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# Functionalized Polydopamine Nanoparticles: A Promising Drug Delivery Platform for the Treatment of Tuberculosis

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## ABSTRACT

Tuberculosis (TB) is considered a major infectious disease by the World Health Organization. The WHO estimates that there are 1.8 million TB deaths, and 10.4 million new cases of the disease reported yearly. While there are conventional therapies for TB, they have drawbacks such as a lengthy pill regimen, rigorous scheduling, and protracted treatment duration, which can result in strains of the disease that are multidrug-resistant (MDR) and extensively drug-resistant (XDR). Future TB control is at risk due to the emergence of MDR strains. This worry has made the hunt for a successful remedy necessary. One biomedical innovation has been the application of nanotechnology, which offers a fresh avenue of treating TB. Such nanotechnology approach includes Polydopamine (PDA) nanoparticles which have demonstrated the ability to reduce these difficulties. In recent times, PDA, which is an intriguing bioinspired polymer, has become a material of choice for designing drug delivery nano-systems. In fact, PDA nanoparticles show several intriguing characteristics, such as easy manufacturing approach, biocompatibility, the ability to scavenge free radicals, and photothermal and photoacoustic features. It is easily functionalized to promote blood circulation, cellular absorption, and drug release, among other functions. As a result, this review has examined the various PDA functionalization techniques aimed at overcoming MDR and enhancing TB treatment.

## 1 | Introduction

Tuberculosis (TB) is one of the deadliest diseases caused by a type of bacteria called "*Mycobacterium*" that primarily damages the lungs which is the organ most frequently infected with, with around 85% of patients' report having lung problems (Nunn et al. 2019). The infectious agent in TB, however, tends to infect any area of the body, most often the kidney, spine, and brain, although not everyone who has the TB germs in them always get sick. These traits allow two types of TB infection to be distinguished from one another: (i) TB disease and (ii) latent TB infection (LTBI) (Yadav 2023). Although TB therapy has made great strides, there are still a number of problems with the available treatment options. Anti-TB medicines face significant obstacles in their successful delivery and penetration due to the intricate host-pathogen interactions and distinct milieu found within TB lesions. Immunological barriers and the varied character of granulomatous lesions make it difficult for treatment drugs to effectively reach and remain at the infection site (Yadav 2023). One of the biggest obstacles to treating TB is drug resistance, which can develop in the bacteria in response to several conventional therapy medicines (Ball 2018). Drug resistance is the decrease in an antimicrobial agent's ability to inhibit bacteria or treat disease. The *Mycobacterium*

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tuberculosis (MTB) can develop resistance to several drugs by resisting the effects of the two most potent anti-TB medications, isoniazid and rifampicin (Chen et al. 2016). The rise of drug-resistant strains of MTB, which reduces the effectiveness of traditional antibiotics and lengthens treatment periods, is one of the main obstacles (Sandhu 2011). The enormous global burden of TB, especially in settings with low resources, adds to the complexity of treating the disease (Koch et al. 2018). This calls for the creation of cutting-edge tactics that can successfully target and eradicate these resistant strains. Nanotechnology platforms, such as the use of nanoparticles (Figure 1), have been promoted as novel strategies for treating TB to solve this difficulty. The use of PDA nanoparticles as a therapy for TB has shown promise (d'Ischia et al. 2014). The unique characteristics of these nanoparticles make them perfect for fighting TB. Surface-functionalized PDA nanoparticles enable precision targeting and regulated drug release, which is especially important for overcoming physiological hurdles in the treatment of TB. These techniques must be specifically designed to negotiate the complex topography of TB pathophysiology.

A major obstacle that frequently results in patient non-compliance and incomplete therapy is the extensive and taxing treatment regimens related to TB (Valencia et al. 2017). Surface-functionalized PDA nanoparticles are a promising solution to this problem because they provide a controlled and prolonged release of the drug, which may lower the frequency of drug administration and increase adherence to therapy. Moreover, it is crucial to have access to treatment modalities that are both affordable and effective, which highlights the need for creative solutions that can maximize therapeutic results while consuming the fewest resources possible (World Health Organization 2011). Considering these difficulties, the development of surface functionalization methods for PDA nanoparticles presents a viable remedy that conforms to the complex requirements of TB. This could lead to an effective tackling of the complex issues associated with current TB treatment modalities and ultimately provide more accessible and effective TB interventions. This review thus highlights the potential of PDA nanoparticle functionalization approaches towards overcoming the difficulties associated with drug resistance and therapeutic failure in the treatment of TB.

## 2 | Overview of TB Management

### 2.1 | Biochemistry of TB

The pathogenic process of active TB is divided into seven distinct stages as depicted in Figure 2. These processes include granuloma formation, TH1 response, phagolysosome obstruction and replication, aerosolization, macrophage phagocytosis, clinical symptoms, and transmission. A) The pathophysiological cycle of TB starts and ends with aerosolization. When an individual with active TB coughs or otherwise exhales aggressively, aerosolization takes place. B) A vulnerable individual will encounter monocytes, dendritic cells, and macrophages if they inhale aerosolized MTB and droplets tiny enough to enter the alveolar sacs (shown in the first magnification). As seen in the second magnification, macrophages that invade will phagocytose the microbes and try to eliminate the invader. T-helper cells will be activated by dendritic cells migrating to lymph nodes. C) MTB starts reproducing, releases DNA, RNA, proteases, and lipids, resists destruction, and stops the phagolysosome fusion. Furthermore, vascular endothelial growth factor (VEGF) and cytokines will be released by the macrophages. VEGF promotes vascularization to the lesion by inducing angiogenesis and the cytokines triggers the innate

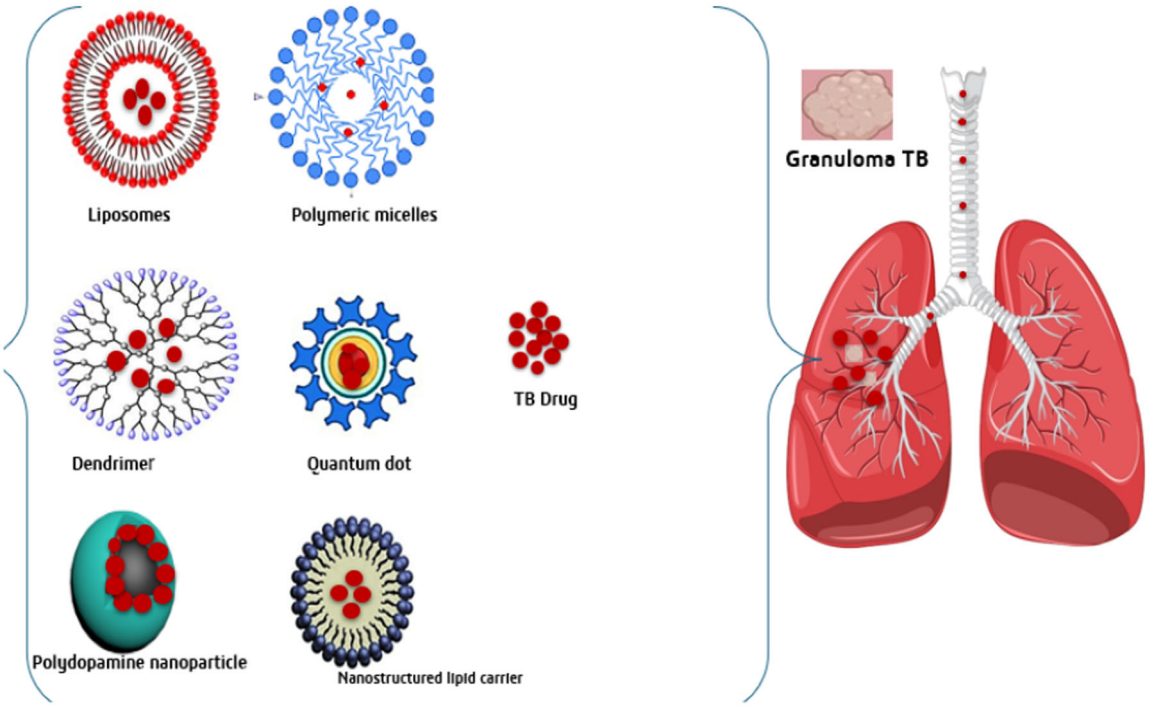



**FIGURE 1** | Schematic illustration of nanoparticle drug delivery in the treatment of TB infected lungs adapted from (Dahanayake and Jayasundera 2021).



