulting in the deactivation of ROS activity by Mtb (Hinchey et al., 2007). Hence inactivation of the secA2 by knockout strain results in impaired SodA secretion leading to enhanced apoptosis associated with increased macrophage antigen presentation to CD8+ T cells (Hinchey et al., 2007). Similarly, the knockdown of the nuoG gene in Mtb reverses apoptosis inhibition and reduces Mtb virulence in mice (Velmurugan et al., 2007). Mtb PtpA further inhibits macrophage apoptosis by dephosphorylating the glycogen synthase kinases α (GSK3α), resulting in anti-apoptotic activity, promoting pathogen survival in early infection stages (Poirier et al., 2014). Apoptosis in macrophages not only helps to eliminate the favourable intracellular environment for Mtb pathogen replication, but it also aids Mtb antigen cross-presentation by delivering apoptotic blebs to non-infected dendritic cells (DCs), ensuring optimal antigen presentation to T cells, a process known as the detour pathway (Lee et al., 2009). Hence apoptosis obstruction in macrophages subsequently results in obstruction of Mtb antigen presentation (Kilinc et al., 2021).

4. Autophagy induction as host-directed tb therapy

Several HDT strategies focus on repurposing already approved medications, vitamins and cytokines with well-defined pharmacokinetics and safety profile for other conditions, such as cardiovascular disease, metabolic disorders, and cancer (Gina et al., 2019; Periyasamy et al., 2020). As a result, the application of HDT in treating Mtb is a ground-breaking concept that offers new prospects that are needed in combating increasing Mtb infection (Zumla et al., 2015b). Most HDT techniques are used in conjunction with existing TB drugs and not as stand-alone treatments (Rao et al., 2019; Gina et al., 2019). HDT can be employed to restrict Mtb growth by modulating several host immune cell responses, such as increasing the production of ROS, antimicrobial peptide synthesis, and autophagy in infected cells (Kolloli and Subbian, 2017; Zumla et al., 2016). HDT drugs can also inhibit pro-inflammatory responses, thus reducing inflammation and tissue damage during the active stage of the disease (Kolloli and Subbian, 2017; Wallis and Hafner, 2015). In addition, HDT adjunct can modulate cell-mediated immune responses, such as antigen-specific T cell responses and alteration of the granuloma integrity and improve drug accessibility (Wallis and Hafner, 2015; Zumla et al., 2016; Young et al., 2020).

4.1. Vitamin D_3 and autophagy induction

One of the most investigated adjuncts for HDT-TB is vitamin D_3 due to the link between vitamin D_3 deficiency and TB susceptibility and its potential to stimulate autophagy and production of antimicrobial peptides (Lee and Bhakta, 2021). Vitamin D_3 exert an immunomodulatory effect on the innate immune system by upregulating its response and inflammatory response, respectively, via its active form 1,25-dihydroxyvitamin D_3 (1,25D) pathway (Chun et al., 2011). Vitamin D_3 acquire its physiological properties by being first hydroxylated in the liver by vitamin D-25-hydroxylase enzyme (CYP2R1), to 25-hydroxyvitamin D (25D), which is then converted into the active form (1,25D) in the kidneys by 25-hydroxyvitamin D-1-hydroxylase (CYP27B1) (Periyasamy et al., 2020; Chun et al., 2011). Some studies have shown that CYP27B1 is expressed in kidneys and intestine and is also expressed in the innate immune cell, which enables macrophages to produce 1,25D from 25D (Periyasamy et al., 2020; Aranow, 2011). Increased expression of CYP27B1 in macrophages is triggered by recognizing Mtb lipopolysaccharide (LPS) by TLRs in the macrophages (Periyasamy et al., 2020). 1,25D, then induces the production of RONS, antimicrobial peptides such as beta-defensin-4 (DEFB4) and cathelicidin antimicrobial peptide (CAMP/LL-37) in macrophages, thus, enhancing bactericidal activity as

seen in Fig. 3 (Sia et al., 2015; Salamon et al., 2014; Rivas-Santiago et al., 2013). In addition,1,25D enhances autophagosome initiation and fusion with the lysosome and inhibits Mtb growth by regulating the expression of autophagy-related proteins (ATGs) such as ATG5 and Beclin-1 (Campbell and Spector, 2011).

In pulmonary TB, 1,25D also act as an anti-inflammatory agent by inhibiting pro-inflammatory chemokines and cytokines such as IL-23, IL-17, IL-12, and IP-10, while increasing the production of anti-inflammatory cytokines (IL-10, TGF-1, and IL-4) (Kolloli and Subbian, 2017). In vivo studies in TB patients found that combining a high dose of vitamin D_3 with standard anti-TB drugs suppressed antigen-stimulated pro-inflammatory cytokine production and accelerated inflammatory response resolution during treatment, thus improving the clinical and radiology outcomes (Coussens et al., 2012; Salahuddin et al., 2013). Another study demonstrated that a combination of traditional anti-TB therapeutics, vitamin D_3, and phenylbutyrate (PBA), a histone deacetylase inhibitor, stimulated CAMP gene expression and inhibited intracellular Mtb growth in human monocyte-derived macrophages (MDMs) (Mily et al., 2013; Mily et al., 2015). In addition, another clinical trial found that adding PBA and vitamin D_3 to standard chemotherapy lowers Mtb growth in MDMs and speeds up clinical recovery compared to a placebo group (Mily et al., 2015). These findings suggest that vitamin D_3 may play a significant role in treating Mtb when paired with other adjuncts such as PBA (Mily et al., 2015). Despite extensive research, the role of vitamins in the treatment of tuberculosis remains uncertain. Nevertheless, in parts of the world where malnutrition and inherent vitamin shortages impair the immune system, it is tempting to make vitamin supplementation a regular treatment for TB-infected people (Lee and Bhakta, 2021). Therefore, more clinical trials are needed to establish Vitamin D_3's efficacy as HDT in treating drug-resistant TB.

4.2. *Trehalose and autophagy induction*

Trehalose is a naturally occurring disaccharide composed of two D-glucose molecules connected by glycosidic linkage, with the α, α-1,1-trehalose form being the most common in living organisms (Adikesavalu et al., 2021; Vanaporn and Titball, 2020). Trehalose is a vital carbon source for many bacteria and can support bacterial development; therefore, it plays a crucial function in protecting bacteria from various stressors (Vanaporn and Titball, 2020). Bacterial capacity to utilize trehalose as a carbon source might thus explain the found correlations between virulence and bacterial proliferation (Vanaporn and Titball, 2020). However, using trehalose as a carbon source is only likely to benefit infections that thrive in carbon-limited environments, such as outside of host tissues or cells (Vanaporn and Titball, 2020). Trehalose is transformed into several glycolipids present on the cell walls of Mtb and other bacteria; Lipooligosacharide, sulfolipids, polyacyltrehaloses, trehalose 6,6 mycolate (TMM), and trehalose 6,6 dimycolate (TDM) are the essential glycolipids identified in Mtb (Kalscheuer and Koliwer-Brandl, 2014). Many of these trehalose-derived lipids have a role in Mtb pathogenicity and are anti-mycobacterial therapeutic targets (Ghazaei, 2018).

