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Review

New Alternatives in the Fight against Tuberculosis: Possible Targets for Resistant Mycobacteria

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Abstract: Tuberculosis (TB) is a bacterial disease that remains a global health threat due to the millions of deaths attributed to it each year. The emergence of drug resistance has exacerbated and further increased the challenges in the fight against this illness. Despite the preventive measures using the application of the Bacillus Calmette-Guérin vaccine, the desired immunization outcome is not as high as expected. Conventional TB treatments exhibit serious limitations, such as adverse effects and prolonged duration, leading to a pressing need for alternative and more effective treatment options. Despite significant efforts, it took nearly four decades for diarylquinoline to become the most recently approved medicine for this disease. In addition, various possibilities, such as the usage of medications used for many other conditions (repurposed drugs), have been explored in order to speed up the process of achieving faster outcomes. Natural compounds derived from various sources (microorganisms, plants, and animals) have emerged as potential candidates for combating TB due to their chemical diversity and their unique modes of action. Finally, efforts towards the generation of novel vaccines have received considerable attention. The goal of this paper was to perform an analysis of the current state of treating drug-resistant TB and to evaluate possible approaches to this complicated challenge. Our focus is centered on highlighting new alternatives that can be used to combat resistant strains, which have potentiated the health crisis that TB represents.

Keywords: *Mycobacterium tuberculosis*; drug resistant TB strains; treatment; diarylquinolines; repurposing drugs; natural products; novel vaccine generation

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1. The Disease Known as Tuberculosis and Relevant Aspects Associated to It

At the end of October 2022, the World Health Organization (WHO) published its *Global Tuberculosis Report*, pointing out that worldwide, this disease represents the 13th leading cause of death and the major infectious killer after SARS-CoV-2/COVID-19 and above HIV/AIDS [1]. Tuberculosis (TB) is caused by *Mycobacterium tuberculosis* (Mtb), whose pathogenic role was demonstrated in 1882 by the research conducted by Koch. TB is transmitted from person to person through the respiratory route, commonly affecting the lungs, but other tissues can also be damaged [2]. Estimations indicate that about a quarter of the world population is infected with Mtb during their lifetimes; however, most people will not develop TB, and in some cases, the infection can even be cleared [1]. Active TB might be manifested with mild symptoms during the first months, developing into a cough with sputum and sometimes blood, chest pains, general fatigue, weight loss, fever, and nocturnal sweating [1]. According to work on TB by Guinn and Rubin [3], published

in a "frequently asked questions" (FAQs) format, pneumonia caused by Mtb exhibits two distinctive features: (1) the impairment of the lung tissue rather than the airways and (2) granuloma. Nonetheless, a major challenge against this disease relies on the bacterial capacity to remain latent and surprisingly persist in most infected individuals for a long time.

One distinguishing and, at the same time, outstanding feature of mycobacteria relies on the chemical nature and architecture of their cell wall. Mycobacterial cell walls are mainly composed of a peptidoglycan layer, mycolic acids, and arabinogalactan [4], rendering, in turn, their acid-fastness capacity and the low permeability to antimicrobial drugs (broad-spectrum antibiotics except for rifampicin). The knowledge about the acid-fast reaction of mycobacteria has mostly been derived from the Ziehl-Neelsen stain [5]. This structure plays a critical role for this class of bacteria, as crucial processes such as protection against hostile elements, mechanical resistance of the cells, solute and protein transport, and cell adhesion via the recognition of receptors take place here [6]. In addition to its role in the viability of Mtb, the chemical structure of its cell wall, particularly the peptidoglycan, renders unique molecular features that are important during dormancy [7].

The difference between active and latent TB, better identified as TB disease and latent TB infection, respectively, resides in the symptoms exhibited by the patients and their capacity to infect other people. In a journey through time (over two centuries), Behr et al. [8] addressed the confusion generated by different concepts related to latent TB and highlighted the relevance of using consistent definitions for research, treatments, and public health affairs. In this sense, patients with TB disease require multiple antibiotics/drug treatments for many months, depending on the regimen. Drug susceptible TB is treated by a 6-month standard course of 4 antibiotics: isoniazid (H), rifampicin (R), ethambutol (E), and pyrazinamide (Z); all four drugs are used for the first 2 months, and the remaining 4 are followed by H and R [1]. According to CDC [9], in the United States, treatments for TB disease shift in time length as follows: (1) 4-month rifapentine-moxifloxacin and (2) 6 or 9-month RIPE (rifampicin, isoniazid, pyrazinamide, and ethambutol). Together with rifabutin (Rbt), these four antibiotics represent the first line of drugs against TB [10]. Even though TB is a treatable disease, several complications are associated with its treatment. Adverse reactions to the medications include nausea, vomiting, loss of appetite, skin rashes, liver toxicity, or peripheral neuropathy, side effects that can affect treatment adherence and may require modifications to the drug regimen [11].

