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Advancement of functional peptides: Promising candidates for antituberculosis therapeutics

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Abstract: Tuberculosis (TB), a chronic infectious disease caused by *Mycobacterium tuberculosis*, is primarily airborne and remains a global health problem, especially in resource-limited countries and regions. The emergence of drug resistance in *M. tuberculosis* has rendered the existing means ineffective in the treatment of TB. Therefore, research in new therapeutic directions has become imperative. In this review, we outline functional peptides in terms of the mechanisms of action, anti-TB attempts, advantages and disadvantages, and latest advances, aiming to analyze the research progress in anti-TB peptides. Furthermore, we investigate the potential applications of bioactive compounds found in traditional Chinese Medicine within the context of peptides.

Key words: Antimicrobial peptides; Antituberculosis; Drug resistance; Multidrug resistance; *Mycobacterium tuberculosis*; Peptides

1. Introduction

Tuberculosis (TB), an infectious disease caused by *Mycobacterium tuberculosis*, was the world's second most prevalent infectious disease in 2022 after coronavirus disease 2019 (COVID-19). Between 2020 and 2022, the incidence of TB (the number of new cases per 100,000 people per year) rose by 3.9%, reversing the downward trend of about 2% per year that has characterized much of the past 2 decades, and the world's efforts to prevent and control TB infections regressed back to the pre-pandemic levels. Globally, Asia remains the region with the highest incidence and prevalence of TB, with the cases accounting for more than 50% of all TB cases worldwide. In addition, TB remains highly prevalent in sub-Saharan Africa.[1] Meanwhile, TB is one of the leading causes of antimicrobial resistance-related deaths.[2] With the continued use of anti-TB drugs, mutant strains of *M. tuberculosis* are subjected to selective action. Moreover, the mutations in the genes linked to drug resistance are reinforced, allowing enhanced drug resistance. Multidrug-resistant tuberculosis (MDR-TB) emerged globally, followed by extensively drug-resistant tuberculosis (XDR-TB). The emergence of drug-resistant tuberculosis (DR-TB) has led to an increase in TB infections worldwide. In the relevant studies, DR-TB shows a high mutation trend, and in some regions, there may even be an outbreak. India, Moldova, and South Africa have been identified as areas with a high likelihood of outbreaks of DR-TB.[3]

TB is categorized as an inflammatory disease. *Mycobacteria* enter macrophages by phagocytosis and are able to block the transport of substances to the lysosome after uptake, thus preventing macrophage activation. In this way, these pathogens can evade immediate eradication, which allows them to survive and proliferate within macrophages.[4] Macromolecules cannot penetrate cells. Because *M. tuberculosis* invades macrophages and replicates within them, anti-TB drugs need to penetrate the cell membrane to enter the host cell to kill *M. tuberculosis* without harming the host cell.[5,6] Existing anti-TB drugs kill *M. tuberculosis* by activating extracellular targets and destroying the cells. Despite multiple measures to control the disease, the continued emergence of drug-resistant strains of *M. tuberculosis* has rendered conventional treatments ineffective.[7,8]

The Industrial Revolution has brought advances in technology and scientific research that led to the formal discovery of *M. tuberculosis* and the development of the first anti-TB drugs, marking the beginning of effective treatment for the disease. With ongoing development, other drugs such as clofazimine (CFZ),[9] moxifloxacin (MOX),[10] and capreomycin (CAP)[11] have emerged, marking a new phase in TB control efforts. Although TB can be treated with medications, it has a long treatment cycle (6 months for newly infected cases and 9 months for MDR-TB cases).[12,13] Currently, the standard treatment for TB consists of a multidrug combination of isoniazid, rifampicin, and pyrazinamide. These are the basis of modern treatment regimens. The treatment of DR-TB is based on the combination of pyrazinamide and second-line drugs such as ethionamide, propionamide, cycloserine, capreomycin, or fluoroquinolones. However, the treatment of DR-TB still faces challenges, primarily due to the toxicity, high costs, and diminished efficacy of second-line drugs.[14,15] Currently, the only available anti-TB vaccine is the bacillus Calmette-Guérin (BCG).[16] BCG, a live attenuated strain of *Mycobacterium bovis*, is not effective in preventing the transmission of TB.[17] It is most effective in infants and school-age children, but less effective in adults. Furthermore, the protective effect of BCG wanes after approximately a decade.[18]