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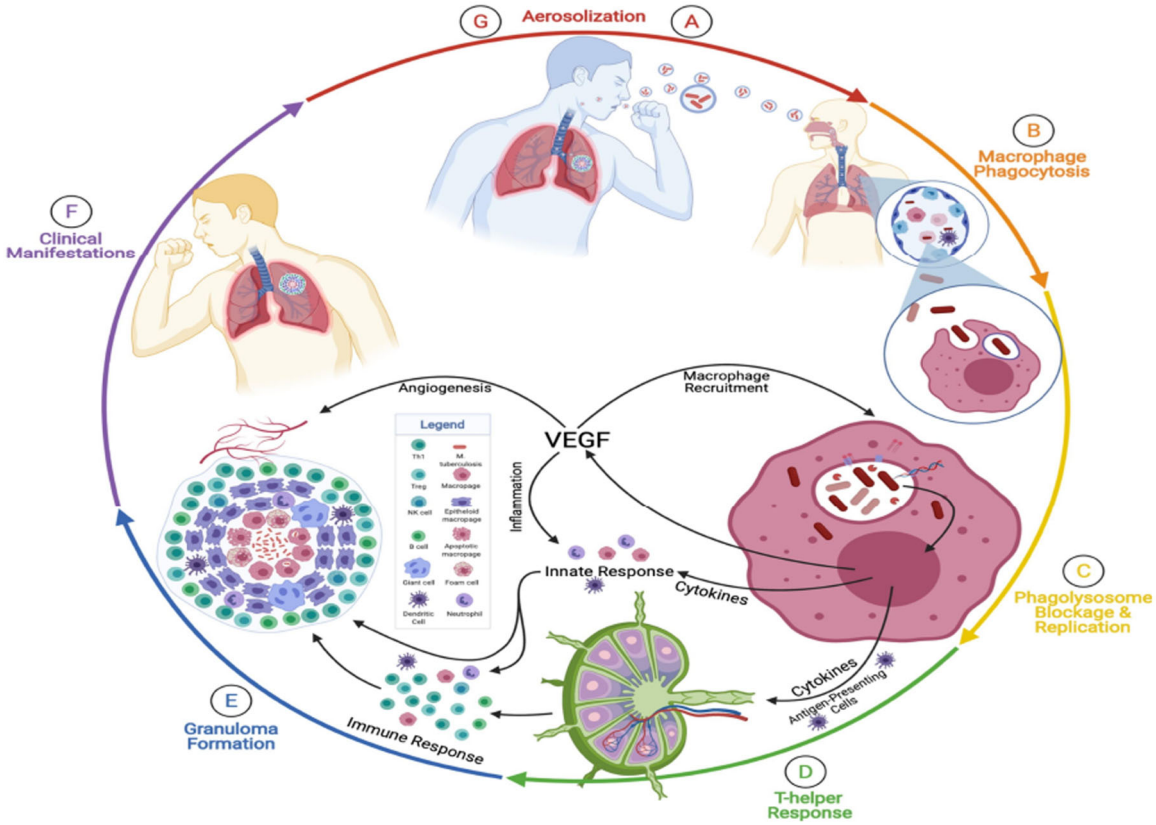



**FIGURE 2** | The illustration of the seven pathophysiology steps of active TB. These steps are aerosolization, macrophage phagocytosis, phagolysosome blockage and replication, $T_H1$ response, granuloma formation, clinical manifestations, and transmission (Maison 2022:2).

response and draw in various types of neutrophils, macrophages, dendritic cells, and natural killer (NK) cells. D) TH1, Tregs, and B cells primed in the germinal center will migrate as part of the T-helper cell response. The granuloma is formed by the combination of these cells (E). To prevent the bacteria from spreading throughout the body, the granuloma acts as a jail. F) Immunocompromisation, either present or later, stops the granuloma from holding the germs, the bacteria will proliferate and spread. G) The bacteria may be aerosolized by the initial susceptible host, who has recently been infected, during this phase, restarting the cycle (Maison 2022: 3).

## 2.2 | Existing Drugs for TB Management

The term "management of tuberculosis" refers to methods and strategies used to treat TB, or simply a TB treatment strategy. A short-term course of treatment consisting of isoniazid, rifampicin (sometimes called Rifampin), pyrazinamide, and ethambutol for the first 2 months is the recommended clinical treatment for active TB (Figure 3). Isoniazid and pyridoxal phosphate are given together during this early stage to prevent peripheral neuropathy. For the final 4 months of treatment, isoniazid and rifampicin are administered together (6–8 months for miliary TB). After 6 months of treatment for pulmonary TB or eight to ten months for miliary TB, a patient should be rid of all viable TB bacteria. Isoniazid alone is used to treat latent TB or latent TB infection (LTBI) for three to 9 months (Sterling et al. 2011). Hepatotoxicity is frequently a danger of this prolonged treatment. It has been demonstrated that taking isoniazid and rifampicin together for between three and 4 months is a comparably effective way to treat LTBI while lowering the danger of hepatotoxicity to stop active TB from spreading, LTBI treatment is crucial (Nunn et al. 2019).

## 2.3 | Drug Mechanism for TB Treatment

Early days of TB burden were marked with the lack of chemotherapeutic drugs, diagnostic *x*-ray facilities, and TB control programs, which led to the emergence of the sanatorium movement around the globe. The popular justification for sanatoria was that the best possibility of the patient's immune system "walling off" TB infection was provided by a regimen of rest, healthy food, open fresh air, and high altitude (Heidary et al. 2022). Chest radiography was later introduced as a TB diagnostic tool. However, the first real victory over the disease was immunization against TB using the BCG (bacillus of Calmette and Guerin) vaccine, created from an attenuated bovine strain of TB (Doherty and Andersen 2005). TB management has improved over the years, a testament to continuous research and drug development. Currently, the recommended treatment for drug sensitive (DS) TB involves the combination of 4 antibiotics, namely: rifampicin, isoniazid, ethambutol and pyrazinamide (Sotgiu et al. 2015). These drugs are administered in phases for a minimum period of 6 months while patients' compliance is closely monitored to ensure treatment success (Zumla et al. 2013). Although these drugs are effective, they present several adverse effects including gastrointestinal tolerance, peripheral neuropathy, central nervous



