Tuberculosis (TB) is a major global health problem, and Mycobacterium tuberculosis (M. tuberculosis) has infected one-third of the world’s population.\(^1,2\) There were 10.4 million new cases and 1.8 million deaths due to TB in 2016.\(^2\) M. tuberculosis enters the human respiratory system through the inhalation of aerosols, typically through coughing. M. tuberculosis then colonizes inside alveolar macrophages and forms granuloma. After infiltration, M. tuberculosis is ingested by phagocytosis by resident alveolar macrophages and tissue dendritic cells.\(^3,4\) Finally, the immune cells are contributed, and the pathological mark of TB, the granuloma, is formed. In the granuloma, macrophages differentiate into epithelioid cells or foamy macrophages, or fuse to form giant cells and become surrounded by lymphocytes, fibroblasts, and extracellular matrix proteins. M. tuberculosis survives until the granuloma fails due to immunosuppression.\(^5,6\) In fact, M. tuberculosis uses the granuloma for their benefit upon initial infection, recruiting new macrophages to allow spread between host cells.\(^7\) In active tuberculosis, the caseous granuloma center contains necrotic macrophages. When the granuloma rupture, spillage of M. tuberculosis into the airways achieved, and M. tuberculosis also allows spread to new individuals.\(^5,6\)

The main component of TB pathogenesis is that the bacilli survive, grow, and replicate within the host macrophages. These attributes are partly thanks to the ability of M. tuberculosis to prevent maturation of
the phagosome by blocking phagosome integration with lysosomes to form the phagolysosome. It has been proven that the successful parasitization of macrophages is a clever action by which M. tuberculosis keeps away the immune response of the host cells.

M. tuberculosis can also attenuate human immunological function through replicating within macrophages as target cells. The intracellular replication of M. tuberculosis into the macrophages finally led to the death of macrophages and the release of extracellular pathogens. Support of M. tuberculosis into the macrophages requires that the pathogen continuously set up the infection into the sensitive macrophages.

The treatment of patients with multidrug-resistant M. tuberculosis and extensively drug resistant M. tuberculosis strains has become a serious challenge. The treatment of patients with TB requires long-term use of multi-drug regimens. Some of these multi-drug regimens interact with other antibacterial drugs, increasing the possibility of drug toxicity. Studies indicate that rifampicin can induce liver injury in mice, and some antitubercular drugs have hepatotoxicity effects. Therefore, there is always a need for simple, long-term, and effective antitubercular drug regimens to treat M. tuberculosis.

Researchers found that the mixed colloidal silver (Ag) and zinc oxide (ZnO) metallic nanoparticles (MeNPs) can inhibit M. tuberculosis H37Rv, even within THP-1 cell lines. In addition, mixed AgZnO nanocomposites can also eliminate H37Rv M. tuberculosis and MDR-TB after phagocytosis by the THP-1 cell lines. Recent studies show that mixed AgZnO nanocomposites and rifampicin have synergism effects against M. tuberculosis. In the last years, researchers concentrated on preparing co-delivery mixed MeNPs containing antitubercular antibiotics encapsulated to non-toxic and biodegradable polymers. Of course, the toxic effects of MeNPs on THP-1 and normal human lung cells (MCF-7 cell lines) should be considered.

Studies show that MeNPs in human tissues and cell-cultures produce several toxins that can increase the oxidative stress and production of inflammatory cytokines. MeNPs might contribute to the apoptosis of cells. MeNPs can penetrate through the cell membrane bilayer, mitochondria, and the nucleus. Thus, they might destroy the mitochondria and cause mutations in DNA. The size, dimensions, chemical composition, shape, surface structure, surface charge, density, and solubility of MeNPs are major factors determining toxicity. Studies also indicated that the initial concentration of MeNPs plays a key role in their toxicity against human cells, especially in THP-1 cell lines.