TDM is the most well-known trehalose-derived lipid on the Mtb cell surface. It shields bacterial cells from macrophage killing by inhibiting phagosome fusion with lysosomes and increasing Mtb cell wall Impermeability, resulting in drug resistance (Hunter et al., 2006; Vanaporn and Titball, 2020). On the other hand, Trehalose has been shown to successfully induce autophagy in different cell lines (HEK293T and U937, U1.1) against Mtb and non-Mtb strains, either alone or in combination with HIV-1 infection (Sharma et al., 2021). This is because Trehalose increases the mucolipin transient receptor potential (TRPML)

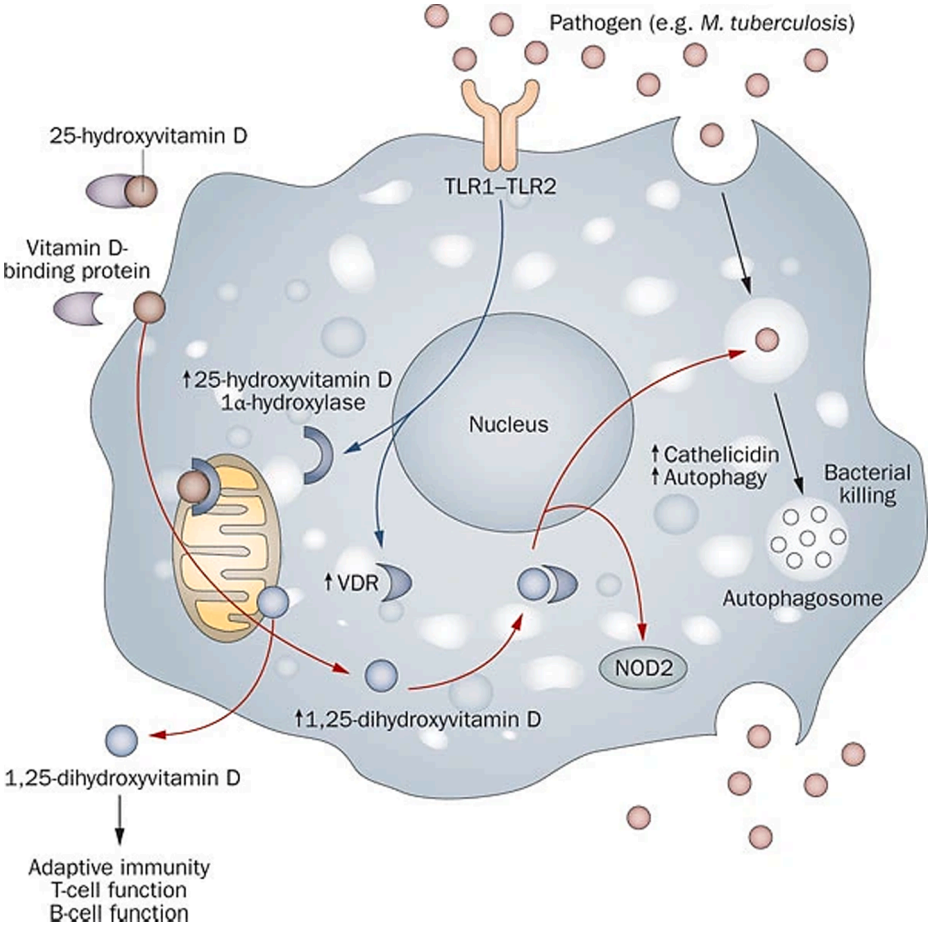

Fig. 3. Induction of autophagy by Vitamin D_3 and its metabolites (Reprinted from Hewison, 2011 with permission).

channel agonist production and therefore increases the release of Ca^{2+} from the lysosomal lumen to promote autophagic flux (Dong et al., 2010). The generated Ca^{2+} stimulates calcineurin, a serine-threonine phosphatase that dephosphorylates Transcription factor EB (TFEB), resulting in TFEB nuclear translocation driven by trehalose and autophagy activation independent of mTOR in macrophages (Sharma et al., 2021).

A more recent study by Sharma et al., 2021 discovered that trehalose therapy significantly decreased bacterial load in H37Rv–infected U937-derived macrophages and that excess trehalose did not interfere with or enhance bacterial growth (Sharma et al., 2021). The study further reported that trehalose also induced autophagy via mTOR inhibition and AMPK activation, resulting in a pseudo-starvation response by competitively blocking glutamate transporters (Sharma et al., 2021). Despite the numerous studies on trehalose and its bactericidal function, the specific mechanism of trehalose-mediated autophagy induction remains unknown; its role in virulence and autophagy induction is a topic that warrants more research.

4.3. *L-arginine and autophagy induction*

L-arginine is a semi-essential amino acid that becomes necessary in certain illnesses and situations (Schon et al., 2003). Dietary consumption and citrulline renal production help keep plasma levels of L-arginine normal (Schon et al., 2003). L-arginine serves as a critical metabolite for many cellular processes in macrophages. It has been shown to improve innate immune function response, particularly when driving macrophage's nitric oxide (NO) production (McKell et al., 2021). Inducible NO synthase (iNOS) catalyzes the synthesis of NO from l-arginine in macrophages activated by TLRs and cytokine (IFN-γ and TNF-α) stimulation (Crowther and Qualls, 2020). The produced NO can kill Mtb bacteria with a molar potency greater than standard anti-TB drugs (Ralph et al., 2013a; Long et al., 1999). Several studies have found that NO concentration correlates with Mtb killing in mice and that mice with low NO concentrations fail to control Mtb infection (Scanga et al., 2001; Garcia et al., 2000; MacMicking et al., 1997). NO and iNOS production has also been detected in human macrophages in vitro and the lungs of Mtb-infected patients, indicating that NO plays a role in human immune responses to Mtb infection (Crowther and Qualls, 2020). In a randomized clinical study of TB patients without HIV infection, arginine supplementation resulted in greater sputum conversion rates, quicker symptom improvement, and an increase in weight gain (Swanson et al., 2002; Schon et al., 2003); These benefits, however, were not observed in individuals with HIV in the same or another study. Another study published in 2013 by Ralph et al. found that decreased pulmonary NO bioavailability is linked to severe illness and delayed mycobacterial clearance. (Ralph et al., 2013b). However, the contribution of NO in the pathogenesis of human Mtb infection remains highly debated and controversial (Crowther and Qualls, 2020; Farazi et al., 2015). Nonsteroidal anti-inflammatory drugs (NSAID), tyrosine kinase inhibitors, inflammatory modulators, antihyperglycemic medications, and other HDT adjuncts with great potential in Mtb therapy are summarised in Table 1.