The emergence of DR-TB has underscored the need for the development of new therapeutic modalities. The review of

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existing anti-TB research revealed the significant role of peptides in combating TB. Peptides hold great promise in the development of next-generation anti-TB drugs. A large number of antimicrobial peptides (AMPs) have evolved in bacteria, plants, and animals, and they readily exhibit biological activity and are distinguished by their diversity. A wide range of AMPs are capable of producing rapid bactericidal effects against a large number of microorganisms. In addition, due to the diversity of AMPs, the probability of pathogens developing drug resistance is low.[5] Studies have demonstrated the considerable potential of peptides in the anti-TB field. Through a review, we find that the existing studies have shortcomings: most of the studies treat peptides as a separate therapeutic agent without considering the effectiveness of combining antimicrobial peptides with other therapeutic means; the studies mainly explore the effectiveness of peptides against TB, but lack the in-depth understanding and utilization of their complex mechanisms.[19–21] Furthermore, existing related research has primarily concentrated on synthetic compounds as the primary objects of study. In the future, there is potential to further explore the potential applications of traditional Chinese medicine (TCM) bioactive components in the field of treatment.

2. Potential of peptides as new avenues of anti-TB therapy

2.1. Definition of peptides

A polypeptide is a small molecule usually composed of 10 to 50 amino acids. Broadly speaking, peptides that protect against invasive bacterial infections are collectively referred to as AMPs. These peptides have been called the "ancient weapons of evolution,"[22] and they are found in a wide variety of species, including insects, nematodes, microorganisms, and mammals. AMPs play an important role in the defense of the human immune system against foreign pathogens. In this context, host defense peptides are significant elements of innate immunity, exhibit adjuvant activity and have been demonstrated to exert broad-spectrum antimicrobial effects against mycobacteria.[23]

2.2. Discovered anti-TB peptides

Scientists have discovered a variety of peptides that can be used to treat TB. Peptides can be naturally occurring or chemically synthesized. Most naturally occurring peptides belong to the cationic host defense peptides of AMPs.[24] There are 3 main types of defensins: alpha-helical AMPs, beta-defensins, and theta-defensins.[25–27] Defensins possessed in the human body include human neutrophil peptide-1 (HNP-1) and the body-specific LL-37.[28–30] In addition, natural peptides include cathelicidin-related antimicrobial peptide (CRAMP) and the cyclic peptide ecumicin.[30,31] Chemically synthesized peptides are more diverse, including peptides extracted from *M. tuberculosis* latent antigen Rv1733c, tetrameric alkylated cationic peptide analogues (1-C13$_{4mer}$),[32,33] etc., as shown in Supplemental Table S1, https://links.lww.com/STCM/A77.

2.3. Antimicrobial mechanisms of peptides

With the in-depth study of AMPs, different explanations for their antimicrobial mechanisms have been proposed.[34] The mechanisms of AMPs have been explained from different factors.

2.3.1. Disruption of bacterial membranes

M. tuberculosis has a complex cell wall structure,[35] which has low permeability, leading to resistance to treatment.[36] Therefore, comprehensively understanding cell wall biosynthesis has been a major research goal over the past decade. It has been hypothesized that the main mechanism by which AMPs achieve their antimicrobial function is by disrupting the cell wall of *M. tuberculosis* to form pores.[37]

This cell wall consists mainly of large amounts of lipids and carbohydrates.[38] Most of the hydrocarbon chains present in these lipids assemble into asymmetric bilayers of unusual thickness. Studies indicate that the mobility of the inner layer of the bilayer is abnormally low and gradually increases outward. These structural features may affect the fluidity and permeability of the bilayer, resulting in different susceptibility of mycobacteria to lipophilic and hydrophilic inhibitors.[36] This may explain why existing anti-TB drugs are ineffective.

Many microorganisms have negatively charged lipid molecules (e.g., phosphatidylglycerol and cardiolipin). Similarly, the surface of *M. tuberculosis* is negatively charged. However, the net charge of mammalian cell membranes (rich in phosphatidylethanolamine and phosphatidylcholine) is usually neutral.[6,39] Thus, AMPs are more selective for microorganisms than for mammalian cells.