This work’s major objective was to introduce MeNPs as a growth inhibitor of M. tuberculosis and inducers to phagosome maturation into the infected macrophages. Given this goal, we investigated the survival mechanisms of M. tuberculosis into macrophages and presented the novel chemicals, phytochemical, and encapsulated mono-metallic or bimetallic Ag, ZnO, and gold (Au) antitubercular MeNPs to inhibition of intracellular M. tuberculosis and gallium (Ga) MeNPs to enhance phagosome maturation. We also evaluated the role of magnetic iron (Fe) MeNPs as nanocarriers of antituberculosis drugs.

**M. tuberculosis pathogenesis**

TB is known as an airborne disease caused by M. tuberculosis. M. tuberculosis and M. tuberculosis complex species, including M. bovis, M. africanum, M. microti, M. caprae, M. pinnipedii, M. canetti, and M. mungi may cause disease in humans.

Mostly, TB infection arises when people suffering from pulmonary or laryngeal TB disease have a cough, sneeze, shout, or sing, and another person inhales droplets, including TB bacilli. TB bacilli then try to reach the alveoli of the lungs through the upper respiratory tract and bronchi. The infected droplets are around 1–5 mm. After that, bacilli are phagocytosed to form tubercles in the tissue-resident alveolar macrophages to the inflamed region. Under the week host defense conditions, bacilli may survive for a long time as a source of post-primary infection into the alveolar macrophage. In fact, macrophages that failed to kill the mycobacterial invaders produced chemo-attractants such as chemokines. Chemokines were produced by resident alveolar macrophage and pneumocytes, which invite neutrophils, monocyte-derived macrophages, NK cells, and T cells, which increase inflammation. Then, the cells formed hard shell structures known as granulomas. In this condition, the tubercle bacilli remain in the ‘dormant state’ inside macrophages in the granulomas for years [Figure 1].

In the active form of TB, bacilli can also replicate into the host macrophage, break down the macrophage cell membrane, and is released outside...
The bacilli released from the demolished macrophage move around through the lymphatic system and bloodstream to the brain, larynx, lymph nodes, lung, spine, bones, or kidneys, which is known as military TB.

There are several issues in terms of the efficiency of anti-TB antibiotics. First, there is no direct correlation between the plasma concentration of anti-TB antibiotics and its intracellular concentration. Furthermore, the intracellular activity of anti-TB antibiotics is justified by the rate of internalization, excretion rate, cell transformation, and pH. Moreover, anti-TB antibiotics have a flexible internalization and intracellular accumulation path. In addition, anti-TB drugs may not penetrate granulomas. One of the other critical challenges is the limitation of the administration routes and the prolongation of TB treatment. We know the intracellular survival of *M. tuberculosis* in the host cell pertains to its adaptation-evading of the immune system, dissemination, and selection of aggressive and multi-drug resistant (MDR-TB). Studies have

**Antibiotics therapy challenges in the treatment of *M. tuberculosis* into the macrophage**

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**Figure 1:** The infection pathways of *Mycobacterium tuberculosis* in human macrophage cells leading to the formation of a granuloma (1–4). Resident alveolar macrophages phagocytes inhaled *M. tuberculosis* and produces the pro-inflammatory response and recruitment of fibroblasts, lymphocytes, neutrophils, natural killer (NK) cells, collagens, necrotic tissues, dendritic cells, foamy macrophages, infected apoptotic macrophage, infected apoptotic epithelial macrophages, and epithelial macrophages, and the formation of a granuloma. However, if the human immune system for any reason is weakened, *M. tuberculosis* is activated and replicated within the granuloma structure. In this case, the necrotic nucleus of granuloma develops. When the number of *M. tuberculosis* is increased within the granuloma, it ruptures, and *M. tuberculosis* is spilled into the airways. Each of the bacteria has the potential to infect other alveolar macrophages to the formation of a new granuloma.
shown that the azithromycin could accumulate completely in phagolysosomes; however, it had vastly low antimicrobial efficiency on pathogens. Comparably, moxifloxacin was not only unable to accumulate in the phagolysosome but also has high antimicrobial efficiency.