Table 1
A summary of other potential HDT-TB drugs targeting autophagy and their mechanism of action.

Adjunct-HDT drug	Mechanism of action in mediating innate immune response/autophagy	References
Aspirin	Aspirin enhances vitamin D-mediated anti-mycobacterial effects.	(Tobin and Ramakrishnan, 2013)
Lipopolysaccharides	Activates autophagy and restores Mtb-inhibited immunological function.	(Fang et al., 2020)
PBA and Vitamin D_3	PBA interacts with vitamin D metabolites to increase the production of cathelicidin antimicrobial peptide, which augments Mtb proliferation. Simultaneously, it generates antibacterial and anti-inflammatory responses that benefit the host.	(Mily et al., 2015, Coussens et al., 2015)
Rapamycin	Induces autophagy via mTOR complex inhibition.	(Floto et al., 2007; Gutierrez et al., 2004)
Fluoxetine	Induces autophagy by increasing the secretion of TNF-α.	(Stanley et al., 2014)
Immunoxel	Increases interferon production and boosts the immune system by re-establishing humoral and cellular immunity and enhancing the host's capacity to fight off infectious diseases.	(Efremenko et al., 2012)
Pravastatin	Mediate non-productive inflammation and tissue damage, enhance host bactericidal mechanisms by promoting the macrophage-mediated killing of Mtb and reduce bacterial growth.	(Banerjee and Bhattacharyya, 2014)
Metformin	Increases autophagic flux via enhancing autophagosome-lysosome fusion, and it increases ROS generation	(Efremenko et al., 2012)
Carbamazepine	Reduces MDR-TB burden in the lungs and spleen via depleting inositol triphosphate and activating AMPK.	(Schiebler et al., 2015)
Enbrel	Reduces lung pathology by Neutralizing TNF-α and disrupting granuloma.	(Bourigault et al., 2013)
Bazedoxifene	Enhances autophagosome formation via phosphorylation of mTOR signalling.	(Ouyang et al., 2020)

5. Nanoparticle-based approaches for hdt-tb

The use of NPs as drug nanocarriers or drug delivery vehicles is an emerging approach in the fight against many illnesses. NPs are solid particles with sizes ranging from 10 to 1000 nm (Grotz et al., 2018). When opposed to free drugs, the use of NPs as new immunotherapeutic platforms is attractive for several reasons. To begin with, NPs can encapsulate a high amount of bioactive metabolites that can enhance the immune response against infection (Look et al., 2010). Secondly, they may be made out of materials that can release encapsulated drugs for several days to months at a time (Look et al., 2010; Baranyai et al., 2020). Thirdly, some NPs have innate antimycobacterial activity and serve as a vehicle for various anti-TB drugs, hence being instrumental in reducing the dosing frequency and related side effects (Nabi et al., 2020). Finally, NPs may be extensively modified to improve their bioactivity or distribution to specific cells and organs inside the body (Look et al., 2010). Other benefits include the ability to reduce administered dosages and, therefore, the associated adverse effects and dosing recurrence (Baranyai et al., 2020). NPs desired properties, such as drug-load capacity, cellular absorption, and biodistribution, are influenced by their physicochemical characteristics, such as size, surface charge, hydrophobicity, and composition (Booysen et al., 2013). The material composition and size of the NPs, for example, may be used to adjust the rate of release of an encapsulated substance, and this characteristic has allowed the use of NPs in a variety of applications (Tinsley-Bown et al., 2000; Look et al., 2010).

Bioactive agents for host-directed therapy can also be integrated into NPs by chemical conjugation on the particle surface or by physical encapsulation inside the particle–matrix (Grotz et al., 2018; Nasiruddin et al., 2017). In most cases, the surface of the NP's material is modifiable using ligands, allowing the integrated therapeutics to be targeted to specific cells and organs (Gu et al., 2008; Mohamed and van der Walle, 2008). These ligands can also directly have pharmacologic effects by inducing immunological responses via cell-surface receptor-mediated

signalling events, such as when NPs surface-associated PAMPs stimulate TLRs (Look et al., 2010). NPs are classified into several categories based on their composition, as shown in Fig. 4 and Table 2. Polymeric NPs, for example, are biocompatible and biodegradable materials made from natural or synthetic polymers (Nasiruddin et al., 2017). In comparison, solid lipid NPs (SLNPs) are considered a combination of polymeric NPs and liposomes (LPs) (Grotz et al., 2018). They have a solid lipid core supported by surrounding surfactants, giving them more stability and drug loading capability than LPs on their own (Grotz et al., 2018; Abed and Couvreur, 2014). Based on their composition, other categories of NPs may include micelles, dendrimers, nanogels, inorganic NPs, and nanocapsules (Baranyai et al., 2020).

5.1. Polymeric based HDT-TB drug delivery systems

Polymeric NPs have triggered a vast research interest as a drug delivery system due to their exceptional properties, including passive deposition in the target site, modified release biocompatibility and physicochemical stability (Praphakar et al., 2017). Furthermore, the hydrophilic outer core and hydrophobic inner core of polymeric NPs allow for the entrapment of various drugs within it (Praphakar et al., 2017). Several natural polymer-carriers, including poly (lactic-co-glycolic acid) (PLGA), hyaluronic acid, alginate, carboxymethyl cellulose, and other biodegradable, have been used as nano-based drug delivery systems with high drug loading capacity, drug incorporation feasibility, and variable route of administration feasibility (Hussain et al., 2019). Polymeric-based drug delivery may be engineered for delayed, sustained, and controlled drug release from the matrix (Hussain et al., 2019).

Dube et al. developed a host-directed based polymeric 1,3, Beta-glucan functionalized chitosan PLGA polymeric nanosystem (Glu-CS-PLGA) that increased ROS/RNS, pro-inflammatory cytokine production, and RIF delivery within human alveolar like macrophages (ALM) (Dube et al., 2014). This system further increased ALM secretion of INF-γ (23-fold), IL-12p70 (2.9-fold) and TNF-α (16-fold) over 24 h (Fig. 5), and doubled ROS/RNS production over 6 h (Fig. 6), compared to controls; compared to the RIF solution, Glu-CS-PLGA NPs delivered 4-fold more RIF into ALM (Dube et al., 2014). Recent similar work by D'Souza et al. found that curdlan functionalized PLGA NPs intended for host-directed therapy increased and accelerated the release of pro-inflammatory cytokine TNF-α in macrophages, resulting in lower intracellular Mtb levels within the macrophages (D'Souza et al., 2022). The study also revealed that curdlan has a high affinity for Dectin-1 receptors (D'Souza et al., 2022), giving an advantage in delivering anti-TB therapeutics and AICs directly to macrophages, enhancing drug payload on targeted cells while decreasing immunotoxicity. Furthermore, the study demonstrated that the produced nanosystem was non-toxic, necessitating future research as a host-directed treatment therapy for Mtb intracellular elimination (D'Souza et al., 2022).