Also, due to the small molecular nature of AMPs, they are able to penetrate host cell membranes into the intracellular compartment and bind to *M. tuberculosis*. By virtue of their hydrophobicity and amphiphilicity, AMPs are able to insert themselves into the bacterial membrane, thus facilitating transmembrane permeation and leading to membrane disruption.[13,40,41]

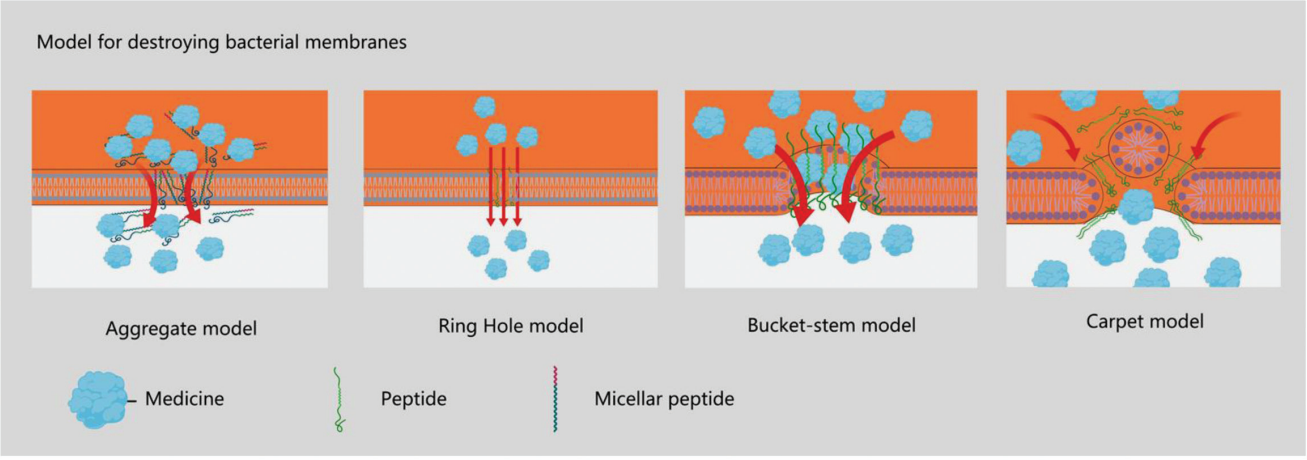

Figure 1. Four main models explaining the disruption of bacterial membranes by AMPs. This figure was drawn with MedPeer (medpeer.cn).

The disruption of bacterial membranes by AMPs has been a subject of considerable research. Current studies have proposed four main models to explain this phenomenon (Fig. 1).

Aggregate model. In the "Aggregate" model,[42] the peptide is reoriented along with the micellar peptide-lipid complexes,[43] penetrating the membrane in the form of aggregates without any specific orientation. This model assumes that the peptide molecules bind as aggregates to form a complex transmembrane structure.

Ring Hole model. In the "Ring Hole" model,[44] a specific orientation is also observed, where the polypeptide is inserted perpendicular to the plane of the bilayer. In this model, the hydrophilic region of the polypeptide binds to the phospholipid head groups, while the hydrophobic region binds to the lipid core, forming a structure that penetrates the membrane vertically.

Bucket-stem model. The "Barrel-stem" model[45] believes that the peptide is inserted perpendicular to the plane of the bilayer, forming a "stem" in a "barrel"-shaped cluster. In this model, the hydrophilic regions of the peptide face the pore cavity, and the hydrophobic regions interact with the lipid bilayer to form a barrel-like structure.

Carpet model. The "Carpet" model[46] proposes that the peptides are inserted parallel to the plane of the bilayer, with the hydrophilic regions interacting with the lipid bilayer and the hydrophobic regions facing the pore lumen. In this model, the peptides aggregate in a parallel direction, covering the localized area in a "carpet" fashion.