25 Cellular accumulation of antibiotics and some local environmental conditions (such as pH) are important parameters for intracellular activity. 25

Survive mechanisms of M. tuberculosis in macrophages
Knowing the intracellular adaptive mechanisms for the survival of M. tuberculosis into the macrophages is essential in formulating convenient therapies. M. tuberculosis has adaptive mechanisms that run away from the human immune system, especially macrophages. These mechanisms will be discussed below.
Prevention the Fusion of Primary Phagosomes with Lysosomes

*M. tuberculosis* can interfere with the transformation of the primary endosomes and phagosome maturation, and subsequently, the fusion with lysosomes is delayed or blocked [Figure 2].

*M. tuberculosis* also can prevent the transformation of primary endosomes into phagolysosome by the reduction of levels of proton ATPase inside the endosomes. *M. tuberculosis* can prohibit connecting of the inducible nitric oxide synthase (iNOS). Studies show that *M. tuberculosis* is also able to eliminate the phosphatidylinositol 3-phosphate [Figure 2].

Demolition of Endosomes or Early Phagosomes Walls and Escape into the Cytosol

*M. tuberculosis* can elude from the degradation in phagolysosomes by demolishing the endocytic vesicle wall and entering the cytosol. Escaping the endocytic vesicle is an essential step in the intramacrophage survival for *M. tuberculosis* in the cytosol [Figure 2]. In 2003, Jafari et al. recorded images showing some of the *H37Rv* strain of *M. tuberculosis* escaping from the phagolysosomes and arriving in the cytosol [Figure 2].

Brown et al. discovered that *M. marinum* is also able to escape from its phagolysosome and move around by the motive force of actin through Arp2/3 complex-mediated actin reorganization dependent on activation of WASP. Besides this, proteins secreted by *M. tuberculosis*, such as ESAT-6, play important roles in virulence. Escaping from the phagosome depends on ESAT-6 alone or in complex with its chaperone CFP-10 (ESAT-6: CFP-10) [Figure 2].

These proteins lead to increased replication rates in the cell cytoplasm. In addition, more likely to the mycobacterial cell envelope can be mistaken...
for a phagosome membrane due to its lipid-rich structures. One explanation for the presence of cytosolic *M. tuberculosis* in some preparations is that it exists of host triacylglycerol in both the prevention of phagosome maturation and persistence in granulomatous lesions.

**INTERNALIZATION IN MACROPHAGES BY NON-PHAGOCYTIC PATHWAYS WHICH ARE NOT LIKELY COUPLING WITH LYSOSOMES**

Internalization of *M. tuberculosis* in macrophages by non-phagocytic pathways involves interactions between *M. tuberculosis* and the membrane of the macrophages causing the formation of vesicles. Macrophage's internalization is achieved by coupling of *M. tuberculosis* with lipid rafts and receptors of which mediate a non-phagocytic endocytosis.

Studies indicated that the synthetic antimicrobial polymers have the ability to induce membrane lysis and bind to the genomic material of mycobacteria, thereby inducing mycobacterial cell death and was also able to kill the intracellular mycobacteria effectively without inducing any toxicity to mammalian cells. Yavvari et al. showed that synthetic antimicrobial polymers has clathrin-independent penetration and escape from hydrolytic lysosomal degradation and effectively kill the intracellular bacteria. *M. tuberculosis* also can interact with the macrophage apoptotic mechanisms to increase expression of anti-apoptotic molecules such as Bcl2.

**The entrance pathway of particles into the macrophage**

Macrophages have the ability to engulf opsonized NPs, modified mannose, IgG, and many complements larger than 500 nm, including *M. tuberculosis* from phagocytic pathways. Macro-pinocytosis is an actin-dependent pinocytic pathway by which macrophages can engulf droplets of extracellular fluid within large vacuoles formed by the fusion of a plasma membrane extension with non-extended plasma membrane. It may be more likely that the macro-pinocytosis pathway is for the swallowing of agglomerated particles. In other words, the macrophage can use macro-pinocytosis pathways to engulf agglomerated particles, ligand-modified NPs, viral NPs, and polyethylene glycol NPs.