In these two separate studies (Dube et al., 2014; D'Souza et al., 2022), the authors' designed drug delivery systems proposed to address the hard-to-treat infectious disease (TB) using NPs modified with ligands that can concurrently modulate the cellular immune response and deliver a drug. Curdlan and 1,3-β-glucan modified PLGA NPs were designed, respectively, following a well-established modified emulsion-solvent evaporation technique. In both studies, the authors showed the effectiveness of designed nanosystems intended for host-directed therapy by applying proteomic techniques such as immunoassays to quantify and analyse various cytokines, producing reliable experimental results. The results obtained in these studies are crucial for future research exploring HDT-TB based nanomaterials and adjuvants.

Sharma et al. investigated the possibility of using PLGA nanoparticles encapsulated with a synthetic Magainin-I analogue peptide (MIAP) as host-directed therapy against TB (Sharma et al., 2018). Porous Nanoparticle Aggregates Particles (PNAP), a micron-sized inhalable platform with nano-scale physiognomies, was created to increase MIAP-peptide delivery and stability. The pathogenic H37Rv TB bacteria was used in antimicrobial and mechanistic research of MIAP-PNAP. The MIAP-PNAP nano-assemblies showed dose and time-dependent antibacterial activity against pathogenic Mtb, considerably lowering the percentage of viable bacteria compared to the non-treated group during 48–96 h in the Mtb infected macrophages shown in Table 3 in detail (Sharma et al., 2018). Furthermore, MIAP nano-formulation improved host defence mechanisms by preventing bacteria-induced inhibition of phagosomal-lysosome fusion and apoptosis, indicating that MIAP-PNAP nanoparticles can be used as an adjunctive host-directed TB therapy to boost the efficacy of standard anti-TB drugs (Sharma et al., 2018).

Rifabutin-loaded Glucan nanoparticles [(RB-NPs)-GP] have also been reported to enhance a robust innate immune response in Mtb-

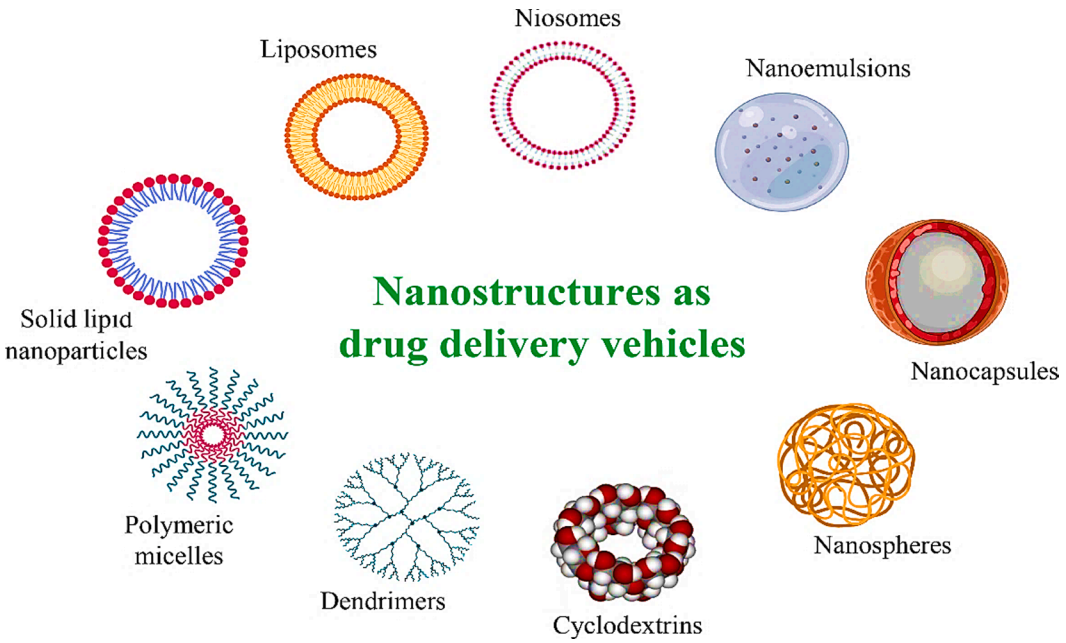

Fig. 4. Different types of the most common nanostructures used as drug delivery systems (Reprinted from Dahanayake and Jayasundera, 2021 with permission).

Table 2
A brief overview of distinct classes of nanostructures as drug delivery vehicles with desirable features employed to deliver host-directed therapeutics and their limitations.

Different classes of nanostructures	Features	Advantages	Limitations	References
Cyclodextrins (CDs) assisted NP drug delivery systems	CD molecules are amphiphilic, consisting of a macrocyclic ring of glucose subunits linked together by α-1,4 glycosidic bonds.	They are safe for oral ingestion since they can bypass gastrointestinal tract absorption and are rapidly removed from the body. They may be used with other NPs to improve hydrophobic drug loading and biological tissue permeability.	Some CDs' derivates, such as - α-CD, and β-CD, are hazardous because they can recrystallize and accumulate in renal tissue, resulting in nephrotoxicity.	(Haimhoffer et al., 2019; Shelley and Babu, 2018; Muankaew and Loftsson, 2018)
Lipid-based nanoparticulate (LNPs) drug delivery systems	They are categorised into several classes based on their synthesis and physicochemical properties, such as Nanostructured lipid carriers (NLCs), which exist as a solid lipid matrix at room and body temperatures like SNLPs but have different interior patterns.	LNPs can integrate lipophilic and hydrophobic drugs with minimal acute and lifelong toxicity. They effectively deter drug leakage and degradation during storage.	They have excessive water content, which can create stability issues, and modification to some crystalline lipids can cause the leaking of the encapsulated drug.	(Khosa et al., 2018; Dhiman et al., 2021)
Polymeric micelles-based drug delivery systems	Polymeric micelles are composed of amphiphilic block copolymers that form nanosized micellar structures with a hydrophobic core and a hydrophilic shell, which provides stability to the micelle.	They can efficiently solubilize various low soluble drugs while encapsulating them within the polymeric micelle core, protecting them against quick clearance from circulation.	Some polymeric micelles are easily degraded when exposed to oxygen, and they have adverse reactions, such as hypersensitive reactions, which may result in anaphylactic shock.	(Jhaveri and Torchilin, 2014; Galetti et al., 2019; Lu and Park, 2013)