Until now, the only prevention against TB is yielded by the licensed but controversial BCG (Bacillus Calmette-Guérin) vaccine. The controversy generated by this vaccine encompasses several topics, such as (1) each country's policy for its application, (2) candidates for receiving the preventive treatment, (3) conferred time of protection, and (4) efficacy in immunogenicity. This last issue represents a crucial point in the research focused on developing new drug therapies for fighting TB. BCG was developed in 1921 at the Pasteur Institute from an attenuated bacterial strain of *Mycobacterium bovis*, starting clinical immunization with it this same year [12]. Since 1924, *M. bovis* BCG has been distributed globally; however, the endemic occurrence of TB, in addition to differences within culture conditions, led to the emergence of genetic variation among strains. At present, more than 20 BCG variants exist worldwide, all with a common genetic loss: the deletion of a region of difference 1 (RD1), an important feature involved in attenuation since the initial *M. bovis* strain [13]. Today, it is well known that phenotypic and genotypic heterogeneity of the different strains is related to their efficacy for protecting against TB [14].

In summary, the delay in the elimination of TB is caused by multiple factors, such as the complex biology of Mtb and the complications of treatment that have led to the generation of resistant strains. The lack of readily available preventive interventions and the rise in illnesses among vulnerable individuals round out the list. Therefore, the aim of this review paper centers on the state of the art in the development of alternative drugs/medications and new generation vaccines to combat this disease.

2. Tuberculosis as a Public Health Problem: An Old Challenge Still Present Due to Drug Resistance

From historical records, i.e., Egyptian and Peruvian mummies, it has been postulated that Mtb has infected human beings since very ancient times [12]. TB has a significant economic impact at the individual and social levels: (1) affecting children, the elderly, migrants, prisoners, and people living in poverty and (2) exacerbating health disparities [15,16]. In high-burden countries, many individuals with TB are asymptomatic in a latent state for many years and can be reactivated to cause disease [2]. Another setback of this illness relies on the fact that it affects vulnerable populations such as immunocompromised patients, which include cases positive for HIV/AIDS, malnourished individuals, and/or people with underlying health problems such as diabetes and cancer.

In 1995, "*Directly Observed Treatment*" (DOT) was launched by WHO to ensure proper medication intake as prescribed and to monitor responses to treatment. Van Deun et al. [17] reported on a standardized program known as "*the Bangladesh Regimen*" consisting of kanamycin, gatifloxacin, prothionamide, high-dose isoniazid, clofazimine, pyrazinamide, and ethambutol for 9 to 11 months and attaining an 88% of success. Nevertheless, combining several drugs over long periods continues to be a struggle in completing treatment and enhancing the generation of resistant strains. Finally, in 2014, a new action plan called "*End TB Strategy*" was implemented. However, inadequate health services interfere with the timely diagnosis, treatment of the disease, and follow-up of TB cases, often leading to scheme failure and illness relapse and hindering the success of WHO's strategies [1].

Drug-resistant TB (DR-TB), which can be broadly divided into intrinsic and acquired, poses an escalating worldwide threat to health security. Intrinsic resistance comprises the innate capacity to render antibacterial compounds less effective; meanwhile, in the specific case of Mtb, the acquired resistance is a result of specific chromosomal mutations [18]. Key mechanisms of drug resistance include loss of enzymatic action in the activation of pro-drugs, drug targets, overexpression of the drug target, and overexpression of the efflux pump. At a molecular level, research focused on finding genes responsible for drug resistance to isoniazid (katG), rifampin (rpoB), pyrazinamide (pncA), and quinolone (gyrA) has been conducted [19]. The emergence of drug-resistant TB, such as multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB), complicates treatment and control efforts even further. Medicines used to treat drug-resistant strains often exhibit more toxicity, need longer treatment, and are more likely to present adverse effects. To make things worse, drug-resistant strains increase costs; for example, in patients with DR-TB, hospitalization was longer for cases exhibiting this feature compared to susceptible TB: 202 +/− 130 vs. 123 +/− 81 days (mean +/− SD; $p = 0.015$), respectively [20].