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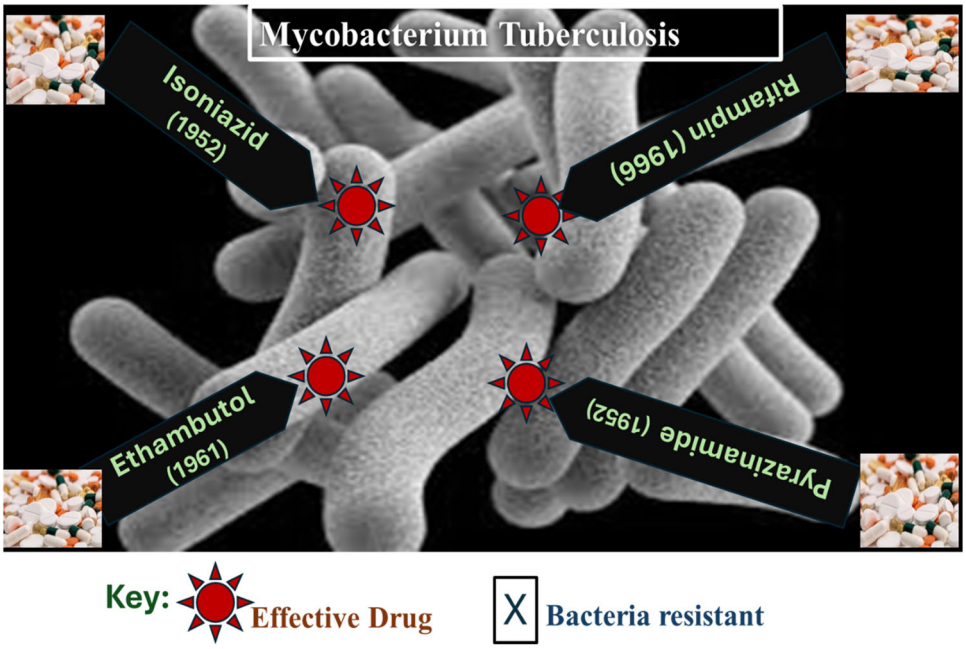



**FIGURE 3** | Demonstration of the first-line drugs used for TB treatment: Isoniazid, Pyrazinamide, Ethambutol and Rifampicin and year of approval adapted from (Rossini and Dias 2023).

system toxicity, liver dysfunction, skin rashes and erythromelalgia. These unwanted side effects, in addition to prolonged duration of treatment and discomfort of swallowing multiple pills, lead to poor patients' compliance and misuse of the antibiotics, resulting in the development of multidrug resistant (MDR) TB strains (Yee et al. 2003; Chiang and Schaaf 2010; Alsayed and Gunosewoyo 2023). Drug resistant TB presents a complicated challenge with regard to clinical management as the approach depends on the resistance pattern.

MDR-TB is classified as resistance to rifampicin and isoniazid, which are the two most potent first-line anti-TB drugs. According to WHO guidelines, detection of MDR-TB is done using culture methods and rapid molecular tests to confirm TB bacteria as well as drug resistance. Treatment for MDR-TB was initially designed to last for 18–20 months, however, in 2020, WHO recommended a shorter oral regimen (9–11 months) to enable easier treatment completion by patients. This treatment is called the second-line regimen for MDR-TB, consisting of a cocktail of four drugs, three from group A (bedaquidine, linezolid, moxifloxacin/levofloxacin), and one drug from group B (clofazimine, or terizidone/cycloserine) (WHO 2020). It is recommended that bedaquidine is only used for 6 months, while at least three of the other drugs are prescribed for the rest of the treatment period as part of the continuation phase (usually for 5 months) after bedaquidine is stopped. For MTB strain resistant to one or more of group A and B drugs, drugs from group C (streptomycin/amikacin, ethambutol, pyrazinamide, delamanid, ethionamide/prothionamide, high dose isoniazid) should be added (WHO 2020; Alsayed and Gunosewoyo 2023). Occasionally, extensively drug-resistant (XDR)TB may develop. These are subset of MDR-TB (i.e. TB resistant to isoniazid and rifampicin) with additional resistance to one or more fluoroquinolones (e.g moxifloxacin or levofloxacin) and second-line TB drugs (such as amikacin) (Nahid et al. 2019). XDR-TB present a very serious challenge due to limited treatment options, resulting in high mortality and projects the danger of returning to the sanatorium era when antibiotics were not available (Alsayed and Gunosewoyo 2023). Generally, MDR-TB and XDR-TB are treated for longer periods, could be up to 2 years, compared to DS-TB. The second-line drugs recommended for these TB strains are generally more expensive, toxic and less effective than the first-line anti-TB drugs (Ginsberg and Spigelman 2007). All these compound patients' adherence issues lead to the spread of drug-resistant TB in the community. Indeed, despite significant efforts and successes recorded with TB treatment, the challenge of effective anti-TB drugs, particularly with regard to the treatment of MDR-TB, remain. Therefore, improvement of TB drug development channel with precise and highly efficient delivery systems should facilitate revolutionary TB therapies for better outcomes.

## 3 | Smart Properties of Polydopamine Nanoparticles

Dopamine, which is white, self-polymers to create polydopamine (PDA), a black biopolymer that is colorless in alkaline solutions with molecular oxygen. It is composed of monomers of dopamine, indoledione, and dihydroxyindole bound by covalent bonds. Dopamine polymerization produces PDA nanoparticles (Figure 4), which are highly attractive for drug delivery and biomedical applications because of their biocompatibility, ease of manufacture, and adaptability in surface modification. These nanoparticles possess natural ability to bind to different biological surfaces. This intrinsic adhesiveness of PDA nanoparticles is one of their most useful smart properties, as it enables targeting of diseased cells or tissues, thus, particularly useful for delivering drugs to infected cells or tissues in a targeted manner (Fan et al. 2016). PDA's ability to bind to nearly any substrate is inspired by the binding capabilities of proteins found in mussels, which accounts for its popularity in



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**FIGURE 4** | Structural presentation of PDA and drug loaded PDA nanoparticles adapted from (Wang et al. 2019).

chemical and pharmaceutical industries (Smith et al. 2019). Additionally, PDA nanoparticles' adjustable nature enables exact control over drug loading and release kinetics, potentially providing a remedy for the problems associated with drug resistance in TB treatment (Palanisamy et al. 2016).

As an end oxidation product of dopamine or other catecholamines, PDA has garnered a lot of interest as a flexible coating that can be applied to nearly any substrate to provide a conformal layer with a thickness that can be adjusted to approximately 100 nm (Amin et al. 2017). These PDA layers can then be changed by adding metallic nanoparticles from solutions containing metallic cations or molecules with nucleophilic groups. The reaction products that are concurrently obtained from the oxidation of catecholamines in solution precipitate during the PDA film's deposition on the surfaces. This enables surface modification with appropriate chemical moieties to produce desired effects. PDA is thought to be the best-suited polymeric carrier for drug delivery applications, according to investigations on drug delivery. Demonstrating this, Städler et al. proved that PDA-coated liposomes increased myoblast cell adhesion and proliferation and that cells with thicker PDA coatings had lower fluorescence intensity (Bedhiafi et al. 2023). This suggests that the polymerization time may regulate the amount of PDA absorbed by cells, indicating that PDA may be used as a vehicle for delivering other PDA applications, such as cell imaging and sensing (Bedhiafi et al. 2023; Xu et al. 2023). PDA has recently gained popularity as a coating material due to its use in the modification of the surface characteristics of Teflon microchannel walls, thus, enabled the creation of Teflon chips with PDA modifications (Goel et al. 2024). PDA has also been utilized for drug encapsulation. The chemotherapeutic substance doxorubicin was entrapped within PDA capsules as a potential drug carrier, and the results showed that this boosted the drug's ability to eradicate HeLa cancer cells when compared to free drug, thus, highlights the encapsulation efficacy of PDA nanoparticles as a delivery platform (Hao et al. 2019). Importantly, determining PDA's toxicity is an essential step in assessing its uses in nanomedicine (Goel et al. 2024).