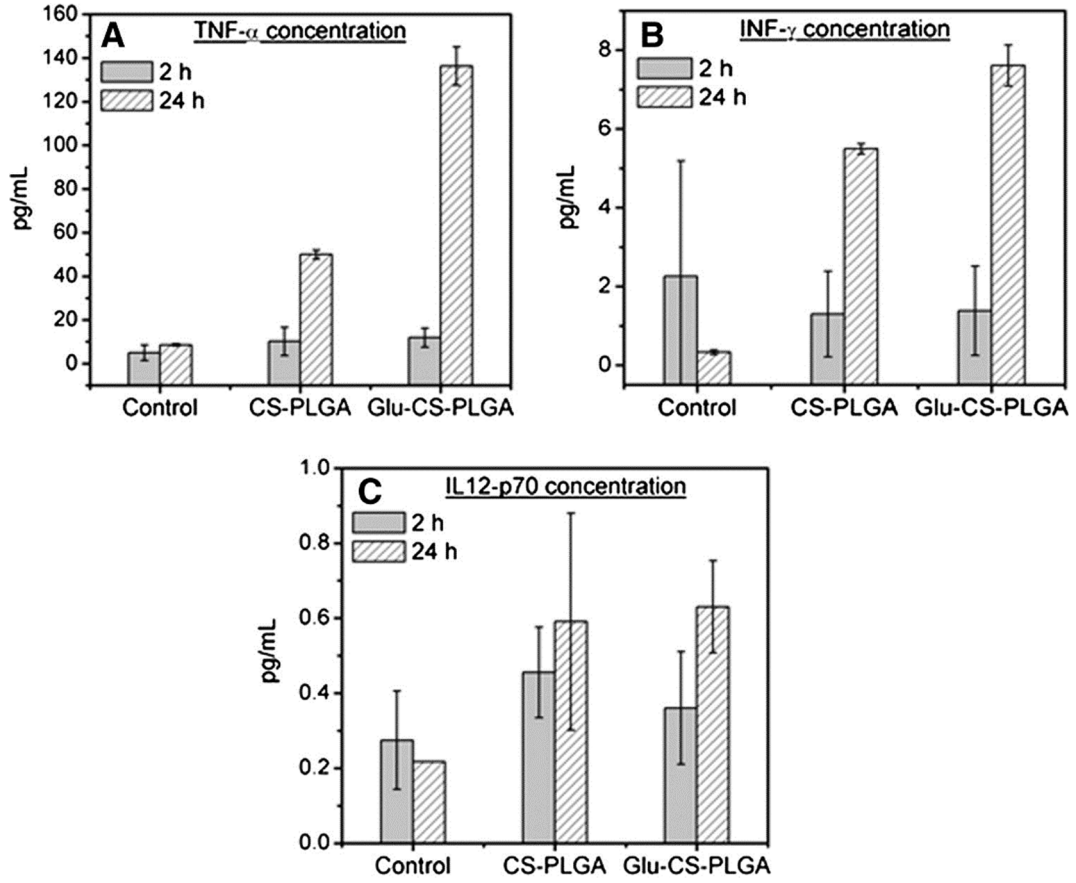

Fig. 5. Results from Dube et al., 2014 showing concentrations of (A) TNF-α, (B) IFN-γ and (C) IL-12p70 in ALM supernatants in different groups after 2 and 24 h. (Reprinted from Dube et., 2014, with permission).

infected J774 macrophage cells, including the production of ROS/RNS, Autophagy, and apoptosis (Upadhyay et al., 2019). The efficacy testing of these NPs in murine macrophages revealed that the (RB-NPs)-GP formulation increased the efficacy of the RB drug by 2.5 fold, implying that the set of innate responses conducive to killing intracellular bacteria elicited by (RB-NPs)-GP play a critical role in impeding intracellular Mtb survival (Upadhyay et al., 2019). This study found that the (RB-NPs)-GP formulation not only activates Mtb-infected, immune-suppressed macrophages for host-directed therapy but also increases the effectiveness of the loaded drug. Thus making (RB-NPs)-GP formulation a viable

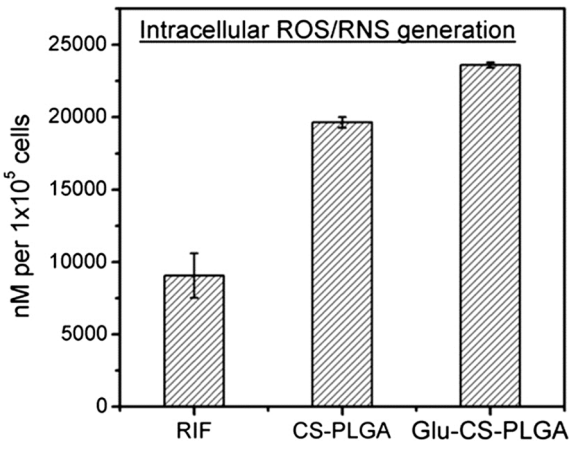

Fig. 6. Results from Dube et al., 2014 showing total ROS/RNS generated after six hours of incubation of ALM with free drug solution (RIF), CS-PLGA, and Glu-CS-PLGA nanoparticles (Reprinted from Dube et al., 2014, with permission).

Table 3
Detailed results from Sharma et al., 2018 showing **the** total number of Mtb CFU recovered after dose- and time-dependent treatment with bare and encapsulated MIAP and INH in a Colony Forming Assay (Reprinted from Sharma et al., 2018, with permission).

Treatment groups	Log10 CFU/ml of Cell lysate			
		24 h	48 h	96 h
	Untreated	6.14 ± 1.15	6.09 ± 1.04	6.21 ± 0.89
Placebo	Blank-PNAP	6.09 ± 0.78	6.08 ± 0.57	5.98 ± 0.51
Isoniazid Solution	INH (3 μg/ml)	2.08 ± 0.31	2.05 ± 0.88	1.25 ± 0.24
MIAP-PNAP group	MIAP-PNAP (10 μM)	5.57 ± 0.57	5.15 ± 0.78	4.92 ± 0.49
	MIAP-PNAP (50 μM)	5.36 ± 1.04	4.25 ± 1.12	4.02 ± 0.48
	MIAP-PNAP (100 μM)	3.65 ± 0.41	3.64 ± 0.74	3.18 ± 0.12
MIAP Solution group	Pure MIAP (10 μM)	5.96 ± 0.54	5.86 ± 0.65	5.53 ± 0.28
	Pure MIAP (50 μM)	5.58 ± 1.08	5.49 ± 1.18	5.41 ± 0.47
	Pure MIAP (100 μM)	5.42 ± 0.19	4.89 ± 0.41	4.64 ± 0.58
MIAP + INH-PNAP	MIAP-PNAP (100 μM) plus INH (1 μg/ml)	2.14 ± 1.26	1.85 ± 1.25	1.17 ± 0.14

strategy that should be investigated further as an alternative or complement to the current TB treatment and host-directed regime (Upadhyay et al., 2019).

