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COMMENTARY

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Recent research progress in the plant contribution to the management of tuberculosis

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1 | INTRODUCTION

Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis*. Despite the successes in the development of diagnosis and treatment of this disease, it still poses a significant threat to humanity, especially in countries with an average and low level of healthcare development (Maiolini, 2020). The newest World Health Organization, Global Tuberculosis Report (2023) revealed that the reported global number of people newly diagnosed with TB was 7.5 million in 2022. This is the highest number since WHO began global TB monitoring in 1995, above the pre-COVID baseline. Globally in 2022, *M. tuberculosis* caused an estimated 1.30 million deaths. Also, the number of people with multidrug-resistant (MDR) or rifampicin-resistant tuberculosis increased with 450,000 new cases (World Health Organization, Global Tuberculosis Report, 2023). Moreover, the last decade has seen an increase in the number of cases of extremely drug-resistant tuberculosis (XDR-TB), defined as MDR-TB with additional resistance to at least one of the fluoroquinolones and one of the drugs administered in the form of injections (amikacin, kanamycin, capreomycin) used in MDR-TB treatment regimens. In the era of global population movements, the emergence of MDR-TB and XDR-TB makes the fight against tuberculosis an ongoing challenge (World Health Organization, Global Tuberculosis Report, 2019). Current treatment recommendations require the use of combinations of different drugs for periods ranging from 6 months to 9–20 months (MDR-TB). However, in the case of XDR tuberculosis, or when the treatment results are not satisfactory, the duration of treatment may be much longer (World Health Organization, Global Tuberculosis Report, 2019). Failure in antituberculosis therapy is caused mainly by its long duration, complicated drug regimens, strong side effects of antituberculosis drugs, and their interactions with drugs used in other disease units (Shehzad, 2013). What is more, in 2021, for the first time in 9 years, the estimated number of deaths from tuberculosis increased, which was caused by limited access to health care due to the COVID-19 pandemic. As a result, an estimated half of the infections went undiagnosed and untreated. The report also indicates that there has been a reduction in funding for tuberculosis treatment and BCG vaccines in children. The COVID-19 pandemic outbreak in 2020 disrupted essential health services and placed an additional burden on people with tuberculosis (World Health Organization, Global Tuberculosis Report, 2021). Nevertheless, the fight against tuberculosis is still ongoing and plant products play an important role in it.

Plants are essential for human living. Besides providing food for people and feed for animals, plants create a natural environment, produce oxygen, and supply various raw materials. Since ancient times people used plants for their benefits, including disease prevention and cure. The plant kingdom is an invaluable source of biologically active molecules, which nowadays are searched very rapidly, due to the access to the huge and systematically updated databases and the application of numerous bioinformatic tools. Moreover, the connection between different medical conditions and diet was already confirmed.

In the case of tuberculosis, Scopus database search results revealed that the first report for "tuberculosis and food" is from 1896, while for "tuberculosis and plants"

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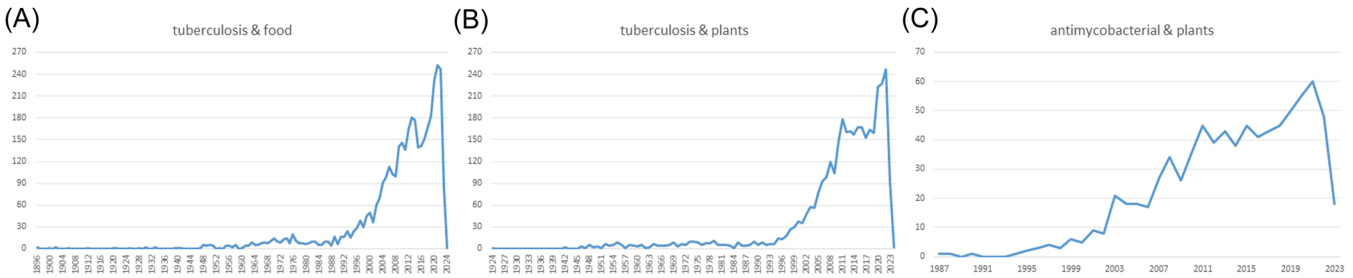


FIGURE 1 The Scopus database TITLE-ABS-KEY search results broken down by years of publication. (A) 3832 documents for "tuberculosis AND food"; (B) 3501 documents for "tuberculosis AND plant"; and (C) 811 documents for "antimycobacterial AND plants."