## 4 | Significance of PDA Nanoparticle Functionalization Chemistry in TB Treatment

The way in which nanoparticles interact with biological systems and how effective they are as targeted drug delivery platforms depends critically on how their surfaces are functionalized. The chemistry of surface functionalization has a crucial role in determining the specificity of PDA nanoparticles against MTB and in maximizing the delivery of anti-TB drugs when used in TB treatment (Carmignani et al. 2022). Surface functionalization (Figure 5) entails the chemical conjugation of certain ligands or antibodies onto the surface of PDA nanoparticles. Numerous chemical reactions and modification approaches, each specifically designed to assure the effective and selective attachment of targeted moieties, can be used to accomplish this (Zhu and Su 2017). Selecting the right functionalization chemistry is essential for the nanoparticles to be able to identify and attach to the pathogen in a targeted manner, improving the delivery of anti-TB medications. Also, PDA nanoparticles' surface functionalization adds new chemical moieties that may affect how they interact with biological settings. In order for the nanoparticles to be effective in treating TB, it is essential that their stability, biocompatibility, and precise targeting abilities be determined by the chemical characteristics of the functionalized surface (Hong et al. 2012). The chemistry of surface functionalization affects not only selective targeting but also the regulated release of anti-TB drugs from the nanoparticles. Researchers can precisely control the release kinetics of pharmaceuticals, assuring appropriate therapeutic concentrations at the infection site while avoiding systemic exposure, by designing specific chemical links and responsive functions into the surface modifications. Therefore, tackling the difficulties brought on by medication resistance in tuberculosis requires an understanding of the chemistry of surface functionalization (Ball et al. 2012).

Understanding the chemical principles governing nanoparticle interactions with MTB is essential for designing and engineering surface modifications that improve the bypassing of bacterial defense mechanisms and enable effective intracellular drug delivery. Drug-resistant TB presents obstacles that could be overcome, and tailored drug delivery methods could be revolutionized,



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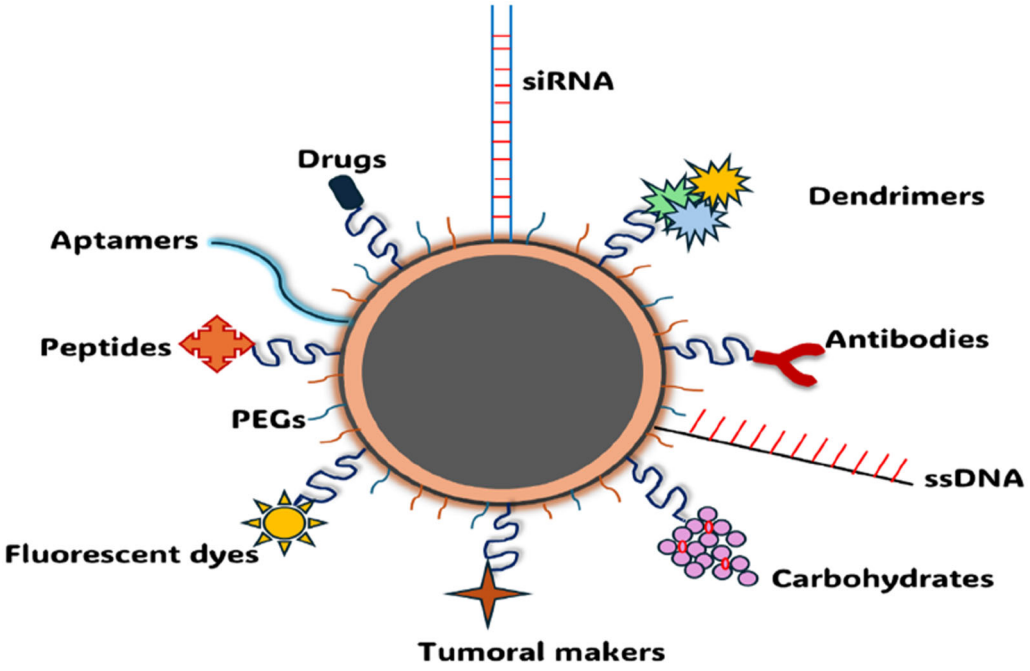



**FIGURE 5** | Diagrammatic illustration of multi-functionalized nanoparticles with different targeting agent adapted from (Conde et al. 2014).

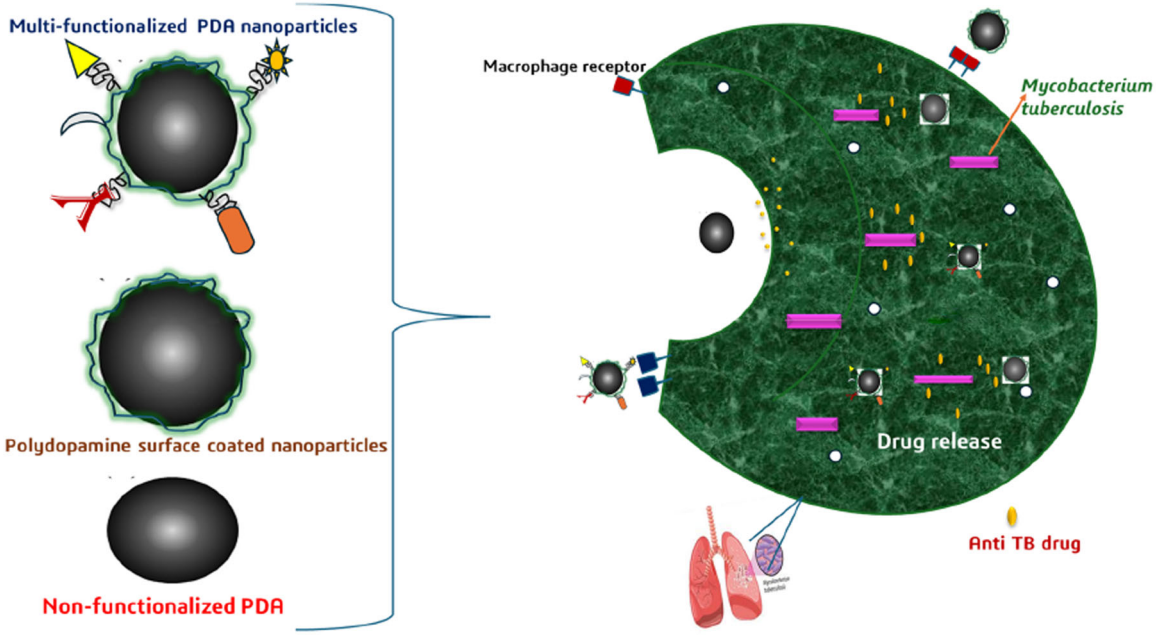



**FIGURE 6** | Demonstration of PDA nanoparticle functionalization and the drug release in TB treatment adapted from (Wu et al. 2021).

opening the door to more individualized and successful treatment approaches. This is all made possible by the complex understanding and manipulation of nanoparticle chemistry (Huang et al. 2021).