N-acetyl-L-cysteine (NAC) is an FDA approved antidote for a hepatotoxic dosage of acetaminophen that has been listed as an essential medicine by WHO (Puri et al., 2022). NAC acts as an antioxidant, mucolytic agent, anti-inflammatory, and antimycobacterial effect by enhancing interleukins and INF-γ production (Amaral et al., 2016). Puri et al. used the double emulsion method to fabricate inhalable NAC modified PLGA mucus penetrating particles for target delivery to AMs, minimizing dose-related adverse effects, efficiently encapsulating hydrophilic drug, with sustained release profile, and prolonging the retention time for the treatment of TB (Puri et al., 2022). Coated NAC-PLGA-MPPs showed favourable results in terms of emitted dose (86%), MMAD value (2.57 μm), GSD value (1.55 μm), and FPF of 62% for deposition and targeting the lungs in an in vitro lung deposition investigation. Finally, in vitro effectiveness experiments revealed that NAC-PLGA-MPPs had more antibacterial activity than NAC alone against the Mtb H37Rv strain (Puri et al., 2022). As a result, PLGA-based particles may be a better strategy for delivering NAC to the lungs while also acting as an excellent HDT-TB agent.

5.2. Solid lipid nanoparticles based HDT-TB drug delivery system

SLNs are made up of polymeric NPs and LPs, as previously stated. Compared to vesicular drug delivery systems and polymeric NPs, SLNPs have longer/higher stability, improved encapsulation efficiency and require a small amount of organic solvents (Nasiruddin et al., 2017). Superior tolerability (owing to their genesis in physiological lipids), scaling up practicality, the capacity to integrate hydrophobic or hydrophilic drugs and enhanced drug stability are the main defining features of SLNPs (Kaur and Singh, 2014). Pereira and colleagues developed a host-directed strategy against Mtb infection by designing a biocompatible nanocarrier for phage-derived protein delivery, using M. smegmatis as a model (Pereira et al., 2015). The rationale behind the study design was that Mtb pathogenicity is strongly supported by the presence of lipids in the cell wall. Thus, its degradation induces bacterial destruction through cell wall hydrolysis (Pereira et al., 2015). The proposed Ms6 LysB-containing lipid nanocarrier (SLN LysB) investigated the known benefits of nano-based systems for selectively targeting phagocytic cells, allowing LysB intracellular accumulation and more effective Mtb infection eradication (Pereira et al., 2015). The adsorption efficiency value suggested the system's potential as a protein nanocarrier.

Furthermore, encouraging results were achieved in host-infected macrophages treated with SLN LysB. The results demonstrated that the proposed technique was more potent than free LysB in preventing the proliferation of M. smegmatis, which might be attributed to nanocarrier internalization (Pereira et al., 2015). The protein-guided delivery in the infected phagocytic cells enabled it to exert its hydrolytic activity on the Mtb lipid layer, indicating the effectiveness of the protein nanocarriers as an alternative host directed-TB therapeutic (Pereira et al., 2015).

In another work, Ma et al. created a mannose-modified macrophage-targeting SLN (MAN-IC-SLN) loaded with the pH-sensitive prodrug of INH to cure latent TB infection. To target macrophages, the surface of SLNs was modified with a synthetic 6-octadecylimino-hexane-1,2,3,4,5-pentanol (MAN-SA), and the modified SLNs demonstrated a greater cell uptake in macrophages than unmodified SLNs (Ma et al., 2021). The prodrug isonicotinic acid octylidene-hydrazide (INH-CHO) was synthesized to produce a pH-sensitive release of INH in macrophages. The pH-sensitive release profile of the INH-CHO-loaded SLNs was observed, with a higher pH medium achieving a more significant cumulative release than a lower pH medium (Ma et al., 2021). M smegmatis was used in place of Mtb. Because of the pH-sensitive degradation of INH-CHO and MAN-SA in SLNs, the MAN-IC-SLNs demonstrated a fourfold increase in intracellular antibiotic effectiveness and improved macrophage uptake (Ma et al., 2021). In the in vivo antibiotic effectiveness test, the SLNs group had a considerably more extensive reduction in colony-forming units than the free INH group. The research found that macrophage targeting and pH-sensitive SLNs might be a suitable platform for latent TB treatment (Ma et al., 2021). SLNs serve as an excellent carrier that can be further modified and employed further for further development of host-directed-TB therapy in future.

Aside from the nano-formulations mentioned above, the area possesses a surplus of other nanocarriers yet to be fully explored in the HDT-TB niche. For example, a dual drug-loaded (RIF and INH) SNLPs system was designed in a more recent work by Banerjee et al., exhibiting a sustained in vitro release pattern. The developed carrier system successfully localized within the various compartments of THP-1, and in vivo tests indicated that the relative bioavailability from the SLNPs was 7.5 times more than that of the drug solution, demonstrating the efficacy provided by SLNPs (Banerjee et al., 2020). In another separate study, a single oral administration of SLNPs formulation enclosing INH resulted in a six-fold increase in plasma drug concentration and a four-fold

increase in brain concentration compared to a free drug at the same dose with improved relative bioavailability (Bhandari and Kaur, 2013). Lastly, SLNPs formulations for pulmonary administration of RIF utilizing stearic acid and taurocholate were also shown to be capable of delivering large drug loads to the lung's AMs, with in vitro studies on the J774 cell line indicating non-cytotoxicity on cells (Maretti et al., 2014).

5.3. Vesicular based HDT-TB drug delivery systems: liposomes and niosomes

Vesicular based drug delivery systems (liposomes and niosomes) are closed vesicles made up of a phospholipid bilayer that encases an aqueous region (Nasiruddin et al., 2017; Hussain et al., 2019). They have been extensively investigated as a potential drug delivery platform for bioactive molecules due to their unique ability to encapsulate hydrophilic and hydrophobic molecules (Nasiruddin et al., 2017; Hussain et al., 2019). Owing to their biocompatibility and biodegradability, vesicular systems as carriers offer immense potential for drug delivery systems; nevertheless, novel LPs systems suffer from a lack of reproducibility and poor stability during storage due to drug-carrier complex alterations (Rodrigues et al., 2003). LPs are phagocytised by macrophagic cells to meet their fate, making them a possible choice for delivering anti-TB therapeutics to the host (Nabi et al., 2020). Niosomes, on the other hand, resemble LPs except that they are made up of a surfactant bilayer with hydrophilic ends exposed to the aqueous phase on the outside and interior of the vesicle and hydrophobic chains facing each other within the bilayer (Hussain et al., 2019; Mozafari, 2007). Niosomes can be employed as orally controlled release systems; for example, orally active anti-TB hydrophilic drugs like INH and PZA demonstrated sustained drug release from the tyloxapol niosomes membrane (Mehta and Jindal, 2013). The biocompatible surfactant tyloxapol in the production of niosomes drug delivery systems encapsulating anti-TB drugs resulted in a very stable nanosystem with considerably increased dissolution rate and high drug entrapment efficiency with no drug-carrier interaction (Mehta and Jindal, 2013).