2.3.2. Inhibition of bacterial nucleic acid or protein synthesis

Some AMPs can kill bacteria without damaging cell walls. These AMPs do not interact directly with the bacterial membrane but rather inhibit important intracellular pathways, thereby leading to bacterial death.[47] For example, bufalin II can diffuse into cells and bind to DNA and RNA without disrupting the cell membrane. This affects bacterial replication and achieves rapid bacterial death without lysing the cell. In addition, there is evidence that these peptides may also disrupt protein synthesis. It has been demonstrated that pleurocidin and dermaseptin are capable of impeding the uptake of deuterated leucine in *Escherichia coli*, while PR-39 and indolizidine-treated cells also exhibit reduced protein synthesis rates.[48–51]

2.3.3. Induction of mycobacteria into lysosomes

M. tuberculosis parasitizes host macrophages by impeding normal phagosome maturation.[52] Phagosomes are located in compartments with high pH and are unable to fuse with lysosomes. Lysosomes contain a complex mixture of hydrolytic enzymes, including proteases and lipases. It has been shown that ubiquitin-derived peptides can synergize with other compounds within the lysosome, thereby facilitating the entry of *Mycobacterium* into the lysosome and enhancing the bactericidal capacity of the lysosomal environment.[53]

2.4. Factors affecting the antimicrobial activity of peptides

Factors affecting the antimicrobial activity of peptides include the following.

(1) **Amino acid composition and sequence:** The properties (e.g., charge, hydrophobicity, and polarity) of different amino acids affect the structures of AMPs and their interaction with bacterial membranes.[54,55]

(2) **Secondary structure:** The structural variants of AMPs are called secondary structures, including α-helices, β-strands with 1 or more disulfide bonds, loops, and extensions.[23] Secondary structures such as α-helices, β-folds, and loops play important roles in antimicrobial activity. α-Helices facilitate insertion into bacterial membranes, while β-folds may provide a more stable framework. The broad-spectrum resistance of AMPs is enhanced by the diversity of secondary structures.

(3) **Cationic structure:** AMPs are usually positively charged (there is an excess of positively charged amino acids, lysine and arginine, in AMPs)[6,56] and are called cationic AMPs. These positively charged AMPs interact with negatively charged cell membranes through electrostatic interactions and undergo membrane adsorption and conformational changes.[6] The cationic structure enables antimicrobial peptides to interact with bacterial membranes, which are negatively charged, resulting in the disruption of bacterial cell walls.[57] Studies have shown that changing the cationic structure of AMPs can enhance their biological activity, thus improving the antimicrobial effect.[58–61]

(4) **Hydrophobicity and amphiphilicity:** The hydrophobicity of AMPs has a major impact on their interaction with bacterial membranes. The hydrophobic ends of AMPs can be inserted into the bacterial plasma membrane by means of the flexibility of the linkage structure in the molecule,[40] thereby disrupting the bacterial outer membrane and leading to bacterial cell rupture, protoplasmic leakage, and death.[41] The amphiphilicity of AMPs, the ability to have both hydrophilic and hydrophobic portions, facilitates transmembrane permeation and membrane disruption.[62] The hydrophobic portion of the peptide facilitates insertion into the hydrophobic bacterial membrane, while the hydrophilic portion facilitates interaction with the membrane surface. These structural features contribute to the effective binding and disruption of bacterial membranes by AMPs.

(5) **Peptide modification:** Chemical modifications (including methylation, phosphorylation, and glycosylation) of AMPs can alter their physicochemical properties and thus affect their antimicrobial activity.[63] In addition, factors affecting the functional activity of AMPs include length,[59] environmental conditions, and stability.

3. Peptides in anti-TB applications

3.1. Anti-TB drugs

Peptides are used in anti-TB therapy alone or with other drugs (Supplemental Fig. S1, https://links.lww.com/STCM/A77).

3.1.1. Used alone in immunotherapy

In patients with TB, there is a decrease in the Th1 response and an increase in the Th2 response, which affects the immune system and suppresses the cellular immune function. This is a key factor in the development and progression of TB.[64] Therefore, restoration of immune homeostasis has become the goal of pharmacological immunotherapy. It has been shown that small molecules enhance macrophage functions and control inflammation.[65] As an important part of the innate immune response, small-molecule AMPs are capable of linking the innate and adaptive immune systems, modulating the strength of the immune response to ward off infection, reduce inflammation, and restore immune homeostasis.[66] Glutathione has been shown to enhance macrophages, thereby inhibiting the replication of mycobacteria within cells.[67]