from 1924 (Figure 1). Since that time the slow but consistent increase in the number of articles published on this topic is visible, suggesting that the link between plant/food and tuberculosis treatment exists. The significant rise in the number of publications combining "tuberculosis and food/plant" started in 2000, with the trend only slightly different for "food" and for "plant." In both cases, years 2020–2022 yielded more than 200 publications each year, underlining the great interest in plant products and tuberculosis. Interestingly, Scopus search for the combination of terms "antimycobacterial AND plants" returns results published since 1987 (Figure 1). The "antimycobacterial" means in vitro or in vivo activity against mycobacteria, suggesting that since the nineties of the last century, researchers focused their interests on the screening of plant extracts and searching for new drug leads of plant origin. Based on the available literature sources few directions in which plants contribute to the management of tuberculosis were described (Figure 2).

2 | PLANTS' CONTRIBUTION TO THE MANAGEMENT OF TUBERCULOSIS

2.1 | Nutritional value

The most obvious role of plants in every disease is to provide nutritional value. The nutritional state is crucial in the course of tuberculosis. A well-balanced diet helps to keep correct immune responses against intracellular pathogens. On the contrary, malnutrition may lead to nutritionally acquired immunodeficiency syndrome, which due to impaired cell-mediated and humoral immune responses significantly increases patient's susceptibility to progression of infection into symptomatic disease (Chandrasekaran et al., 2017). Moreover, malnutrition increases the risk of adverse treatment outcomes, including treatment failure, loss of follow-up, and death (Ockenga et al., 2023). For these reasons, plant protein-based food may be helpful in maintaining a proper nutritional state in tuberculosis. As an example, Saleem et al proved that 6 weeks of administration of cookies prepared from mung bean, flaxseeds, peanuts, and chickpeas increased body mass index, mid-upper arm circumference, and serum total protein level in the intervention group suffering from pulmonary tuberculosis (Saleem et al., 2021).

Besides the nutritional aspect of food, the idea of compatibility of "medicinal and edible" emerged. This approach was proposed in numerous patents for food preparations and additives, or for pharmaceutical compositions for tuberculosis patients' consumption. By mixing together medicinal and edible herbal extracts, peptides, prebiotics, amino acids, carbohydrates, vitamins, and minerals these preparations aim not only to meet the nutritional needs of patients with pulmonary tuberculosis but also to tonify lung and spleen, reduce phlegm, relieve cough, and to improve immunity (Hu et al., 2015, CN104872645 A). Exemplary, basic fuchsin was patented as an active component combined with broken rice, wheat germ, or cereal for the treatment of tuberculosis and leprosy (Qi et al., 2013, CN103054839 A). Mixture of *Grifola frondosa, Agaricus blazei*, and *Lycium barbarum* polysaccharides with cooked corn starch and calcium bicarbonate was indicated as food preparation that can stimulate and improve T lymphocyte immunological response, directly improve immune macrophage activity, and improve cell interleukin sensitivity in tuberculosis (Wu & Lin, 2010, CN101897400 A). Also instant food recipes from extracts of Radix Glycyrrhizae, donkey-hide glue, *Cordyceps sinensis*, almonds, *Dioscorea opposita*, medicated leaven, *Morus alba*, *Codonopsis pilosula*, *Chrysanthemum morifolium*, Bulbus Lilii, *Platycodon grandiflorum, Poria cocos*, *Ziziphus jujuba*, and lotus seeds, vitamins, and minerals were claimed to improve the nutritional status and boost immunity of patients with pulmonary tuberculosis (Hu & Ye, 2014a, 2014b, CN104126792 A). The other interesting bioactive food additive patented for preventing and treating tuberculosis is propolis derived from birch or pine trees in Russia and Siberia, mixed with butter. The suggested administration of the product is 1.5 h before the meal by adding half or one spoon into milk, 2–3 times daily for 2 months, followed by a 2-week break, and again administered for 2–4 months (Gorev & Goreva, 2000, RU2150950 C1). Moreover, different pharmaceutical compositions containing plant extracts (Zanthoxyli Fructus extract, *Toxicodendron vernicifluum*) (Kim et al., 2006; H. W. Kim, 2018) or individual