The key pathogenetic event of Mtb and HIV coinfection is chronic immunological activation (Poerio et al., 2021). In an in vitro model of Mtb-HIV coinfection, Poerio et al. evaluated the therapeutic potential of phosphatidylserine-liposome (PS-L). PS-L inhibited nuclear factor- κB activation and the downstream generation of IL-1β, TNF-α, and IL-6 in BCG-infected macrophages, as well as TNF-α and IL-1 β in Mtb-HIV-coinfected macrophages. Notably, there was a considerable decrease in intracellular Mtb viability and HIV replication (Poerio et al., 2021). These findings suggest that PS-L might be used as a host-directed treatment for Mtb-HIV coinfection in the future.

A novel liposomal adjuvant including N, N-Dimethyltryptamine (DMT), a potent inducer of Th1-biased immune response, dimethyldioctadecyl-ammonium (DDA), and two pattern recognition receptor agonists, monophosphoryl lipid A and trehalose 6,6′-dibehenate (TDB), was developed (Tian et al., 2018). The pCMFO antigen-loaded DDA liposomes were formulated and evaluated with and without monophosphoryl lipid A (MPLA) and TDB. In vivo studies on experimental mice were conducted with various treatments: pCMFO, pCMFO/DDA, or pCMFO/DMT. The immunogenicity and efficacy of BCG-vaccinated mice against Mtb were also compared and assessed. In vaccinated mice, the DDA liposome alone or in combination with TDB or MPLA triggered early IL-17 and interferon responses (Tian et al., 2018). Thus, the controlled release function of the DMT liposome may be linked to the improved efficacy of DMT (adjuvant) vaccination against TB, illustrating the practical benefits afforded by liposomes (Tian et al., 2018).

Kulkarni et al. synthesised dual drug-loaded self-assembled niosomes containing ethionamide and D-Cycloserine to treat MDR-TB effectively. Box Behnken design was used to improve the niosomes, which were then evaluated for the antibacterial test, osmotic shock and in vitro haemodialysis, among other studies (Kulkarni et al., 2019). The haemodialysis tests demonstrated that dual drug-loaded niosomes may be safely administered intravenously and that dual drug-loaded niosomes had the lowest MIC compared to pure drug and single drug-loaded niosomes. The delayed release of lipophilic ethambutol and the early burst release of D-Cycloserine contributed to its efficacy (Kulkarni et al., 2019). As a result, the synergistic impact of two drugs in niosomes proved to be an efficient TB therapy (Kulkarni et al., 2019). In a separate study, Rani et al. investigated the bactericidal activities of prepared niosomes of RIF and gatifloxacin against sensitive (H37Rv) and resistant (RF 8554) Mtb strains, revealing inhibition and a reduced bacterial growth index, indicating that niosomes provided an extensive release of drugs, allowing for a lower dose, fewer days of treatment, and greater patient compliance (Rani et al., 2010). However, because most studies on NPs with potential HDT-TB applications around the world have gone unnoticed, there has been a scarcity of data on the use of liposomes and niosomes for host-directed therapy in TB. Table 4 summarizes some nanosystems that can be investigated further for use as host directed-TB

Table 4
Summary of anti-mycobacterial nanoparticles-based carries that can be employed for HDT-TB.

Drug/s encapsulated	Nanocarrier composition material	Outcome observed or achievements	References
RIF	Gelatine NPs	Better biodistribution of RIF and higher blood levels in mice.	(Saraogi et al., 2010)
INH	Monnosylated Gelatine NPs	Reduced bacteria in TB-infected mice and hepatotoxicity of the drug.	(Saraogi et al., 2011)
RIF	CS-coated PLGA NPs	Enhanced intracellular trafficking and drug concentration compared to free drugs.	(Kutscher et al., 2019)
RIF	Solid-lipid NPs	Increased RIF levels into alveolar macrophages.	(Chuan et al., 2013)
RIF	Monnosylated Cationic lipid NPs	Higher uptake efficiency by alveolar macrophages was observed.	(Song et al., 2015)
RIF and ascorbic acid	CS-coated alginate-tween 80 NPs	NPs significantly suppressed Mtb at the same concertation when compared to free drug and enhanced cell viability even more.	(Scolari et al., 2019)
INH/RIF	Chitosan NPs	It improved in vitro and in vivo efficacy of INH/RIF compared to free drugs.	(Pourshahab et al., 2011; Garg et al., 2016)
RIF	Lactose conjugated PLGA NPs	Significantly Increased lung uptake of RIF.	(Jain et al., 2010)
Tuftsin	Pluronic F127 coated PLGA NPs	Significantly increased internalization of the drug within the macrophages.	(Horvati et al., 2018)
RIF	Poly (ethylene oxide) monomethyl ether-block poly(e-caprolactone) NPs	The NPs were easily taken up by the macrophages and quickly associated with the lysosomal compartment.	(Trousil et al., 2017)
INH	Mycolic acid-PLGA NPs	Increased uptake and fusion with lysosomes containing mycobacteria.	(Lemmer et al., 2015)

therapies in the near future due to their favorable observed outcomes.

5.4. Delivery of NPs to targeted host

Material modification with suitable transport mediating molecules can further assist with the preferred NPs delivery route, which could be via the gastrointestinal system, topical, urogenital tract, or pulmonary route as shown in Fig. 7 (Woodrow et al., 2009; Look et al., 2010). As a result of these distinct properties, NPs can be easily loaded or coupled with immunomodulatory substances such as immune cell-specific ligands or cytokines and be administered through various routes to improve immunity against infectious disease (Look et al., 2010). In Mtb treatment, oral, intravenous, and pulmonary delivery of nanocarriers has shown great potential, with oral administration as the most preferred delivery route (Baranyai et al., 2020). Because oral administration is less intrusive and more convenient, it may boost patients' compliance to complete the treatment (Plapied et al., 2011, Baranyai et al., 2020). However, the extreme environment present in the stomach, medium–low pH and highly proteolytic media – as well as the hepatic first-pass metabolism, restrict the possible formulations that may be used and impairs bioavailability (Plapied et al., 2011). While Intravenous administration bypasses the first-pass metabolism, allowing drugs to be absorbed quickly and directly into the systemic circulation while allowing for more accurate administered dosage control (Monopoli et al., 2012).

In pulmonary TB, direct targeting of the Mtb with pulmonary administration is the most promising approach because it allows for far more efficient therapy with lower administration doses and lower toxicity than the oral route (Costa et al., 2016; Baranyai et al., 2020). Most anti-TB drugs have low water solubility, low biodistribution, and adverse effects when administered orally; therefore, pulmonary delivery is more efficacious and promising (Costa et al., 2016). The significantly improved bioavailability also advances the use of the pulmonary route since the activity of the drug-metabolizing enzymes is restricted compared to parental routes of administration (Costa et al., 2016). It can also improve patient compliance because it is non-invasive and self-administrable (Momin et al., 2019). The respiratory system's structure and function, on the other hand, play a role in pathogen defence; as a result, overcoming anatomical and biological obstacles in the respiratory system might be difficult (Baranyai et al., 2020).