Studies indicated that ligand-modified NPs and some viral NPs can enter into the macrophage by specific receptors such as clathrin-mediated, caveolin-mediated, or clathrin/caveolin-mediated pinocytosis. Interestingly, MeNPs and dendrimers with dimensions between 4 and 10 nm can directly penetrate macrophages [Figure 3]. Based on the transmission electron microscopy images of previous study, THP-1 cells exposed to Ag and ZnO NPs could penetrate the cell bilayer membrane and enter the cell [Figure 3].

**The role of phagosomes maturation in antitubercular properties**

The phagocytosis of *M. tuberculosis* is thanks to the role of receptor-mediated phagocytosis of macrophages. After phagocytosis of *M. tuberculosis*, the phagosome is formed, and subsequently, a series of fusion events is achieved into endocytic pathways called 'phagosomal maturation.' The phagosome of which interact with endosomes and then lysosomes obtain a wide range of antimicrobial properties designed to completely destroy *M. tuberculosis*. The phagosomal maturation stages in macrophages can be identified based on the proteins present on the phagosomal membrane. In fact, the proteins correspond to the endosome type with which the phagosome has interacted. The connection between the phagosome and endosomal network and lysosomes have two hypotheses; the kiss and run-hypothesis and the fusion hypothesis. In addition, phagosomes can obtain hydrolases from the 6-thioguanine nucleotide. A microtubule-based transport system also is more likely to be responsible for providing the scaffold for endosome movement. In addition, membrane rafts and glycol lipoprotein microdomains play a key role in phagosomal maturation. The fusion and fission events eventually occur in an oxidative, acidic, and degradative phagolysosome environment, which is designed to eliminate invading microbes effectively. In fact, the main antimicrobial mechanisms of the mature macrophage phagosome are as a result of acidification, activation of the NADPH oxidase NOX2, activation of iNOS, antimicrobial peptides, and protein degradation.

**The intercellular antitubercular impact of mono-metallic/bimetallic nanoparticles and nano metallic carriers**

The MeNPs are accepted as antitubercular agents that destroy the integrity of bacterial membranes.
The MeNPs are potentially capable of attaching and sticking to the cell wall of *M. tuberculosis* and subsequently destroy it, mechanically. In general, the toxicity of MeNPs is thanks to oxidative stress and free radicals called reactive oxygen species. Conceptually, antitubercular mechanisms of MeNPs arrived from the interaction between the *M. tuberculosis* and NPs, as well the bio-reactive properties of the dissolved ionic fraction [Figure 3].

Ag and ZnO NPs are considered antibacterial agents against pathogenic bacteria. It was reported that Ag NPs increase bacterial cell permeability by motivating the aggregation of proteins in the periplasmic space, forming nano-sized pores in the bacterial membrane. Increasing bacterial membrane permeability may facilitate increased penetration of intracellular antibiotics. Zn is a natural metal used by alveolar macrophages to increase bactericidal pressure against internalized *M. tuberculosis* within the endosome. For this reason, ZnO NPs can interact with the membrane of bacteria, which leads to the formation of surface pores and the release of intracellular nucleotides. To date, many researchers have synthesized the colloidal, nanocrystals, and encapsulated antitubercular Ag and ZnO NPs by chemical and biological methods [Figure 3].