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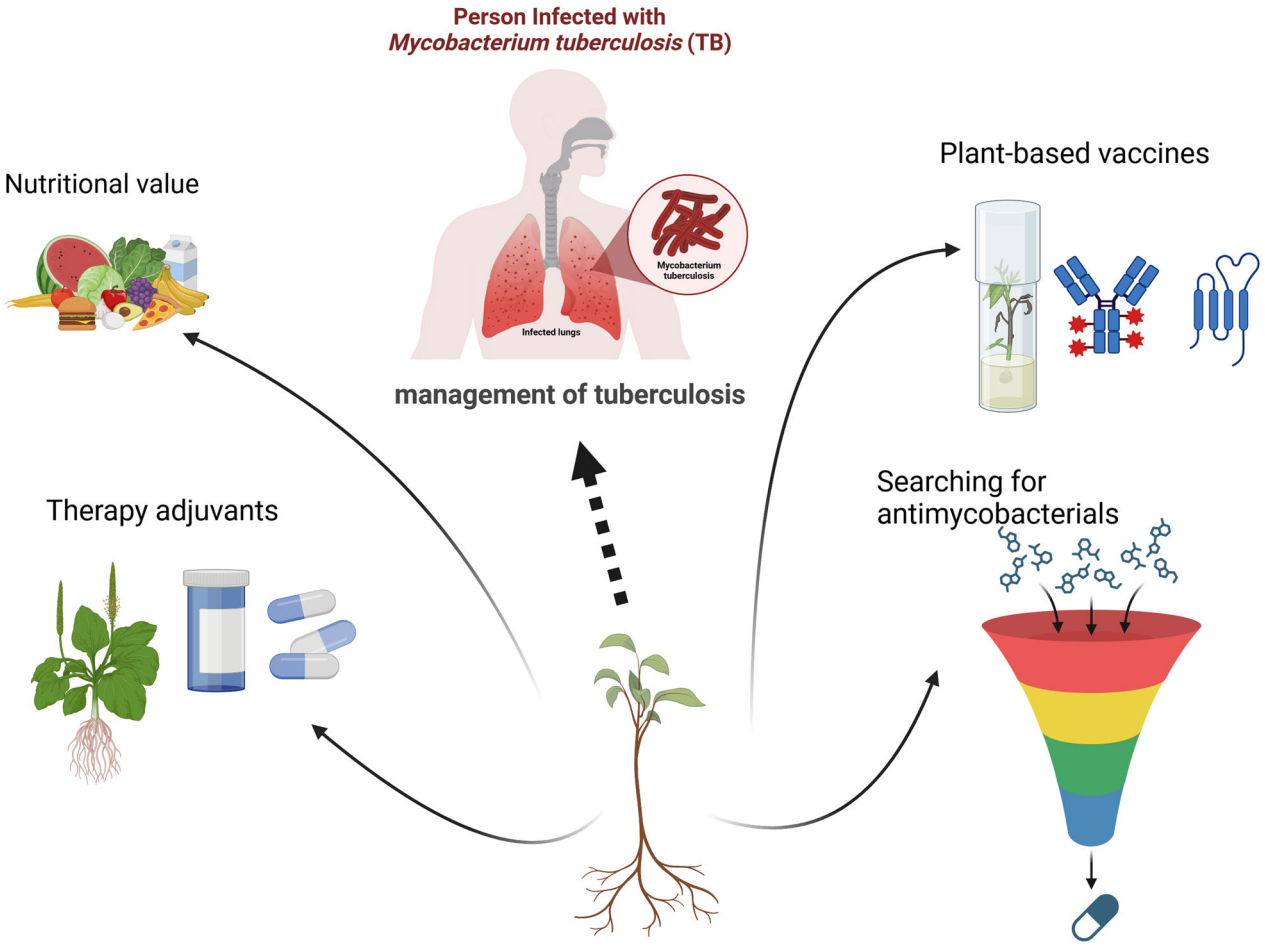


FIGURE 2 Directions in which plants contribute to the management of tuberculosis.

compounds (rhamnetin, artemether, lumefantrine, phloretin) (Choi, 2017a; 2017b; Kim & Jeon, 2018; Y. M. Kim, 2018) were designed to alleviate or prevent tuberculosis.

2.2 | Therapy adjuvants

Medicinal plants are also well-known therapy adjuvants in many complaints including tuberculosis (Figure 3). Several recent reviews summarized the potential of plants used traditionally for the management of symptoms of this disease in India (Gupta et al., 2018; Sarangi et al., 2021), East Africa (Obakiro et al., 2020), or in the Himalayas (Adnan et al., 2019).