MDR-TB is defined as resistance to the two main first-line anti-TB drugs (isoniazid and rifampicin), while XDR-TB includes resistance to many second-line drugs, such as bedaquiline, linezolid, moxifloxacin, levofloxacin, clofazimine, cycloserine, para-aminosalicylic, propylthiouracil, and amikacin [21]. In addition, XDR-TB encompasses strains resistant to any fluoroquinolones and at least one of three injectable second-line drugs (amikacin, kanamycin, and/or capreomycin) [22,23]. MDR-TB requires the use of specific alternative TB chemotherapy regimens. These regimens involve the combination of second-line anti-tuberculosis drugs, which are typically more expensive and toxic and require longer durations. Alternatively, fluoroquinolones, better tolerated by patients, are central to the treatment of MDR-TB [24]. Prevention of transmission of MDR-TB and XDR-TB- requires robust TB control actions, including early diagnosis, appropriate treatment regimens, infection control measures, and monitoring systems for detection of drug resistance. Fighting against these challenging forms of DR-TB requires (1) ensuring universal access to quality TB care, (2) improving diagnostics, and (3) developing new anti-TB drugs and/or treatment regimens [25].

Of special interest in the field of bacterial resistance are mycobacteria transmitted via close contact with infected animals or via the consumption of contaminated products [26]. The *Mycobacterium tuberculosis* complex (MtbC) includes some mycobacteria that

can cause zoonosis in humans. Alarmingly, among different species of the MtbC, some exhibit resistance to antibiotics used in the treatment of TB. Current research suggests that the transmission of MtbC is not only transmitted via the interfaces between humans and animals but also by the environment, including soil, water, pasture, air, dust, etc. [27]. A recent study found the presence of extracellular DNA (eDNA) in slow-growing mycobacteria, related to the formation of biofilms and the generation of resistance to isoniazid and amikacin [28]. Mtb could survive for extended periods in nature, which would make it easier for other mycobacteria to take eDNA directly from the environment and thus favor the appearance of new resistant strains. Actual methods for the diagnosis of tuberculosis are inefficient in differentiating Mtb from other mycobacteria, and this misleading diagnosis makes proper treatment impossible. The complications for correct diagnosis, the permanence of wild reservoirs, and the persistent infections in cattle have underestimated the number of actual cases of zoonosis, which, in addition, can have a significant impact on the natural course of TB [29].

3. Alternative Treatments and Their Availability

The discovery of new drugs is usually a costly and slow process; in the case of TB, it has been even more complicated. The slow growth rate of the bacteria, the need to work with a biological safety level type 3 (BSL-3), and the long time invested in animal models have led to further delays in this process. On the other hand, the regulatory processes required in preclinical and clinical trials require a minimum of 2 months of culture conversion rate data and 2 years of relapse rate data after treatment. Therefore, more than four decades have been required for the emergence of new effective medications. By 2018, only three new drugs were in the last phase of clinical trials (Phase 3): bedaquiline, delamanid, and pretomanid [10]. Currently, bedaquiline and delamanid have been approved for treating MDR-TB.

Bedaquiline is a diarylquinoline effective against active and non-replicating Mtb, also providing an alternative treatment for latent TB [30]. However, the long-term adverse risks of bedaquiline remain questionable regarding toxicity [31]. New diaryloquinolines that offer a safer alternative to their toxicity are in development, with BTZ-043, PBTZ-169, and OPC-167832 as the most optimistic and highly potent ones [32].

A promising alternative is repurposing old drugs. Since these medications have previously come through the requisite validation processes for their usage, the time required for their approval in other conditions is reduced. The most common cause of this situation is given by acetylsalicylic acid, which was approved as an analgesic and years later as a vascular protector [33]. Tree-repurposed drugs were approved by WHO for the treatment of tuberculosis: linezolid, used in nosocomial pneumonia, clofazimine (an antileprosy drug), and meropenem, a β-lactam antibiotic [34]. Table 1 summarizes the mechanisms of action of (1) currently approved drugs, (2) new drugs being introduced into new regimes, and finally, (3) the repurposed drugs that have been reported to be used in combat versus TB.