**CHEMICAL MONO/BIMETALLIC SILVER AND ZINC OXIDE ANTITUBERCULAR NANOPARTICLES**

In 2017, Jafari et al. synthesized colloidal Ag and ZnO NPs using chemical reduction and deposition methods. The average size of colloidal Ag and ZnO NPs was estimated at 13±3.14 nm and 4±0.88 nm. They reported that the colloidal Ag NPs were not able to eliminate intracellular *M. tuberculosis* into the macrophages, completely (minimum inhibitory concentration (MIC) ≥ 25 ppm). Whereas, the colloidal ZnO NPs demonstrated antitubercular behavior in the macrophage against *M. tuberculosis H37Rv*, but it was toxic against MCF-7 cell lines ex-vivo. Based on this assumption, 0.663 ppm of 5Ag:5ZnO not only was able to kill *M. tuberculosis H37Rv* but also showed the lowest cytotoxicity effects on MCF-7 and THP-1 cell lines. They also synthesized a mixture of Ag/ZnO nanocrystals by oxalic reduction method with an average size of 12 nm. The results showed that mixture nanocrystals were not able to eliminate *H37Rv* strain of *M. tuberculosis ex-vivo*. It seems more likely that the ability of metallic colloidal NPs to penetrate macrophages is more than agglomerated metallic nanocrystals. Furthermore, the antituberculosis properties of MeNPs likely arise from the formation of metal ions in the aqueous medium, and subsequently due to penetration into the macrophage [Figure 3].

**ENCAPSULATED OF SILVER AND ZINC ANTITUBERCULAR NANOPARTICLES**

Studies show that Ag and ZnO NPs encapsulated into a biodegradable and biocompatible polymer such as poly lactic-co-glycolic acid (PLGA), forms a multi-metallic microparticle. Encapsulated NPs have the ability to transport antibiotics into *M. tuberculosis*-infected macrophages. Co-delivery of Ag and ZnO NPs into a larger micron-sized carrier collaborated to selective metallic/metal oxide NPs uptake by macrophages through passive targeting, initial burst release of ions from the encapsulated Ag and ZnO NPs, and eventually, reduction of metallic/metal oxide NPs toxicity [Figure 3]. Pati et al., in 2016, synthesized Zn and rifampicin, and encapsulated it into transferrin-conjugated Ag quantum-dots to improve delivery in macrophages. They found that encapsulated Zn and rifampicin into the transferrin-conjugated Ag quantum-dots NPs play a pivotal role in increasing antitubercular activity compared to Zn-rifampicin, rifampicin, and Zn [Figure 3].

**PHYTogenic MONO-METALLIC/BIMETALLIC SILVER, ZINC, AND GOLD ANTITUBERCULAR NANOPARTICLES**

Biosynthesis of antitubercular MeNPs should be taken into consideration due to its economic feasibility, low toxicity, and simplicity of the procedure. Punjabi et al., synthesized extracellular Ag and ZnO NPs with an average size of 40 and 60 nm by *Pseudomonas hibiscicola*. The MICs value in both of Ag and Zn NPs against *H37Re* strain and MDR strain of *M. tuberculosis* were reported as 1.25 mg/mL. Banu and Rathod reported antituberculosis activity of biosynthesized Ag NPs against *M. tuberculosis* and clinical isolates of MDR-TB. Ag NPs were biosynthesized utilizing the alcoholic extract of *Plumbago auriculata* and used to investigate the antitubercular effects against *M. tuberculosis*. Ag NPs with an average size of 15–45 nm showed antitubercular activity with a MIC value of 1.6 μg/mL. In 2016, Singh et al.,...
synthesized Ag, Au, and bimetallic Ag/Au NPs using *Barleria primotis* leaf extract, *Plumbago zeylanica* root extract, and *Syzygium cumini* bark extract. The Ag NPs synthesized using the *Psidium guajava* leaf extract demonstrated an inhibitory effect on *M. tuberculosis*.56 Bimetallic Ag/Au NPs were able to inhibit 90% of mycobacterial growth at 3 μg/mL, and it presented great mycobactericidal potency in contrast with Ag NPs alone.56 Bimetallic Ag/Au NPs possessed the high efficiency to inhibit *M. tuberculosis* ex-vivo THP-1 infection model [Figure 3].56,57