Network analysis of indigenous Indonesian medical plants used in tuberculosis revealed interesting findings that plant-derived compounds have direct interactions with proteins related to tuberculosis. Most of the identified targets had a significant role in the immune system, suggesting that medical plants contribute to the treatment through immunomodulation (Aristyani et al., 2018). Both, immunomodulatory and antimycobacterial properties of medicinal plant extracts and plant-based active constituents were described as possible mechanisms of tuberculosis management (Sarangi et al., 2021; Tiwari et al., 2019). Herbal medicines included in clinical therapeutic regimens of patients with intractable bacterial infections, like tuberculosis were also analyzed. Their immunoadjunctive effects were related to Th17 cell-mediated protective immunity (Tomioka et al., 2021). Likewise, the role of medicinal plants and their bioactive derivatives as alveolar NLRP3 inflammasome regulators during *M. tuberculosis* infection was explored, providing information about the mechanism in which they can inhibit excessive stimulation of the inflammasomes and its associated factors, and as a consequence reducing immunopathological response in the host (Mvubu & Chiliza, 2021). Later, the immunomodulatory activity of some diterpenes was confirmed in a human alveolar epithelial cell line infected with *M. tuberculosis* (Hernández-Herrera et al., 2023), while sinaphyl alcohol diacetate and ergosterol peroxide were proved to reduce interleukin-12 levels and Toll-like receptor-2 protein expression, and to increase the human leucocyte antigen-DR protein expression in diabetic patients with tuberculosis