## 5 | Innovative PDA Nanoparticles Functionalization Strategies

As the exploration of PDA nanoparticles in TB treatment advances, various functionalization strategies have emerged, each with unique approaches to address the complexities of combatting the disease. These strategies encompass a spectrum of innovative techniques aimed at enhancing the efficacy of PDA nanoparticles in targeted drug delivery (Figure 6) and tailored therapeutic interventions for TB (Kumar et al. 2023). Some of these innovative strategies with their specific TB treatment purposes have been summarized in Table 1.

### 5.1 | Surface Modification Strategy

Surface modification of PDA nanoparticles (Figures 6 and 7) involves the attachment of ligands or antibodies that can recognize and bind to specific biomarkers expressed on the surface



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**TABLE 1** | Applications of novel PDA nanoparticles and derivates for TB drug delivery.

| Material | Preparation technique | Application | Innovative PDA nanoparticles | Ref. |
|---|---|---|---|---|
| Pluronic F126, dopamine hydrochloride, Tris (dimethyl amino)methane, D-mannose | Ultrasonication | Photothermal and host immune activated therapy of cutaneous TB | macrophage targeted mesoporous PDA nanoparticles | Fan et al. (2024) |
| Graphene oxide, norepinephrine hydrochloride, dopamine hydrochloride, gold nanoparticles, | Simplified Hummers and Offeman approach | Biosensing of MTB | Bio-inspired polynorepinephrine based graphene oxide/gold PDA nanoparticles composite | Bisht et al. (2023) |
| Graphite flakes, dopamine hydrochloride, Avidin-biotin coupling, | Hummers modified method, self-polymerization | Rapid and early MTB detection | reduced graphene Oxide-PDA-Gold nanoparticles | Chaturvedi et al. (2023) |
| poly(lactide-co-glycolide), alginate, dopamine hydrochloride, calcium chloride, isoniazid | Dip coating/casting method | Osteoarticular TB | Dopamine-assisted fixation of drug-loaded polymeric multilayers | Li et al. 2017 |
| Dopamine hydrochloride, PLGA, polyethylene glycol, | Conjugation via amide reaction | MTB fusion with protein to induce comprehensive immune responses | poly(I:C)-decorated PLGA-PEG dopamine modified nanoparticle | Du et al. (2022) |
| $Ti_3AlC_2$, dopamine hydrochloride, biotinylated single-stranded probe DNA (ssDNA), noncomplementary DNA | Self-polymerization | Early and sensitive detection of MTB | PDA functionalized $Ti_3AlC_2$ MAX electrochemical biosensor | Goel et al. (2024) |
| Silver nitrate, dopamine hydrochloride, rifampin | Self-polymerization and In Situ reduced silver ion | Enhanced antibacterial activity against MDR Strain of MTB | Rifampin loaded Mussel-Inspired silver nanoparticles | Yu et al. (2021) |



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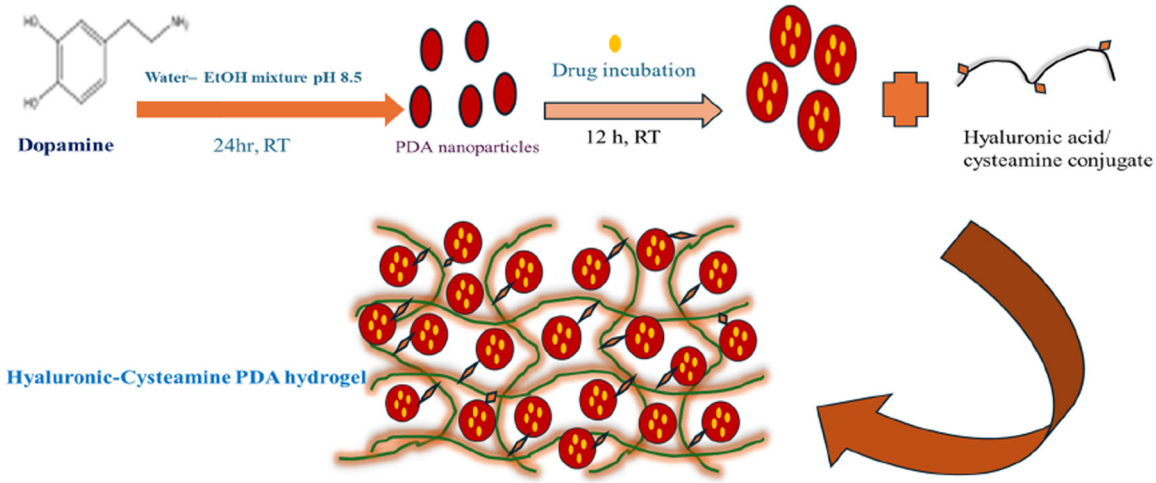



**FIGURE 7** | Depiction of surface functionalized hyaluronic acid PDA nanoparticles adapted from (Yegappan et al. 2019).

of TB-infected cells. This allows for enhanced targeted delivery of the therapeutic agents encapsulated within the nanoparticles, increasing their efficiency in reaching and entering the infected cells (Singh et al. 2024). By specifically targeting TB-infected cells, surface-modified PDA nanoparticles can bypass healthy cells, resulting in reduced off-target effects and improved overall treatment outcomes. Functionalization of PDA nanoparticles with ligands specific to TB-associated receptors or antigens enables enhanced targeting of the nanoparticles to infected macrophages, the primary host cells for MTB (Chehelgerdi et al. 2023). Chaturvedi et al. (2023) investigated the anti-TB effect of a ternary nanocomposite comprising PDA, gold nanoparticles, and reduced graphene oxide (rGO-PDA-AuNP). This nanocomposite is a highly selective and sensitive electrochemical biosensor that may be used to identify MTB. Via the Avidin-Biotin coupling, they bonded the MTB probe DNA to the rGO-PDA-AuNP modified glassy carbon electrode (ssDNA/avidin/rGO-PDA-AuNP). It was shown that the electrode detected target DNA up to $0.1 \times 10^{-7}$ mM with a response time of 5 s and a sensitivity of $2.12 \times 10^{-3}$ mA $\mu M^{-1}$. A unique technique for early TB diagnosis is provided by this integrated genosensor, which also boasts outstanding sensitivity and stability. Likewise, there is a great deal of promise in developing biosensor systems for the identification of different infectious pathogens and therapeutically important biomarkers employing rGO-PDA-AuNP/GCE-based electrochemical platform (Chaturvedi et al. 2023). In another study, Goel et al. (2024) designed an electrochemical platform based on MAX and functionalized with PDA to detect MTB, Avidin-biotin coupling causes the probe DNA to immobilize on the surface of a new class of 2D layered material (MAX) and PDA, creating a modified biosensing electrode made of ssDNA, avidin, and MAX/PDA. High charge transfer kinetics, good redox behaviour, and exceptional stability in the modified electrode are confirmed by the results of differential pulse voltammetry and cyclic voltammetry. Additionally, the altered biosensing electrode achieves a very low threshold for detection as well as great selectivity, outstanding sensitivity, and a quick response time when dealing with MTB. This discovery is critical as the created PDA functionalized MAX bio-electrodes may be applied to the detection of various infectious diseases (Goel et al. 2024). Through the incorporation of tissue-specific ligands or surface moieties that facilitate homing to sites of infection or immune activation, these engineered nanoparticles can exert their therapeutic influence with heightened precision and efficacy. This strategic refinement in tissue targeting holds profound implications for optimizing the localization and activity of the nanoparticles within the complex landscape of TB-affected tissues (Su and M. Kang 2020).