3.1.2. Combination with conventional anti-TB drugs

Studies have shown that combination therapies can enhance antimicrobial efficacy through a variety of mechanisms, thereby minimizing the resistance of *M. tuberculosis*, which is important in improving the efficacy of anti-TB treatment.[68–70] Peptides can act synergistically with antibiotics by forming pores in membranes[71] and accelerate antibiotic penetration,[72] thereby enhancing the anti-TB effect. Potential synergism between CFZ and MOX or CAP enhances the anti-TB effect.[73] In addition, the combination of f-MLLLPD peptide and antitubercular drugs (ATD) significantly reduced the bacterial load in the lungs of infected mice,[74] further supporting the effectiveness of the combination therapy. Anti-TB drugs have no effect on bone formation and can significantly enhance osteoblast functions by combining with teriparatide, thus helping to prevent fractures and promote bone reconstruction with unchanged activity.[75] Some studies have demonstrated the potential utility of AMPs as an adjunct to clarithromycin for the treatment of drug-resistant Mab infections, as assessed by *in vitro* activity.[76] The combination of rifampicin or colistin with cationic AMPs has been demonstrated to inhibit remodeling of the mycolic acid layer in *M. tuberculosis* by reducing the sensitivity of mycobacteria to drugs, thereby extending the lifespan of the drug.[77] These findings underscore the potential and significance of drug combinations in anti-TB therapy. As previously mentioned, glutathione has the potential to be utilized as a standalone pharmaceutical agent in the treatment of TB. Glutathione has also been the subject of research in the context of combination adjuvant therapy. Studies have mentioned glutathione's promise as an adjunctive therapy for HIV-TB co-infection, especially in cases involving the central nervous system, where it can improve immune recovery and reduce inflammation.[78] The combination of glutathione and N-acetylcysteine has been recognized as an adjunctive therapy with potential clinical and immunomodulatory benefits. It has been demonstrated that glutathione and N-acetylcysteine have a significant impact on lung function, with improvements observed in sputum conversion and hepatoprotective effects. Glutathione, particularly in a liposomal form, has been demonstrated to potentially augment immune responses by modulating cytokine levels and reducing oxidative stress.[79]

3.2. Diagnostic tools

Currently, the diagnosis of TB mainly relies on medical imaging, which is not yet fully mature. Diagnostic tools not only help in the detection of the disease, but also play an important role in the research on anti-TB drugs (Supplemental Fig. S2, https://links.lww.com/STCM/A77). Some studies have found that peptides can be used in the diagnosis of TB.[80,81] AIEgen-peptide conjugates have been demonstrated to function as effective phototherapeutic agents for the eradication of phagosome-encapsulated bacteria. These conjugates possess the ability to selectively and sensitively detect and eliminate intracellular bacterial infections.[82] It has also been found that leukocyte-targeted peptide probes can be used as potential tracers for imaging TB granulomas to show lymphocyte infiltration in TB granulomas.[83] Additionally, it has been demonstrated that the combination of small molecules with fluorescent materials can be utilized to elucidate the process and mechanism of *M. tuberculosis* replication in cells.[84]

3.3. Vaccines

One strategy for combating TB is to target mycobacterial proteins and virulence factors.[85] By inhibiting these components, peptide vaccines achieve the anti-TB function. In this process, the peptide serves as a carrier.[86–88] In anti-TB peptide vaccines, the peptide acts as a reliable carrier that effectively enhances the binding affinity of antigens or virulence factors, thereby better activating the immune system (Supplemental Fig. S3, https://links.lww.com/STCM/A77).

ESAT-6 is a potent human T-cell antigen and putative vaccine candidate that has been demonstrated to enhance virulence, mediate cytolysis, and suppress host cell immune responses.[86,87] ESAT-6 can help *M. tuberculosis* evade phagocytosis of lysosomes and disperses,[89] inhibit the expression of interferon (IFN)-γ and interleukin (IL)-12 in macrophages,[87,90] and induce macrophage apoptosis, thus inhibiting the antigen-presenting function and suppressing human T-cell immune responses.[87,89,90] Therefore, inhibition of ESAT-6 and its associated interactions may be a potential avenue for anti-TB therapy. It has been shown that the fusion protein (ESAT-6/CFP-10/Rv1985c) induces the release of IL-2 and IFN-γ in patients, with IL-2 showing higher specificity and IFN-γ showing higher sensitivity.[91]