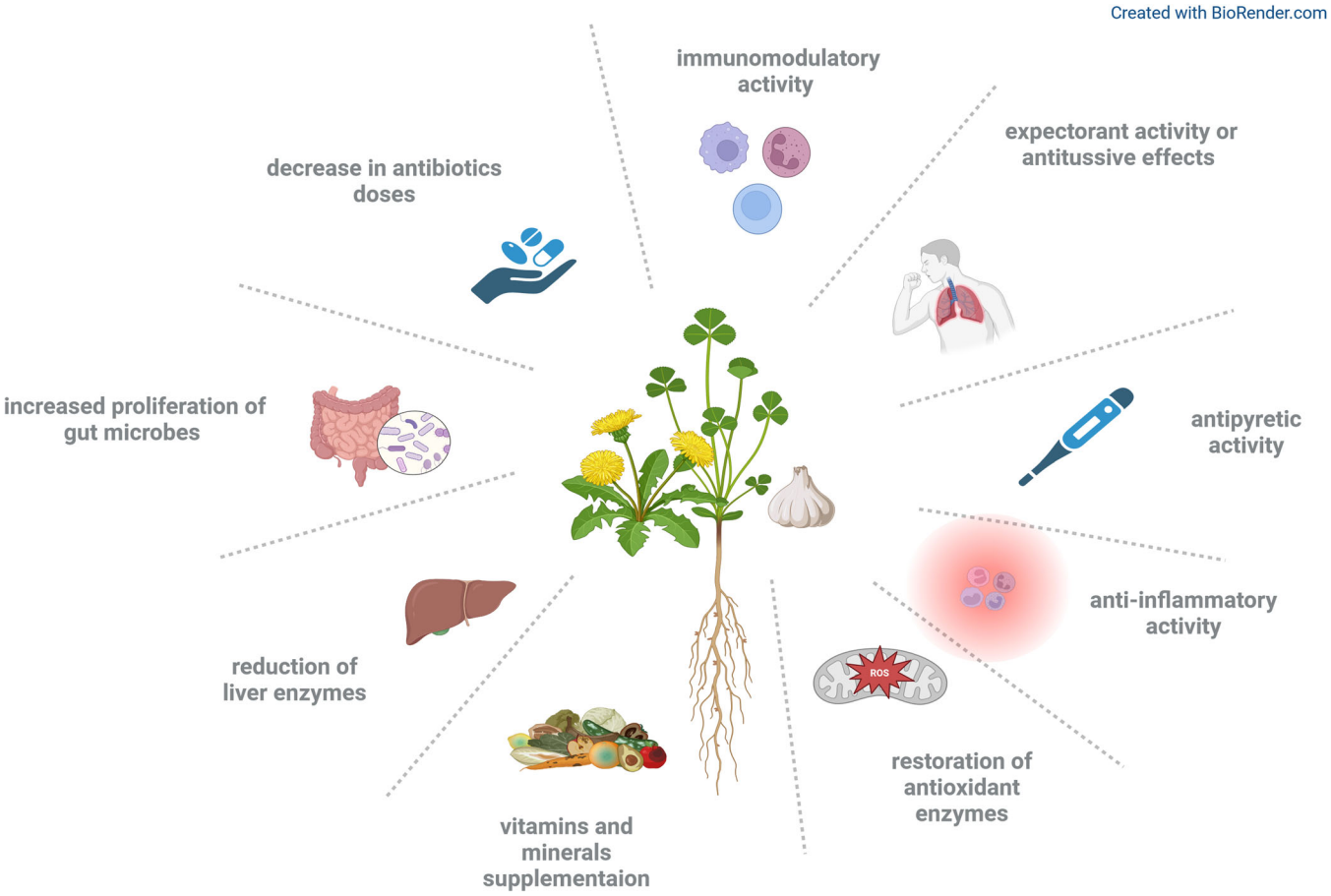


FIGURE 3 Plants as adjuvants in the course of tuberculosis.

(Ilyas et al., 2023). The general concept of immunomodulatory activity of plant extracts administration in tuberculosis is depicted in Figure 4.

The other aspect related to antituberculosis immune response is the state of microbiota. Studies have shown that subjects suffering from tuberculosis and treated with classical drug regimens can have the impaired balance of intestinal flora. This disorder can directly or indirectly affect the patient's immune function (Xie et al., 2021). For this reason, the proper supplementation of probiotics and prebiotics in tuberculosis is crucial. Interestingly, preparations with probiotics as additives for patients with pulmonary tuberculosis have already been proposed (Shovkun et al., 2012, RU2456006 C1; Hu & Ye, 2014a, 2014b, CN104137961 A). Whereas plants' nondigestible (non-)carbohydrates are used as prebiotics that boost the proliferation of gut microbes (Kaur et al., 2021).

2.3 | Searching for antimycobacterials

Screening of plant extracts and isolated molecules for their potential antimycobacterial activity is now rutinously performed as a first step in drug lead discovery. Minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC) values are two basic indicators ranking the activity of studied samples. Numerous research evaluated the antimycobacterial potential of local, endemic, or rare plant extracts, for example, from Iran (Dehestani et al., 2022), Uganda (Oloya et al., 2022), or Namibia (Raidron et al., 2022), or reviewed activity of various plant extracts (Chevtchouk Jurno et al., 2019; Gautam et al., 2023; Li et al., 2013; Sarkar et al., 2021) and endophytes from medicinal plants (Alvin et al., 2014), including potential synergistic interactions of plant products with antibiotics (Rahgozar et al., 2018; Sieniawska et al., 2018).

These still ongoing and huge screening efforts yielded the development of BioPhytMol database, designed to systematically curate and analyze the anti-mycobacterial natural products chemical space. The resource enables the prioritization of the library for drug-like compounds, with the application of whole-cell screening or target-based approaches (Sharma et al., 2014). The other example of curated database of antitubercular medicinal plants is Anti Mtb Medicinal Plants Database (AMMPDB). This repository combines botanical, phytochemical, and bioactivity information for research in computational drug design and discovery (Kanneganti et al., 2023).