Table 1. Common names of current, alternative, and repurposed drugs used for the treatment of TB, including their action mode.

Name	Drug Type	Mechanism of Action	Reference
Approved Drugs			
Isoniazid	Antibiotic, highly specific against mycobacteria	Inhibits the biosynthesis of mycolic acids	[35]
Ethambutol	Antibiotic	Blocks the arabinosyl transferases involved in cell wall biosynthesis	[36]
Moxifloxacin	Third-generation quinolone	Inhibits the DNA gyrases	[37]
Rifampicin	Antibiotic	Inhibits the DNA-dependent RNA polymerase of Mtb	[38]

Table 1. *Cont.*

Name	Drug Type	Mechanism of Action	Reference
Alternative new drugs			
Bedaquiline	Diarylquinoline	Inhibits mycobacterial ATP synthase	[39]
Delamanid	Nitro-dihydro-imidazooxadole derivative	Inhibits the synthesis of mycolic acids	[40]
Macozinone (PBTZ1698)	Benzothiazinone	Inhibits cell wall synthesis; has synergic effect with first-line antibiotics	[41]
Pretomanid	Nitroimidazo oxazin	Inhibits respiratory chain and synthesis of mycolic acids	[42]
PNU-100480	Oxazolidinones	Inhibits translation of the initiation phase of bacterial protein synthesis by selectively inhibiting ribosomal peptidyl transferase	[43]
Pyrazinamide	Antiuricosuric drug	Targets the mycobacterial fatty acid synthase I gene	[44]
R-207910	Diarylquinolones	Inhibits mycobacterial ATP synthase	[45]
Telacebec	Anti-TB drug	Inhibits the mycobacterial cytochrome bc1 complex	[46]
Repurposed drugs			
Artemisinin	Treatment against malaria	Isolated from the wormwood plant *Artemisia annua*; works by forming free radicals	[47]
Biapenem	Carbapenem antibiotic used for *Pseudomonas* spp.	Inhibits cell wall synthesis	[48]
Chloroquine	Antifungal	Inhibits efflux pump	[49]
Clofazimine	Anti-leprosy	Binds to the guanine bases of bacterial DNA, blocking the template function of DNA	[50]
Isoprinosine	Anti-viral	Stimulates host immune system	[51]
Linezolid	Used to treat infections, including pneumonia, and infections of the skin	Inhibits protein synthesis by targeting the 50S ribosome; active against XDR-TB	[52]
Meropen/Clavulanate	Riminophenazine	Inhibit the enzyme β-lactamase	[53]
PA-824 and OPC-67683 (delamanid)	Derivative of metroniazole	Inhibit the synthesis of ketimycolates, component of mycobacterial cell wall	[54]
Spectinamides	Treatment of gonorrhea in patients who are allergic (or resistant) to penicillin	Reduces susceptibility of the former to drug efflux; active against MDR-TB and XDR-TB clinical isolates	[55]

4. Potential Use of Natural Products as Alternatives against Antibiotic Resistance

The use of natural products (NPs) focused on combating a variety of human diseases has been in practice for many years. Nature has provided a virtually infinite supply of bioactive chemicals whose structural variety and diverse action mechanisms have drawn the attention of researchers worldwide. Currently, NPs constitute a valuable resource for treating complicated diseases like TB, and natural compounds with antimycobacterial potential represent an alternative method to avoid side effects from conventional medications. In recent times, the discovery of numerous and novel NP features for the treatment of TB has been promising; in the last 10 years, at least 1000 different papers on this subject have been published. Selected examples of these compounds are described in this section. However, a deeper look into more NPs with inhibitory properties against mycobacterial enzymatic targets is presented in Table 2.

Table 2. Natural products with inhibitory properties against mycobacteria, including their source and action mode.