The peptide vaccine MP3RT is able to induce high levels of IFN-γ and lymphocytes in humanized mice, which impedes the action of ESAT-6, resulting in anti-TB effect.[88] Furthermore, it has been shown that ESAT-6-derived lipopeptides also have the potential as vaccine candidates against *M. tuberculosis*.[92] Meanwhile, studies of SL3 may provide new ideas. SL3 has been found to accelerate the clearance of *M. tuberculosis* from the lungs and spleen in a mouse model of TB, while being less therapeutically toxic compared to combination with ESAT-6.[93] ECM-64 is a promising peptide vaccine with the advantage of inducing high levels of Th1/Th2 cytokines, antibodies, and $CD3^+CD4^+$T and $CD3^+CD8^-$T lymphocytes in mice.[94] Two major histocompatibility complex class I/II-restricted peptides in *M. tuberculosis*, Rv2588c and Rv0148, have been demonstrated to be highly immunogenic. These peptides have been observed to stimulate adaptive and innate immune responses in peripheral blood mononuclear cells from both healthy individuals and TB patients.[95]

3.4. Preclinical and clinical landscape

These peptides have demonstrated excellent anti-TB efficacy in the laboratory. However, as these studies are primarily based on mouse experiments or *in vitro* human cell models, their effectiveness in actual human use remains uncertain due to the lack of clinical data. Furthermore, compared with conventional anti-TB drugs, peptide drugs lack sufficient preclinical and clinical trial data to assess potential toxicity issues in humans.[96]

In recent years, a number of representative anti-TB peptides have entered the clinical research stage, with related experiments have been conducted or planned in human populations, which has enabled researchers to have a more intuitive understanding and verification of the pharmacological effects of these innovative therapies.[97,98]

4. Challenges and future directions of peptides against TB

4.1. Advantages and disadvantages of peptides

The use of peptides in anti-TB therapy demonstrates both potential benefits and some challenges.[99]

4.1.1. Advantages

Excellent anti-TB capability. Although microorganisms can continuously adapt to antimicrobial substances through coevolution,[100–102] peptides leverage fundamental characteristics of bacterial cells and multiple mechanisms,[100,103] which make it difficult for *M. tuberculosis* to develop resistance.[104] Furthermore, peptide structures are easier to design than proteins. They can be engineered based on the mycobacterial

proteins and virulence factors,[99] allowing continuous optimization of peptide structures to enhance their anti-TB efficacy.

High efficacy. Peptides exhibit a high degree of potency *in vivo*, maintaining a significant antibacterial effect even at trace amounts. This allows peptides to achieve the desired efficacy at smaller doses in therapy, reducing the amount of medication used and lowering the potential side effects and toxic reactions of the drug.[105–107]

4.1.2. Disadvantages

Low utilization rates. The structural instability of peptides makes peptide drugs susceptible to enzymatic degradation in the body.[25,108] Conventional methods cannot achieve effective drug delivery. These reduce the concentrations and consequently affect the utilization rates of peptides.[55]

High peptide costs. Despite the simple structures of peptides, designing peptides and validating their efficacy and pharmacotoxicity in experiments are lengthy processes. The transition to production is also challenging due to insufficient product capacity. These factors result in high peptide costs.[109,110]

4.2. Outlook

The research on anti-TB peptides is gradually becoming mature and focuses on the overcome of shortcomings.

4.2.1. Improvement of peptide stability

Synthetic analogs of AMPs have been found to avoid the drawbacks of natural analogs while maintaining or even improving antimicrobial efficacy.[111] It may therefore be possible to enhance the stability and efficacy of a polypeptide through chemical modification, carrier binding, and related techniques. Chemical modifications include amino acid substitutions,[112] folding spatial structure modification,[113–115] tryptophan content enhancement,[116–118] and charge optimization.[59,119,120] These changes make peptides more stable and reduce their risk of being broken down by proteases.