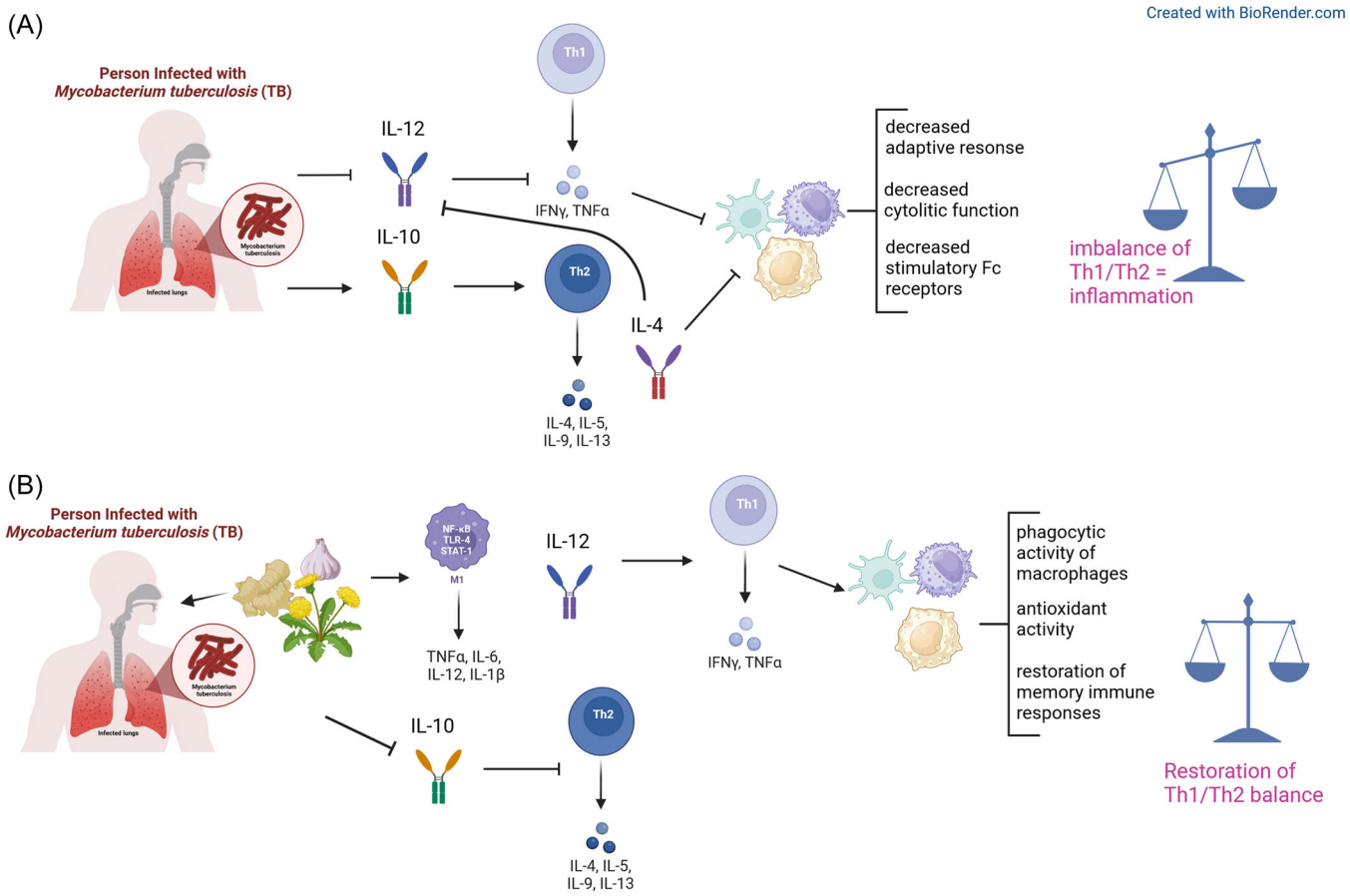


FIGURE 4 The immunological balance in tuberculosis. Patients infected with *Mycobacterium tuberculosis* have disrupted Th1/Th2 balance resulting in decreased ability to control infection (A). Administration of plant extracts restores Th1/Th2 balance and enhances bacteria killing (B). Based on Sieniawska et al. (2020a).

Various bioinformatics tools are used for the virtual screening of chemical entities to identify novel potential enzymatic targets in mycobacterial cells (Kumar et al., 2021; Kumari & Subbarao, 2020), while metabolomics and transcriptomics are applied for the determination of the mechanism of action of compounds with antimycobacterial activity (Sawicki et al., 2022a; Sieniawska et al., 2021a; Tuyiringire et al., 2018). The research efforts in this field revealed mechanisms of action in which plants' secondary metabolites directly influence mycobacterial cells. The inhibition of bacterial enzymes was identified as an interesting target correlated with the activity of plant polyphenols. Empirical studies showed that epigallocatechin-3-gallate in combination with triclosan inhibited enoyl-ACP reductase from *M. tuberculosis* (Sharma et al., 2008). Quercetin 3-O-glucoside was found to have the potential to inhibit glutamine synthetase (Safwat, et al., 2018), while such phenolic acids as ferulic, caffeic, and coumaric were screened against the β-class carbonic anhydrases (mtCA1, mtCA2, and mtCA3) of *M. tuberculosis*, and the results indicated that mtCA3 was inhibited by most of these polyphenols (Maresca et al., 2013). Additionally, molecular docking studies suggested that epigallocatechin-3-gallate may bind with pantothenate synthetase of *M. tuberculosis* (Mahanta et al., 2021), while quercetin with mycobacterial β-lactamase and topoisomerase IV (Sharma et al., 2019). The other frequently described antimycobacterial mode of action is related to the cell envelope disruption. Such activity was confirmed for terpenes: limonene, myrcene, bisabolol, and α-pinene, which changed the *M. tuberculosis* cells shape and cytoplasm homogeneity (Sieniawska et al., 2015), but also for cinnamon essential oil composed proximately of cinnamaldehyde, which caused remodeling of the cell wall and membrane in mycobacterial cells (Sieniawska et al., 2020b). Importantly, the disorganization of the cell membrane leads to nonspecific secondary effects, like the dysfunction of the efflux pumps and disturbances in energy production affecting other cellular processes and leading to cell death (Gautam et al., 2023). Some of the effects observed in mycobacterial cells exposed to natural products are common (upregulation of the lipid molecules needed in the formation of the cell wall layers; activation of detoxification mechanisms and reactive species scavengers; changes in genes coding stress-responsive sigma factors) (Sawicki et al., 2022a; Sieniawska et al., 2020b, 2021a), while others specific for the stressing agents (disruption of bacterial cell envelope surface and release of cell components to the medium caused by