## 5.2 | Redox-Responsive Strategy

The functionalization of PDA nanoparticles can be tailored to exhibit redox-responsive drug delivery, allowing for adaptive action within the dynamic microenvironment of TB lesions (Mitchell et al. 2021). The presence of different redox states in the intracellular and extracellular milieu presents an opportunity to design nanoparticles that can selectively release therapeutics in response to these specific redox signals (Chibh et al. 2020). By integrating redox-responsive drug release mechanisms, PDA nanoparticles can harness the oxidative stress characteristic of the TB microenvironment to initiate targeted drug delivery, thereby enhancing the efficacy of therapeutic interventions (Y. Liu et al. 2024). This approach also capitalizes on the ability of PDA nanoparticles to undergo structural transformations in response to changes in redox potential, enabling precise and controlled release of therapeutic agents within the specific microenvironment of TB infection. This adaptive drug delivery system ensures that the drugs are released only when they reach the infected site, minimizing systemic exposure and improving the efficacy of treatment (Elaissari et al. 2009). This action holds significant potential in addressing the challenges posed by the complex and evolving nature of TB infection, where tailored responses to the dynamic redox landscape can optimize the delivery and impact of anti-TB agents within the intricacies of the disease microenvironment. The development of redox-responsive drug delivery systems represents a sophisticated leap towards personalized and adaptive treatment strategies for TB, marking a paradigm shift in the pursuit of therapeutics that effectively interface with the dynamic host-pathogen interplay inherent in TB pathology (Mashabela et al. 2019). The incorporation of redox-responsive drug delivery mechanisms further enriches



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the functional diversity of PDA nanoparticles in the fight against TB. The microenvironment of TB lesions is characterized by distinct redox potentials, providing an opportune target for tailored therapeutic interventions. Through stimuli-responsive release systems that capitalize on redox potential alterations, PDA nanoparticles can dynamically modulate the delivery of therapeutics in response to the unique redox landscapes within TB-affected tissues (Bilal et al. 2021). This microenvironment-adaptive action facilitates a nuanced and precisely orchestrated release of anti-TB agents, fostering a heightened therapeutic impact by aligning drug deployment with the specific pathophysiological cues of the infection site (Kareem et al. 2022). Yu et al. (2021) studied PDA coated silver nanoparticles (Ag-PDA NPs) in moderate environment and loaded with the anti-TB drug Rifampicin (RF). The antibacterial efficacy of various ratios of the formulated Ag-PDA NPs/RF against multi-drug resistant (MDR) strains of MTB was assessed using minimum inhibitory concentration (MIC). According to the MIC data, Ag-PDA NPs and RF worked synergistically to provide the best antibacterial activity against the MDR strain of MTB. The findings additionally implied that RF@Ag-PDA NPs might be regarded as promising nanoparticle therapeutics to prevent the MDR strain of MTB from growing and maintain the effectiveness of RF in clinical settings.

### 5.3 | Enzyme-Responsive Functionalization

Enzyme-responsive drug release represents another innovative approach to enhance the precision of TB treatment using PDA nanoparticles. PDA nanoparticles can be functionalized with enzyme-responsive moieties that selectively release encapsulated drugs in response to specific bacterial enzymes involved in drug resistance mechanisms (De La Rica et al. 2012). This targeted strategy tackles the issue of pharmacokinetic drug resistance by directly inhibiting or neutralizing bacterial enzymes responsible for drug inactivation, thereby enhancing the efficacy of anti-TB agents. The incorporation of enzyme-responsive systems in PDA nanoparticles enables a two-pronged attack on TB, combining the direct inhibition of drug-inactivating enzymes with the localized and controlled release of therapeutic agents, ensuring maximum effectiveness in combating drug-resistant strains of MTB (Di Mauro et al. 2017). By integrating enzyme-responsive drug release mechanisms, PDA nanoparticles can effectively counteract the development of drug resistance, ensuring sustained therapeutic concentrations in the local environment while reducing the impact on healthy tissues (Mazlan et al. 2021). In a study by Bisht et al. (2023), an electrochemical genosensor for the detection of MTB was created using polynorepinephrine (PNE), the sister compound of PDA. PNE had demonstrated potential grating and coating qualities as a coating material for reduced graphene oxide (RGO) and gold nanoparticles (Au). Using biotin-Avidin chemistry, MTB-specific probe DNA (ssDNA) was covalently immobilized on the nanocomposite surface of glassy carbon electrodes (GCE) to construct biosensing electrodes. Electrochemical experiments utilizing cyclic voltammetry (CV) and linear sweep voltammetry (LSV) revealed a considerable enhancement in the charge transfer kinetics of the RGO/PNE/GCE and RGO/PNE/Au/GCE electrodes. Using ssDNA/avidin/RGO/PNE/Au/GCE bioelectrode, the developed sensor showed a broad detection range with good selectivity, low response time, low detection limit, and high sensitivity. More enzyme loading, improved electrochemical responsiveness, and improved biosensing were demonstrated by RGO/PNE/Au in contrast to the comparable RGO/PDA/Au material system (Bisht et al. 2023).

The innovative integration of enzyme-responsive drug delivery systems with PDA nanoparticles offers a multifaceted strategy in the battle against TB. It not only addresses the challenges of drug resistance and off-target effects but also contributes to the precision and adaptability of therapeutic interventions (Nair et al. 2023). The synergistic combination of enzyme-responsive drug release and targeted drug delivery through PDA nanoparticles provides a comprehensive and tailored approach to combat the complexities of TB pathology. This approach holds immense potential in advancing the efficacy and precision of therapeutic interventions against MTB (Kia et al. 2023).

### 5.4 | Multifunctional Nanoparticle Platforms

Recent developments have also seen the emergence of multifunctional PDA nanoparticles designed to elicit synergistic therapeutic effects in TB management. These platforms integrate multiple functionalities, such as drug delivery, imaging capabilities, and immunomodulatory properties, into a single nanoparticle system (Zhu and Su 2017). Major elements of multi-functionalization include improvement of properties, namely, mechanical, electrical, magnetic, optical, thermal, or chemical properties. These enhance the stiffness and strength, thermal conductivity, resistivity, emissivity, permeability, reactivity and heat capacity of the nanoparticles (Song et al. 2022). By harnessing the synergistic effects of these multifunctional platforms, PDA nanomaterial can function as a substrate material in loading other nanomaterials like gold, quantum dot, silver nanomaterials utilizing their combined properties (Figure 5). This will enable researchers aim to not only improve the delivery of therapeutic agents including anti-TB agents but also modulate the host immune response to enhance the clearance of M TB (El Yakhlifi and Ball 2020). The multifunctional nature of these nanoparticles allows for a comprehensive approach to TB treatment, addressing the complex interplay between the pathogen and the host immune system. Through the controlled and simultaneous delivery of therapeutic agents and immunomodulators, multifunctional PDA nanoparticles hold the potential to reshape the landscape of TB management by offering a holistic and integrated therapeutic strategy (M. Li et al. 2023). Andoy et al. (2020) explored the possibility of combining an antimicrobial peptide's (AMP) lytic activities and membrane targeting with the intrinsic photothermal capability and good biocompatibility of PDA nanoparticles to create a multifunctional and stimuli-responsive (NIR laser-activated) antimicrobial platform. The resulting PDA-nanoparticles-AMP nanosystem may specifically target and compromise the mechanical integrity of *Escherichia coli*'s outer membrane, as determined by measurements made using atomic force microscopy. Furthermore, the laser-induced nanolocalized heating of PDA-nanoparticles, which takes place close to the bacterial envelope that has already been weakened, results in further damage to the membrane. This increased the



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efficacy of PDA-nanoparticles-AMP's laser-activated bacterial killing mechanism against drug-resistant *E. coli*. This application can also be employed in tackling drug-resistant TB.