6. Conclusion and future research perspective

Several potential research and development opportunities exist in using immunomodulatory nanoparticles for improving infectious disease outcomes, particularly in the treatment of Mtb infection. Despite the tremendous work done to contain the Mtb pandemic, Mtb has developed numerous strategies to circumvent the host's protective response. The rise in Mtb resistance to a range of current anti-TB therapeutics has become a global health concern. As a result, developing novel therapeutic techniques has become the main priority. At least three new requirements necessitate extra attention in developing immunomodulatory nanoparticle-based therapies for Mtb infection: Multidrug-resistant infection, co-infection with several diseases (HIV/TB), and host-directed treatment. Nanotechnology solutions coupled with immunomodulatory agents/AICs as part of HDT therapies (HDT-TB) may assist in meeting this demand by increasing treatment regimen efficacy, minimizing the development of drug-resistant strains, and possibly decreasing the frequency and expense of dosing while boosting the host's immunological response to infection. This will further enable more targeted drug delivery, reducing harmful side effects while increasing drug concentration in target cells.

Despite many AICs and NPs accessible, there is still a small amount of research on using AICs and therapeutic NPs to treat Mtb.

Aside from reducing treatment time and antibiotic effectiveness, another objective of host-directed TB therapy is to prevent irreparable lung damage caused by an ineffective inflammatory response. Immunocompetent individuals with active TB have significant pro-inflammatory immune responses that fail to control bacterial growth, resulting in tissue damage and ineffective inflammation. As a result, numerous AICs that have the potential to minimise non-productive inflammation and potentially severe tissue damage may be explored

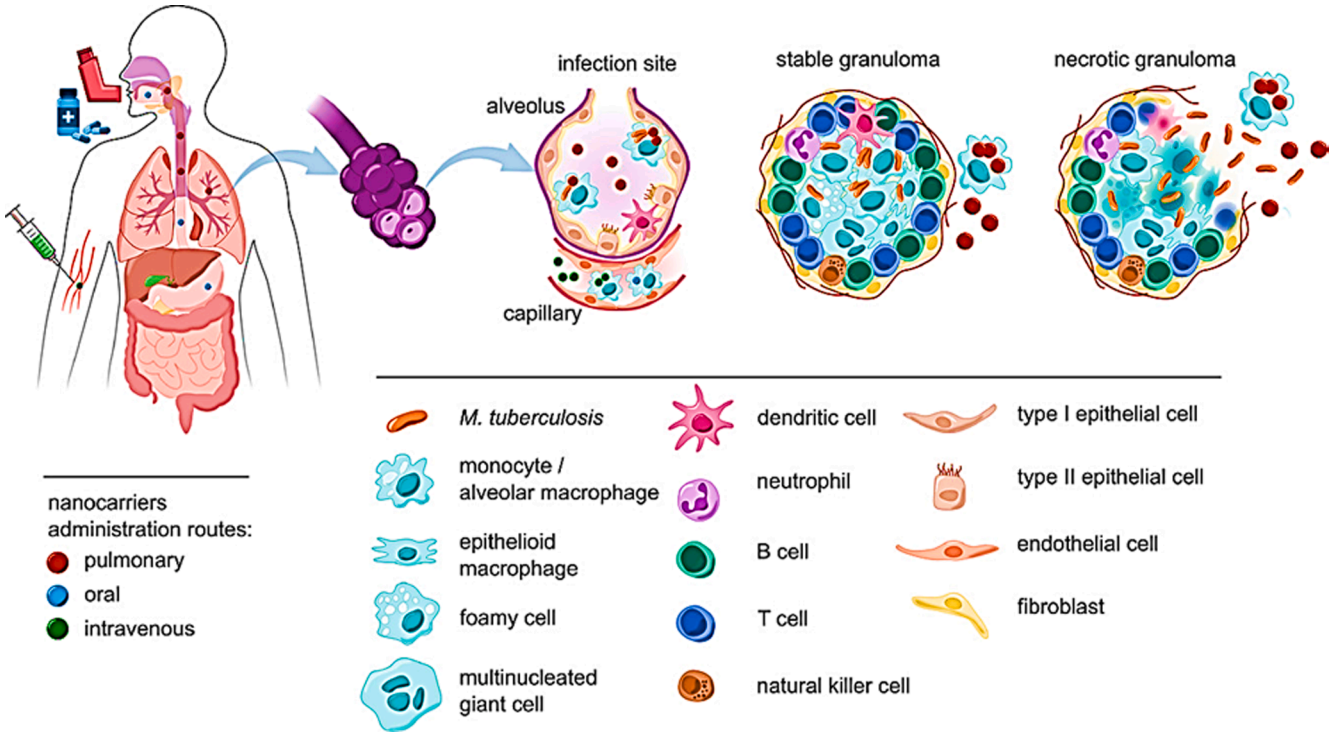

Fig. 7. Different routes of nanoparticles administration targeting the host and granuloma (Reprinted from Baranyai et al., 2020, with permission).

further by incorporating them into NPs for active targeting. Matrix metalloproteinase inhibitors, TNF antagonists, and corticosteroids are examples of these. Modulation of individual immunosuppressive immune responses, on the other hand, may increase the immune system's innate bactericidal activity and hence speed up bacterial clearance. As a result, repurposing immunosuppressive reagents such as phosphodiesterase inhibitors, Treg-depleting immunotherapies, and anti-IL-10 therapies may benefit the HDT-TB strategy.

In addition, many vitamins have been studied for their involvement in pathogenic and bactericidal activity. Further investigation into these vitamins combined with nanotechnology and traditional anti-TB therapeutics may further pave the way forward for HDT-TB therapeutics. As discussed in section 4.1, supplementing standard anti-TB therapeutics with some vitamins decreased antigen-stimulated pro-inflammatory cytokine production and expedited inflammatory response resolution throughout therapy, improving clinical and radiological results. This, in combination with nanotechnology, may further allow for lower doses of standard anti-TB therapeutics, resulting in a shorter treatment duration and the development of treatment-resistant TB.

In conclusion, mechanical elements of the macrophage response to Mtb and its Inhibition of Autophagy must be explored further to enable rational nanomedicine design against this infection. Although nanotechnology and HDT-TB appear promising, they have not provided any product in the market for this disease, and the number of patents in the sector is significantly low due to limited safety and biocompatibility profiles. To make ground-breaking progress, concerns regarding nanotechnology biocompatibility must be addressed regarding their application as immunomodulators. As a result, developing clinical effectiveness, cost, accessibility, and toxicity studies will boost the overall value of new HDT-TB therapies and nanotechnology, paving the way for commercialisation.

CRediT authorship contribution statement

Leon J. Khoza: Writing – original draft, Investigation. **Pradeep Kumar:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Admire Dube:** Supervision, Writing – review & editing. **Patrick H. Demana:** Methodology, Writing – review & editing. **Yahya E. Choonara:** Conceptualization, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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