tanshinones, or induction of N6-tuberculosinyladenosine formation in mycobacterial cells by garlic sulfides) (Figure 5) (Sawicki et al., 2023; Sieniawska et al., 2021b). These underline the antibacterial potential of natural products, which often target other, and different than antibiotics, cellular metabolic pathways. Supported by bioinformatics, this field of research is rapidly growing and gives a chance for the identification of a novel drug-like moieties from plants.

2.4 | Plant-based tuberculosis candidate vaccines

Plants are valuable platforms for the production of biopharmaceuticals. However not only as a source of active molecules. Because plant tissues have a high biosynthetic capacity to synthesize complex proteins, plants can be applied for the production of recombinant vaccines. It makes plants a low-cost source of target antigens, which after purification may be formulated in complex viral-like particles-based vaccines for parenteral administration. The other possibility is the application of plant biomass as a delivery vehicle for oral vaccines (Rosales-Mendoza et al., 2015). Several plant-based tuberculosis candidate vaccines have been reported so far. The proposed routes of administration were oral, intranasal, subcutaneous, or intradermal. Among these, oral vaccines containing freeze-dried transformed plant biomass were considered the most beneficial, because this type provides immune responses at the systemic level (Rosales-Mendoza et al., 2015). The antituberculosis plant-based vaccine prototypes were comprehensively discussed by Rosales-Mendoza et al. (2015). Since that time, a handful of works in this field have been published describing the expression of different mycobacterial antigens in plants. The early secretory antigenic target-6 (ESAT-6) was produced in *Nicotiana tabacum* (Saba et al., 2019), the Alanine- and Proline-rich Antigen was obtained in the same species (Módolo et al., 2018), while N-glycosylated antigen 85A (G-Ag85A) was expressed in *Nicotiana benthamiana* (Kim et al., 2020). Maize seedlings were also used as biofactory for the production of the Ag85B antigen (Rojas et al., 2020).

The innovative and interesting concept for the plant-based production and delivery of antituberculosis vaccines is the development of transgenic ready-to-eat vegetables. Such an approach was first applied to