Natural Product	Source	Mechanism of Action	Reference
Anthraquinone and polyacetylene	Plant-derived secondary metabolite	Inhibit Mtb at a level similar to the first-line anti-TB drug, rifampicin	[56]
Caprazamycins	Liponucleoside antibiotics isolated from *Streptomyces*	Inhibition of the biosynthetic enzyme MraY (translocase I)	[57]
Curcumin	Natural polyphenol derived from turmeric	Significantly decreases hepatotoxicity with INH and is used as an adjuvant therapy regimen; used also against MDR-TB and XDR-TB	[58]
Cyclomarins	Cycloheptapeptides from marine streptomycete	Inhibit the ATPase ClpC1	[59]
Diazaquinomycins	Diaza-anthracene from Streptomyces	Inhibit thymidylate synthase	[60]
Ecumicin	Cyclic tridecapeptide from *Nonomuraea*	Inhibits the ATPase ClpC1	[61]
Ennaitin A1	Obtained from *Quercus* pathogen *Gnomonia errabunda*	Synergistic effects against Mtb with first and second-line anti-TB agents	[62]
Fellutamide B	Peptide aldehydes from the marine fungus *Penicillium fellutanum*	Potent proteasome inhibitor of Mtb	[63]
Flavonoids (naringenin and quercetin)	Citrus-derived flavonoids	Induce membrane damage of Mtb and decrease the functional activity of Mtb-MurI protein; activity against MDR-TB	[64]
Griselimycins	Cyclic peptide from *Streptomyces*	Inhibit the DNA polymerase sliding clamp (DnaN). Shown to be equally effective as rifampicin	[65]
Immunoxel (Dzherelo)	Extract of medicinal plants	Used in immunotherapy for TB and TB/HIV co-infection	[66]
Lactacystin	Produced by *Streptomyces*	An irreversible proteasomal inhibitor (specifically at the 20S proteasome β-subunit)	[67]
Lactoferrin	Human antimicrobial peptide	Additive effect with isoniazide and rifampin	[68]
Lassomycin	Hexadecapeptide from actinomycetes	Inhibits the ATPase ClpC1; activity against MDR-TB and XDR-TB isolates	[69]
Manzamines	Obtained from marine sponges	Insecticidal, cytotoxic, anti-inflammatory, antimicrobial, and anti-viral activities.	[70]
Mycins	Sourced from actinobacteria	b-lactams, tetracylines, and aminoglycosides; exhibit potent activity against MDR-TB	[71]
Phenazines	Aromatic compounds for many species of actinobacteria	Clofazimine is currently used for MDR-TB	[72]
Phenolic compounds	Phytophenolic compounds	Efflux system inhibition, protease inhibition, and mycolic acid biosynthesis inhibition	[73]
Phloretin	Polyphenolic compounds found in fruits, vegetables, legumes, etc.	Inhibits growth of Mtb H37Rv, MDR-TB, and XDR-TB isolates	[74]

Table 2. *Cont.*

Natural Product	Source	Mechanism of Action	Reference
Piperidines	Heterocycline amines extracted from black pepper	Vasodilators, antipsychotics, neuroleptics, and opioids, active against MDR-TB and XDR-TB; work synergistically with bedaquiline, pretomanid, and moxifloxacin	[75]
Polyphenols	Contained in fruits, vegetables, cereals, red wine, and extra virgin olive oil	Antioxidant, anti-inflammatory, and microbicidal activities	[76]
Polyphenols	Isolated from tea plant *Camellia sinensis*	Inhibition of InhA	[77]
Pyridomycin	Isolated from *Streptomyces*	Inhibition of NADH-dependent enoyl-[acyl-carrier-protein] reductase InhA	[78]
Pyrones	Obtained from the bacterium *Pseudomonas sediment*	Inhibition of InhA (enoyl-ACP-reductase, related to the synthesis of cell wall)	[79]
Quercetin	Flavanols, isolated from apples, berries, capers, grapes, and tea	Inhibit Mtb growth by blocking isocitrate lyase and exhibit hepatoprotective effects	[80]
Quinones	Obtained from fungi like *Bostrichonema* and *Nigrospora*	Inhibit MptpB and impair mycobacterial survival in macrophages	[81]
Resveratrol	Stilbenoid polyphenol, found in peanuts, wine, and cranberries.	Activates abyssinone II, possible target for therapy or prevention of TB	[82]
Sequanamycin A	Macrolide produced by *Allokutzneria albata* (actinomycete)	Inhibits bacterial ribosome; derived macrolide antibiotic active on MDR-TB	[52]
Teixobactin	Cyclic depsipeptide obtained from uncultured soil bacteria	Blocks cell wall biosynthesis; activity against TB, including drug-resistant strains	[83]
Tiacumicin B	Glycosylated macrolide tiacumicin from the soil bacterium *Dactylosporangium*	Bacterial RNA polymerase inhibitor	[84]