With a comprehensive platform that incorporates therapeutic, diagnostic, immunomodulatory and stimuli-responsive capabilities, the multi-functionalization techniques for PDA nanoparticles represent a paradigm change in the treatment of TB. With further research in this area, multifunctional PDA nanoparticles may have synergistic effects in treating the intricate host-pathogen interactions in TB, which could improve care quality and open the door for more individualized and efficient treatment approaches.

### 5.5 | pH-Responsive Drug Release for Intracellular Targeting

The implementation of pH-responsive drug release mechanisms in PDA nanoparticles heralds a transformative approach to precise intracellular targeting in the context of TB treatment (H. Li et al. 2021). This pH-responsive drug release strategy (Figure 8) takes advantage of the acidic pH environment (Figure 6) within the phagosomes where the bacteria reside. By harnessing this acidic pH environment, this functionalization strategy orchestrates a targeted and controlled release of therapeutics, optimizing their delivery to the intracellular compartments harbouring the pathogen. This tailored drug release mechanism not only ensures the efficient deployment of anti-TB drugs to the specific site of infection but also mitigates off-target effects, minimizing potential cytotoxicity to host cells (Queval et al. 2017). The ability to modulate drug release in response to the unique pH landscape of the intracellular milieu underscores a pivotal advancement in optimizing the therapeutic impact of PDA nanoparticles, aligning with the imperative to potentiate their efficacy against TB (Zhu and Su 2017).

### 5.6 | Biomimetic Surface Engineering

One avenue of biomimetic surface engineering involves the emulation of specific cellular microenvironments to augment the biocompatibility of PDA nanoparticles. The mimicry of natural cell membranes through biomimetic surface engineering of PDA nanoparticles offers an avenue for enhanced biocompatibility and reduced recognition by the reticuloendothelial system, contributing to prolonged systemic circulation and improved biodistribution to TB lesions (Zhang et al. 2024). This innovative functionalization strategy holds the potential to overcome biological barriers and optimize the interaction of the nanoparticles with the host immune system for enhanced therapeutic outcomes. By incorporating surface modifications that replicate the extracellular matrix or cell membrane components, the nanoparticles can interface more seamlessly with host cells, promoting favourable interactions and mitigating adverse cellular responses (Zhang et al. 2024). Li et al. (2017) produced a hydrogel film based on poly (ethylene glycol) that was bonded to titanium implants using PDA adhesive and embedded with alginate microparticles loaded with isoniazid (INH). The hydrogel film was capped with poly (lactic-co-glycolic acid) membranes to allow for the local and continuous delivery of the anti-TB drug. Four weeks after MTB injection, an inhibitory zone of $4.5 \pm 0.8$ cm formed, indicating that the released INH had a strong antibacterial impact. This approach holds promise in minimizing cytotoxic effects and nurturing a conducive microenvironment for targeted therapeutic actions against MTB. Beyond mimicking static cellular structures, biomimetic surface engineering can be tailored to engage dynamic biological signaling pathways, eliciting tailored cellular responses that align with the objectives of TB treatment. By integrating bioactive molecules or ligands that mimic endogenous cell signaling cues, the nanoparticles can activate specific cellular processes that contribute to immune modulation or pathogen clearance (Alshangiti et al. 2023).

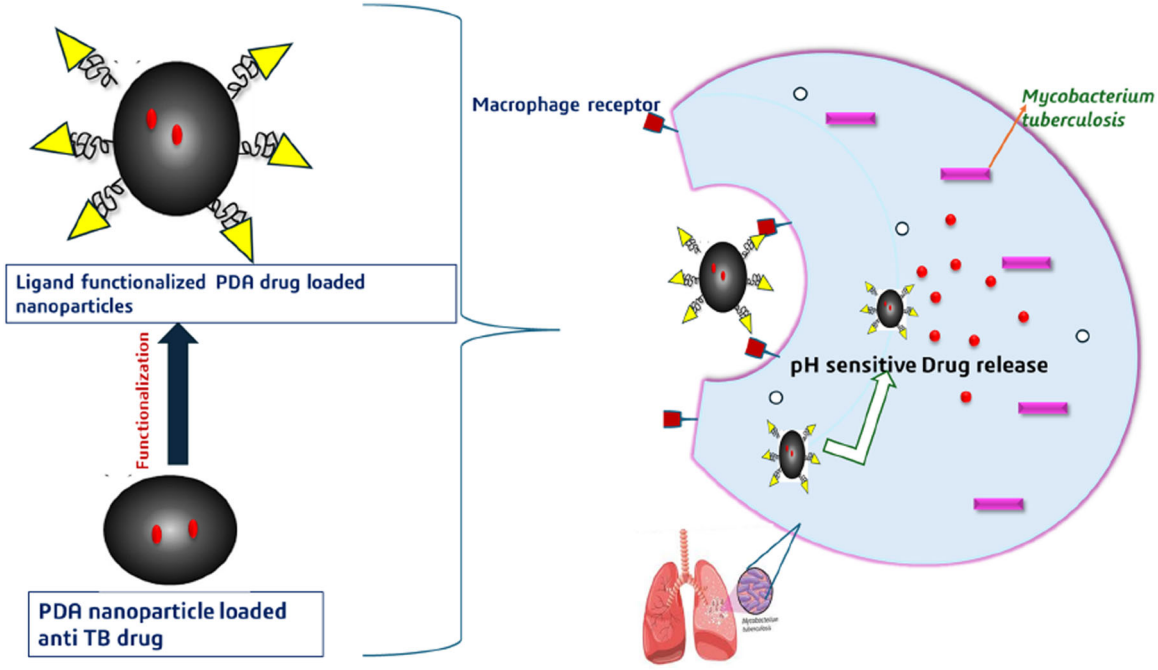



**FIGURE 8** | Demonstration of pH functionalized drug PDA loaded nanoparticle in the treatment of TB adapted from (Wu et al. 2021).



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Furthermore, biomimetic surface engineering endeavors to enhance the tissue-specific affinity of PDA nanoparticles, tailoring their interactions with distinct anatomical niches relevant to TB pathology (Wiesing 2019).

## 6 | Potentials of Functionalized PDA Nanoparticles Against TB

The intrinsic qualities and versatility of PDA nanoparticles position them for use in different ways in the fight against TB. Surface-functionalized PDA nanoparticles can be used for a variety of novel approaches towards addressing the challenges associated with treating TB, in addition to tailored drug delivery (Pai et al. 2022). Anti-TB drugs may be efficiently loaded and released under regulated conditions, by taking advantage of the porous and adjustable character of PDA nanoparticles, which may maximize their therapeutic efficacy while reducing systemic toxicity (Han et al. 2016). Drug resistance presents a significant obstacle to treating TB, but it can be overcome with great potential if these nanoparticles can be designed, synthesized, and applied with an awareness of their intrinsic qualities (Chaturvedi et al. 2023).