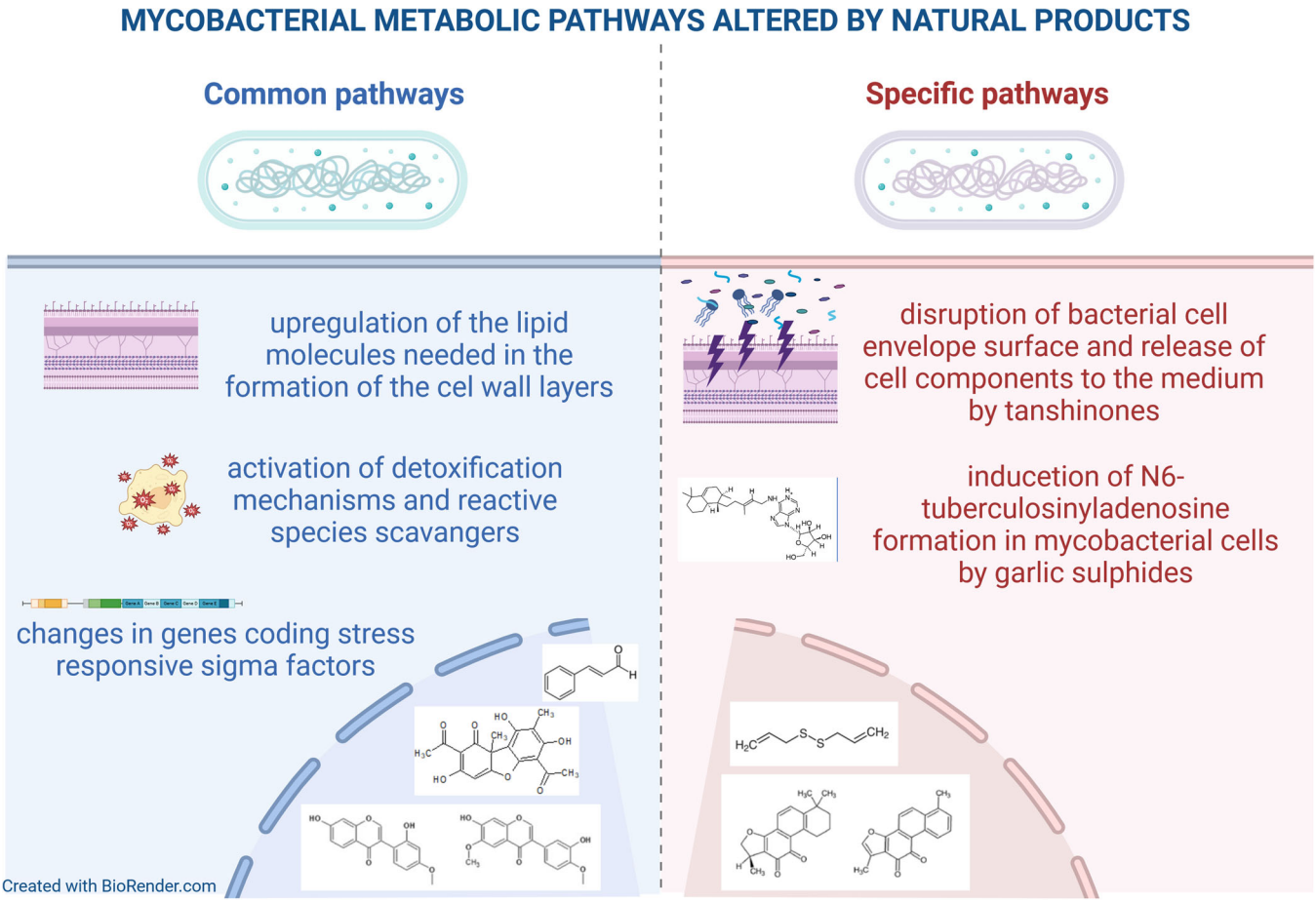


FIGURE 5 Common and specific mycobacterial metabolic pathways altered by natural products. Based on Sawicki et al. (2022a, 2023); Sieniawska et al. (2020b, 2021a, 2021b).

broccoli. ESAT-6 antigen of *M. tuberculosis* was expressed in *Brassica oleracea* var. Italic, which accumulated up to 0.5% ESAT-6 of total soluble protein (Saba et al., 2020). Then, ESAT-6 and 10-kDa culture filtrate protein (CFP-10) lines of transgenic carrot plants were developed to produce *M. tuberculosis* proteins, which were present in carrot storage roots at concentrations not lower than 0.056% and 0.002% of the total storage protein, for ESAT6 and CFP10, respectively (Tahar, 2022). Most recently, the transgenic cucumber plants were developed to produce a recombinant fusion protein (His6x.CTB-ESAT6-MPT64) in the quantity of 0.030% of the total soluble protein. The cucumber fruits eaten raw by rabbits caused a significant increase in serum IgG antibodies specific to the recombinant E-cassette protein compared with rabbits fed with wild (nontransgenic) type plants (Yadav, 2023). The above-mentioned studies indicate the possibility of using transgenic plants as orally delivered self-adjuvanted, safe, affordable vaccines against tuberculosis.

3 | LIMITATIONS AND FUTURE PERSPECTIVES

The great interest and effort is put into screening of crude plant extracts, fractions, and isolated molecules against different *M. tuberculosis* strains. However, active or very active molecules represent only a small percentage of the checked pool. For this reason, the future focus should be placed on the combinations of natural compounds with antibiotics. Not only for the reason of direct synergistic antimycobacterial activity, but more importantly, for numerous other activities described as adjuvant in the course of tuberculosis. The body of evidence proving immunomodulation and hepatoprotection caused by plant secondary metabolites is growing; however, the clinical recommendations still have to be elaborated. The administration of plant extracts in tuberculosis is recognized in Eastern medicine; however, in Western treatment regimens plants still play a marginal role. Nevertheless, the significance of gut microbiota in the infection caused by *M. tuberculosis* is currently being investigated, hence the importance of prebiotics in the management of this disease may be strengthened in the near future, also contributing to the importance of natural plants in the management of tuberculosis.

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