Various natural and synthetic flavonoids were reported for the effective treatment of TB [85]. Also, some compounds extracted from *Haliclona*, a marine sponge, exhibited strong activity versus mycobacteria [86]. The potent efficacy of macrolides, such as SEQ-503, SEQ-9, clarithromycin, and sequanamycin A, was demonstrated in both in vitro and in vivo models of TB. SEQ-9 has the potential to enhance a variety of TB regimens by being effective even against MDR-TB [52]. Polyphenols have been exploited as anti-TB agents, and a positive effect was observed when used in conjunction with antibiotics, as they might reduce the exaggerated inflammation derived from traditional treatment [76]. In this regard, NPs have also been an excellent ally in treatments against resistance. *Lactococcus* produces antibiotics, such as nisin A and lacticin, that are extremely effective against certain MDR-TB strains [87]. In addition, antibacterial activity against Mtb, even with MDR-TB strains, can be obtained via the extraction of essential oils from *Micromeria*, *Eucalyptus*, and *Juniperus* [88]. Epigallocatechin gallate, a major component of green tea catechins, is helpful for the treatment of MDR-TB and XDR-TB [89]. Recently, cyclic peptides from actinomycetes like cyclomarin A, lassomycin, and ecumicin, have shown potent anti-TB effects versus drug-susceptible Mtb, as well as MDR-TB and XDR-TB. These last candidates

are very promising because their target molecule, a very different one from those of existing anti-TB drugs, is ClpC1, an essential Mtb protein [61].

NPs also could improve the efficacy of conventional antimycobacterial therapies and be used as adjuvant therapy. For example, cumin, a seed from the parsley plant, improves the bioavailability of rifampicin and affects the permeability of membranes and propolis, improving the binding affinity of anti-TB medications to bacterial cell structures [90]. A natural substance called silymarin, which has antioxidant and hepatoprotective properties, has been suggested as a supplementary medication to lessen the liver damage caused by traditional anti-TB chemotherapy [91].

Treatment of latent tuberculosis infection is essential for TB control. Pyrazinamide (PZA) is the only drug that kills Mtb in a latent state; however, there is a high resistance to PZA. Alternative novel bactericidal against non-replicating Mtb is vital to reduce the transmission in the population. New chemical molecules against active and latent TB have been found in NPs. Halicyclamine A was isolated from the marine sponge *Haliclona* and showed a high activity against latent Mtb [92]. Trichoderin A, Trichoderin A1, and Trichoderin B are aminolipopeptides isolated from the fungus *Trichoderma* that showed significant activity against latent mycobacteria [93].

A major disadvantage of the use of NPs continues to be the low distribution and absorption of their active compounds, resulting in poor bioavailability. Bioavailability allows us to determine the percent of an administered dose of a drug/medication able to reach the systemic circulation. Unfortunately, in the case of the main components of NPs with biological activity, i.e., treatment for diseases such as TB, their chemical nature renders low solubility in water, thus lowering their bioavailability. In this sense, research in the areas of biotechnology, combined with nanotechnology, has focused on the development of strategies that help to improve their pharmacokinetic and pharmacodynamic properties [94].

5. The Only Preventive Treatment: Novel Generation of Vaccines

Despite the promising features of the treatments described before and as stated previously, vaccination represents the only prevention against TB. Vaccines can be highly effective tools for the fight against antimicrobial resistance by reducing (1) resistant-bacterial infections and (2) drug (antibiotic) consumption [95]. With respect to MDR-TB and XDR-TB, there is no evidence that drug resistance affects susceptibility to immune control; therefore, the development of new TB vaccines offers a crucial alternative in halting the spread of sensitive and drug-resistant Mtb strains [96]. In addition to neonates and infants, novel vaccines should be directed to teenagers and adults as their target population because both represent the most common sources for spreading Mtb.

The constant pressure driven by the necessity of more effective TB vaccines as well as the advances in the field of knowledge of Mtb, have sped up their development. Up to now, four main avenues have been adopted for the synthesis of novel vaccines [97]: (1) immunotherapeutic, (2) immunopreventive, (3) prime-boosting, and (4) priming, classified into four categories according to their immunization mode: whole cell, subunits, viral-based and nucleic acids.

The immunopreventive strategy can be divided into two [12]: (1) preventive pre-exposure (prophylactic) vaccines, which are administered before the first encounter with Mtb and are generally applied to neonates, and (2) preventive post-exposure vaccines, which focus on adolescents or adults, previously immunized by BCG and exhibiting latent TB infection. On the other hand, in conjunction with anti-TB drugs, therapeutic vaccines are employed for treating TB patients. Table 3 summarizes relevant information using selected examples in the field of new generations of TB vaccines.