Carrier binding techniques protect peptides from enzymatic degradation *in vivo* and improve their biostability and targeting properties,[121–123] thereby enhancing the medicinal properties.[124–126] Nanomaterials can be developed in many ways, such as carrier protein,[99,127] metalpeptide complexes,[128] liposome encapsulation,[129–132] and nanoparticle carriers.[133–135] Some studies have shown that nanomaterials can be targeted at treating[136,137] TB by promoting the body's anti-inflammatory and immune pathways[138–140] and enhancing macrophage maturation and apoptosis by targeting oriented macrophages, thus inhibiting *M. tuberculosis* replication in macrophages.[133,141]

4.2.2. Improvement of peptide yields

Improving peptide yields is an key focus in the current research of biotechnology.[142–146] *Escherichia coli* can be applied to peptide production, as its rapid growth and ease of operation can meet the demand for increasing peptide yields.[147] Studies have shown that plants are also capable of expressing AMPs, and the antimicrobial activity of their expressed AMPs is an order of magnitude higher than that of the AMPs expressed in *E. coli*. Moreover, the expressed AMPs are active even without protease cleavage.[146] However, the expression of heterologous AMPs in plants is much lower than that achieved in the *E. coli* expression system. Studies have been conducted to achieve increased yields by incorporating peptide expression genes into crops.[142] In a study, the peptide-expressing gene was stably inherited and expressed in barley after six generations. Transgenic rice seeds produce peptides that express activity without affecting seed vigor and seedling growth.[148] In addition, it has been found that chloroplasts can be used as bioreactors for the production of these proteins[145] to increase the plant yields of peptides, thus further increasing the possibility of plant applications for peptide production.

4.2.3. New drug delivery modes

Because peptide drugs are enzymatically degraded in the body, conventional delivery methods do not work well in delivering the drug to the lesion site. New delivery methods may improve the delivery of peptides. Studies have found that inhaled drug therapy allows drugs to act directly on the respiratory tract and lungs, providing rapid symptomatic relief while reducing the inhaled dose and adverse effects of the drug.[149–151]

5. Conclusion

At present, the research on anti-TB peptides remains in an evolving phase. Such research has significant potential for the application of peptides in the development of drugs, vaccines, and diagnostic tools. Peptide drugs exert anti-TB effects through various mechanisms such as cell wall penetration, inhibition of cellular metabolism, and immunomodulation. In terms of peptide design and optimization, the anti-TB activity and stability of peptides can be significantly improved through the screening of natural peptides, the development of synthetic peptides, the optimization of peptide structures, and the development of carrier systems. Preclinical studies on anti-TB peptides have achieved some important results and hold promise for further clinical applications. However, such research also faces challenges, such as lower stability and bioavailability of peptides *in vivo* and high production costs. To solve these problems, further in-depth studies on the mechanisms of action of peptides, optimization of the structural and functional properties of peptides, and development of efficient and low-cost production processes are needed to promote the clinical translation and application of anti-TB peptides. In order to solve these problems, further in-depth studies on the mechanisms of action of peptides, optimization of the structural and functional properties of peptides, and development of efficient and low-cost production processes are needed. At the same time, efforts should be made to screen active peptides from natural products in TCM and optimize their structures using modern technologies, as well as draw on the experience of TCM formulations to address challenges related to peptide stability and delivery, thereby promoting the clinical translation and application of anti-TB peptides.

AMPs are able to target *M. tuberculosis* more effectively by taking advantage of the lipid molecules and negative surface charge properties of *M. tuberculosis*. Delving into the mechanisms underpinning the multiple effects of AMPs is favorable to the research on anti-TB drugs. On the one hand, AMPs can destroy the complex cell wall structure of *M. tuberculosis*, enabling the destruction of macrophage lysosomes; on the other hand, AMPs can target the removal of *M. tuberculosis* secreted protein ESAT-6, preventing *M. tuberculosis* from inhibiting the expression of IFN-γ and IL-12 in macrophages, thus enhancing the T-cellular immune response of the human body. It provides a new direction and idea for the development of more efficient anti-TB drugs.

Statement of ethics

None.

Conflict of interest statement

No conflict of interest has been declared by the authors.

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Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Author contributions

Bojie Lin, Siqi Lin: investigation, writing—original draft; Jiayi Yang, Xuanyu Yang, Shuhui Wang, Yuting Liu, Qianqian Zhang: writing—review and editing; Junfa Xu, Jiang Pi: review, project administration; Fen Yang: supervision, project administration.

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