GALLIUM NANO PARTICLES

The antimicrobial activity of gallium nanoparticles has been investigated against *M. tuberculosis*10,58 and nontuberculous mycobacterial pathogens, *M. avium* complex, and *M. abscessus*.59 Gallium and Fe have similar chemical properties. Gallium can interfere with Fe acquisition by microorganisms.10 Recently, the blocking of Fe acquisition by the gallium compound in *M. tuberculosis* is confirmed. Gallium has the ability to reduce the growth of intracellular *M. tuberculosis* into the macrophage.10 A report stated that gallium NPs can also interfere with Fe acquisition in *M. tuberculosis* and inhibit intracellular growth within macrophages.10 Another study reported that gallium NPs show significant growth inhibition of *M. tuberculosis* in THP-1 macrophages on days three and six after infection.10 Macrophages infected with *M. tuberculosis* H37Ra exhibited significantly higher expression of cathepsin D – an aspartic endoprotease that is distributed in lysosomes – compared to galactin 3, a member of the beta-galactoside-binding protein family that plays an important role in macrophage activation as well.10 The authors of the study found that uptake of gallium nanoparticles by macrophage led to the promotion of phagosome maturation and subsequently led to increase the antituberculosis effects of the macrophage.10 To sum up, gallium nanoparticles can deliver a drug to macrophages, inhibit *M tuberculosis* and nontuberculous mycobacterial growth,59 and reduce the inhibition of phagosome maturation [Figure 3].10

IRON NANO PARTICLES AS A NANO CARRIER

Iron, an essential nutrient for nearly all living cells, plays a critical role in many important enzymatic reactions as a cofactor. Its ability to redox cycle between Fe(II)/Fe(III) enhances electron transfer.10 In humans, Fe is tightly bound to transferrin, lactoferrin, ferritin, and heme. Pathogenic bacteria must acquire Fe mainly from these Fe complexing proteins for growth and metabolism. Many pathogens possess highly efficient Fe uptake mechanisms. These bacteria release Fe solubilizing (chelating) compounds, siderophores, to obtain Fe (III) from host Fe-binding molecules for growth. Carboxymycobactin and mycobactin are mycobacterial siderophores that chelate Fe (III) extracellularly and intracellularly, and are critical to the virulence of these organisms in vitro and in vivo.10

*M. tuberculosis* within the phagosomes of macrophages can acquire Fe from extracellular transferrin and sources within the macrophage.60 Lu et al.61 in 2018, synthesized encapsulated Fe/O hyperbranched polyester-(2-dodecen-1-y1) succinic anhydride2-Dodecen-1-/isoniazid magnetic NPs with controlled drug release characteristics. They suggested that this encapsulated microparticle containing Fe exhibited good drug release properties and might be suitable to treat TB. In 2017, Saifullah et al,62 designed a novel antitubercular multifunctional formulation containing fabricating graphene oxide with iron oxide magnetite NPs as a nanocarrier of ethambutol. They found this formulation had prolonged sustained release of ethambutol and could reduce the dosing frequency for the treatment of *M. smegmatis* compared to ethambutol alone.62 El Zowalaty et al,63 prepared streptomycin-loaded, chitosan-coated magnetic NPs. Remarkably, the MIC of this formulation against *M. tuberculosis* was 732 μg/mL [Figure 3].

CONCLUSION

A real therapeutic advance in terms of elimination of intracellular *M. tuberculosis* can be done merely by fulfilling careful studies in the field of nanotherapy. Using metal NPs in therapies of respiratory infection may contribute to achieving effective TB treatment. The key role of MeNPs in medicine are diagnosis and target therapy; however, it seems that the time has come to use of antitubercular MeNPs in the treatment of intercellular *M. tuberculosis*. MeNPs and metal ions can penetrate throughout bilayer infected macrophage membrane due to the small size and relative mobility. They can also freely attach to *M. tuberculosis* of which immerse in the cytosol and even may penetrate phagolysosomes. Mixing of colloidal MeNPs can also be a good way
to increase antibacterial properties and, in turn, reduce the toxicity of MeNPs to human cells. In addition, a mixture of MeNPs can be considered suitable for co-delivery along with antituberculosis drugs to eliminate intracellular *M. tuberculosis* into the macrophages and even granuloma. Further advances are needed in terms of changing the concept of nanotechnology into a realistic medical application as the next generation of intracellular antituberculosis drugs.

**Disclosure**

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