Table 3. Different types of vaccines intended for their use in the combat against TB [a].

Vaccine Category	Main Group Type	Main Features
Whole cell: inactivated		
RUTI®	Therapeutic	Detoxified and fragmented Mtb cells delivered in liposomes
Immuvac/MIP	Therapeutic	Heat-killed *Mycobacterium indicus pranii*
Whole cell: live attenuated		
MTBVAC	Pre- and post-exposure	Attenuated Mtb
Whole cell: recombinant live		
VPM1002	Three types (pre-exposure, post-exposure, and therapeutic)	Recombinant BCG (rBCG) expressing listeriolysin gene for lysosome escape and lacking urease gene
Adjuvant protein subunit		
M72/AS01E or Mtb72F	Booster, pre-, and post-exposure	Immunogenic fusion protein (M72) derived from Mtb antigens Mtb32A and Mtb39A, and AS01E adjuvant
Viral-based (recombinant)		
Ad5Ag85A MVA85A	Pre- and post-exposure	Recombinant adenovirus Recombinant vaccinia virus

[a] This table compiled data from [12,95,97–99].

Due to the novelty represented by nucleic acid-based vaccines and their impact during the COVID-19 pandemic, this category will be discussed separately. RNA/DNA-based vaccines are rapidly gaining attention within the immunization framework due to their several advantages. Despite entering clinical trials, the study conducted by Yonsei University with GX-70, a DNA-based vaccine using four antigen plasmids from Mtb together with Flt3 ligand, was finalized due to safety issues [99]. Very recently, preclinical data by [100] reported RNA platforms as a feasible system for TB vaccines. Certainly, in the near future, more studies will be conducted in this area, and better vaccination outcomes will be attained.

6. Final Remarks

Despite the advances in TB research and the different approaches to the fight against this disease, it still constitutes a worldwide threat to health. The aim of WHO's "*End TB Strategy*" for achieving a TB-free world requires global actions, joint efforts from different stakeholders, social and political commitment, and public and private investment. The emergence of Mtb-resistant strains reflects the mismanagement of TB, and its surveillance represents a challenge for TB operations around the world, especially in developing and under-resourced countries, as well as in countries with a prevalence of HIV/AIDS [101]. In this scenario, the importance of co-infections should also be considered; WHO's *Global Tuberculosis Report* [1] exhibited the damaging effect of the COVID-19 pandemic on TB diagnosis, treatment, and burden. The global coronavirus emergency affected medical services at all levels, which could disrupt the treatment of thousands of people with TB, including MDR-TB and XDR-TB. Whereas a large proportion of the population is estimated to be infected and living with latent tuberculosis, the damage to the airways and the decrease in the immune system caused by this coronavirus could favor the reactivation of TB in some individuals. Finally, the consequences of COVID-19 are also factors to be considered in the following year regarding the behavior of TB.

A multi-faceted approach is necessary to eradicate this disease as a public health problem. One fundamental pillar for this goal is investing in new tools and approaches to control TB, such as the synthesis of new drugs and vaccines. New medications for combat-

ing Mtb have been extensively studied, but the timing for their development continues to be a hindrance to their implementation. In this respect, a trend for repurposing old drugs has been adopted. Nevertheless, in both cases (new and old drugs), adverse effects remain a serious issue for the patient's safety. Currently, there is a growing body of evidence that natural products can be effective against TB. Natural products may provide a valuable ally in the fight against TB, outstanding for their easy availability and their low cost. However, their use still faces several challenges, so more research is needed to confirm these findings and to determine the optimal dosage and administration route for these products. An interesting and optimistic avenue that constitutes the only prevention strategy lies in the generation of newer and more effective vaccines compared to BCG. Progress in this area has been attained; nevertheless, all clinical phases are mandatory for the approval and use of these alternatives.

Although TB represents a leading cause of death among infectious diseases, it has been it has been ignored or even neglected in some instances. Many questions regarding this illness continue to arise with the control of it as a central topic. Despite the significant improvements in illness understanding, there is still a long way to go considering it to be overcome. In this work, the joint effort of several researchers in the development of the discovery of alternative treatments was compiled in the hope of attaining a world free of TB.

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