### 6.1 | Specific Targeting

Because of their propensity to attach to biological surfaces, anti-tb drugs are more effectively delivered locally, improving therapeutic effectiveness and lowering systemic toxicity (D.-W. Li et al. 2016). PDA nanoparticles' flexible surface modification properties allow them to be functionalized with ligands or antibodies that identify MTB specifically (Chaturvedi et al. 2023). To improve their specificity towards MTB and raise the localized drug concentration at the infection site, PDA nanoparticles can also be functionalized with ligands or antibodies for site specific targeting (W.-Q. Li et al. 2017). The distinct physical and chemical characteristics of PDA nanoparticles facilitate the effective circumvention of MTB defense mechanisms, thereby augmenting the intracellular transportation of pharmaceuticals to the bacterial sites of residence. This characteristic is very important for overcoming drug resistance since it makes it possible to transport anti-tb medications to intracellular compartments, which are difficult for conventional drugs to reach (F. Liu et al. 2015).

An innovative development in the treatment of TB is the combination of PDA nanoparticles and stimuli-responsive release mechanisms. pH-responsive, redox-responsive, and enzyme-responsive drug delivery techniques offer exceptional promise for precise and targeted drug administration in the complex and dynamic environment of TB pathogenesis. This multimodal method provides a highly targeted and effective treatment plan by minimizing off-target effects while also increasing the efficacy of therapeutic measures. Furthermore, the convergence of these precision techniques represents a paradigm-shifting move towards customized and demand-driven drug administration, thereby coordinating therapeutic interventions with the complex dynamics of TB pathology, avoiding systemic obstacles, and optimizing therapeutic efficacy. Additionally, by conjugating targeting ligands onto PDA nanoparticles, targeted and tailored drug administration can be achieved by guiding the nanoparticles to specific cellular or molecular targets within TB lesions. Therapeutic payloads can be specifically delivered to the sites of infection and immune modulation by taking advantage of ligand-receptor interactions or unique homing mechanisms present in the diseased tissue microenvironment. This approach ultimately maximizes therapeutic outcomes while reducing systemic exposure and related side effects.

### 6.2 | Combinatorial Therapy

The capacity of PDA nanoparticles to operate as a flexible scaffold for the conjugation of different bioactive compounds, such as immunomodulators, antibiotics, and anti-inflammatory drugs, is one of its main characteristics. This flexibility is the hallmark for the adaptability of functionalized PDA nanoparticles. For this reason, combinatorial therapeutic approaches can be designed to address different aspects of the complex host-pathogen interplay in TB infection by incorporating multiple agents onto the surface of the nanoparticles, each with a unique mechanism of action. Multiple treatment drugs are often required to effectively address TB lesions due to the coexistence of various bacterial populations. When surface-functionalized with the ability to load many drugs and release them gradually, PDA nanoparticles provide a vehicle for the co-delivery of various anti-TB drugs (Glaziou 2020). This strategy uses combination therapy to target many pathways involved in TB development, which not only makes treatment easier for patients but also tackles the problem of drug-resistant bacteria. Surface-functionalized PDA nanoparticles can also function as biocompatible vehicles for adjuvant treatments meant to boost the effectiveness of traditional anti-tb medications (Gideon et al. 2022). Adjuvants that improve drug solubility, stability, or immunostimulatory qualities can be added to PDA nanoparticles due to their adaptability. This maximizes the therapeutic efficacy of the medicine while reducing the risk of side effects.

### 6.3 | Immunomodulatory Function

The host immune response and the course of infection are significantly influenced by the immunological barriers found within TB lesions (Dhar et al. 2016). PDA nanoparticles with surface functionalization can be engineered to exhibit immunomodulatory actions, impacting the surrounding immunological milieu to augment the host's capacity to resist the infection. Through the incorporation of immunomodulatory agents or the modification of bioactive molecule release kinetics, these nanoparticles can enhance the host immune response, thus enhancing the direct antibacterial effects of traditional anti-TB medications (Mashabela et al. 2019).

### 6.4 | Theranostic Functions

The combination of therapeutic and diagnostic properties in PDA nanoparticles signals a new chapter in the treatment of TB. Surface functionalization of PDA nanoparticles can achieve



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the construction of theranostic platforms that include both therapeutic interventions and diagnostic capabilities, allowing for the targeted and customized management of TB infections. A theranostic platform can be created by adding diagnostic moieties, such as imaging probes or biomarker-specific substances, to the surface of nanoparticles enabling the non-invasive viewing and exact localization of TB lesions. This allows for simultaneous viewing of disease and focused therapeutic action. In addition to speeding up treatment decision-making and monitoring, this convergence of diagnostic and therapeutic capabilities allows for a more nuanced understanding of the dynamic changes within TB lesions, which in turn informs patient-specific therapeutic regimen optimization.

## 7 | Conclusion

Nanotechnology-based TB treatment has enormous potential to promote tailored and precision medicines. PDA nanoparticles exhibit considerable promise as a therapeutic platform for TB. Further explorations have revealed that combining PDA nanoparticles with stimuli-responsive release mechanisms creates a plethora of opportunities for targeted and tailored therapeutic treatments. The unique characteristics of functionalized PDA nanoparticles offer an intriguing path towards design of novel treatment approaches in the fight against drug-resistant TB. A novel approach to enabling on-demand medication release systems in TB care involves modifying this nanoparticle by adding targeting ligands, antibodies, antigens, stimuli-responsive polymers, or functional groups to the surface of PDA nanoparticles. Engineered PDA nanoparticles can be used to deliver anti-TB drugs exactly at the point of pathogen interception within host cells and the intracellular niches of infection, thus, reduce the possibility of off-target effects and increase the therapeutic intervention efficacy. The ability to control medication release, both spatially and temporally, allows therapeutic approaches to be in tune with the dynamic microenvironment of infectious foci, demonstrating the promise of nanotechnology to address the many facets of treating TB. In this context, the confluence of pH-responsive, redox-responsive, and enzyme-responsive release systems within PDA nanoparticles represents a multifaceted precision for drug delivery. These coordinated stimulus-responsive release mechanisms embody a paradigm-shift towards customized and demand-driven drug delivery, allowing therapeutic interventions to better target the dynamic complexities of TB pathology, avoid systemic obstacles, and increase therapeutic efficacy.

## 8 | Future Prospects

The future of TB treatment holds immense promise for personalized therapies finely tuned to the dynamic microenvironment of TB lesions, which will ultimately translate into improved patient outcomes and a more effective approach to combating this challenging infectious disease. Nanotechnology is still evolving and converging with precision medicine. The special characteristics of nanotechnology, such as biocompatibility, adaptability, and stimulus response, make it a great option for targeted medication delivery in the intricate and dynamic environment of TB lesions. A potential path is therefore provided by the possibilities of developing individualized and precision medicines by the application of PDA nanoparticles in TB therapy. The multifunctional properties of PDA nanoparticles offer prospects for improving therapeutic potential in the treatment of TB, in addition to providing an inventive platform for the detection of the MTB, as well as targeted drug delivery. Essentially, the potential use of surface-functionalized PDA nanoparticles against TB goes beyond the traditional bounds, using a wide range of tactics that together tackle the disease's complex problems (Mudde et al. 2022), thus, opening the door for a significant shift in the strategy for addressing this worldwide health burden.


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The authors have nothing to report.


### Conflicts of Interest

The authors declare no conflicts of interest.

### Data Availability Statement

The authors have nothing to report.

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