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REVIEW ARTICLE

Botanical Compounds: A Promising Approach to Control *Mycobacterium* Species of Veterinary and Zoonotic Importance

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A B S T R A C T

Mycobacterium species are among the most dangerous group of pathogens which have a broad host and disease spectrum. They are resistant to multiple drugs and respond to complex drug therapy, which is also being failed to control them. Vaccination of *Mycobacterium* is being done for a long period globally for the prevention of diseases of *Mycobacterium*. Various types of vaccines are being used, but vaccine failure, lower efficacy, and secondary issues lead to limiting their use. These situations demand researching proper safe control, which may help counter the diseases and issues related to *Mycobacterium*. Multiple therapies are being suggested, but the botanicals remain promising for their control. The therapies to be developed are supposed to have direct antimycobacterial actions like they may target its cell wall, cell membranes, protein synthesis or DNA gyrase activity, and DNA assembly. Botanicals found in plants have been found to possess these activities in the research. Researchers claim direct and indirect activities of botanical compounds and claim that botanicals can be effective for proper control of *Mycobacterium* spp. Although research claims that botanical compounds can control *Mycobacterium* spp. but there is a need to search their pharmacological interactions, long-term use effects, toxic reactions, and efficacy to treat real-world challenges. This review highlights the diseases cause by *Mycobacterium* spp., the identification of *Mycobacterium* spp., specific targets to destroy mycobacterial cell assembly, and important botanicals which have shown anti-mycobacterial activities in research.

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INTRODUCTION

Mycobacterium is a genus of bacteria belonging to the *Mycobacteriaceae* family (Clapasson and Canata, 2022; Silva *et al.*, 2022). *Mycobacterium* spp. are non-spore-forming, non-motile bacteria with a bacillus structure (Parija, 2023). *Mycobacterium* spp. show pleomorphism, i.e., they can alter their structure from round to rod-shaped (Ortiz *et al.*, 2021). *Mycobacterium* spp. are more like gram-positive bacteria, but are stained with acid-fast staining to differentiate from other bacteria (Tran *et al.*, 2021). *Mycobacterium* spp. have diverse organisms in the genus, i.e., they may be pathogenic, opportunistic, saprophytes, or nonpathogenic (Parija, 2023). Mycobacteria cause a variety of diseases with multiple organs, systems, and organisms involved. *Mycobacterium* spp. are notorious for tuberculosis (Bespiatykh *et al.*, 2021), which is a disease of the human lungs but besides it, there are multiple diseases associated with *Mycobacterium* spp. *M. ulcerans* causes widespread cosmopolitan cutaneous problems in humans (Pavlik *et al.*, 2022) likewise, *M. abscessus* can cause cutaneous, subcutaneous, and even visceral infection in humans (Abdelaal *et al.*, 2022). Similarly, *M. avium* complex *M. bovis, M. kansasii,* etc. cause disease in humans and animals (Bay *et al.*, 2021; Ehtisham-ul-Haque *et al.*, 2021). Multiple other species of *Mycobacterium* cause diseases in various species of reptiles, fishes, birds and mammals (Table 1).

Mycobacterium spp. have a huge variety of diseases associated with them. Proper identification of these *Mycobacterium* species is necessary so that they may be identified properly for their accurate diagnosis (AlMasoud *et al.*, 2021). *Mycobacterium* species are identified and differentiated from each other using microscopic and molecular techniques (Cheng *et al.*, 2021). Microscopic techniques involve multiple staining and micrometry techniques, but molecular techniques are necessary for

Table 1: Important species of genus *Mycobacterium* (*M.*), their host ranges, and clinical symptoms in animals.

Sr. No	Species	Host Spectrum	Disease	Disease signs	Reference (s)
1.	*M. tuberculosis*	Human	Tuberculosis	Dyspnea, pain in the chest, pyrexia, weight loss, chronic cough	(Yadav *et al.*, 2022)
2.	*M. avium avium*	Birds	Tuberculosis-like pulmonary disease (avian tuberculosis)	Pus filled vesicles, lowered weight gains, reduced egg production	(Parija, 2023)
3.	*M. avium paratuberculosis*	Ruminants, Human	Jhone's disease	Diarrhea, reduced production efficiencies, muscle loss, edema	(Elmagzoub *et al.*, 2022)
4.	*M. avium intracellulare*	Birds, Humans (immunocompromised), Pigs	Nanotubular respiratory and gastric infection	Cough, dyspnea, diarrhea, weight loss, bone marrow depreciation	(Portell-Buj *et al.*, 2022)
5.	*M. ulcerans*	Human	Buruli Ulcers	Painless nodules which form plaque and ulcers, large ulcers, and bone involvement also observed	(Dhungel *et al.*, 2021; Blasdell *et al.*, 2022)
6.	*M. bovis*	Bovines, Humans, Deer, Pigs, Felids, Canids, Elephants	Bovine tuberculosis	Respiratory issues, production, and reproduction losses	(Dellagostin *et al.*, 2022)
7.	*M. leprae*	Humans, Red Squirrels, Nine-Banded Armadillos	Hansen's disease (Leprosy)	Peripheral nerves of skin, eyes, muscles, nose	(Pfrengle *et al.*, 2021)
8.	*M. africanum*	Human	African tuberculosis	Pulmonary signs, cough, chronic fever, emaciation	(Comín *et al.*, 2021)
9.	*M. abscessus*	Human	Chronic lung infection, Skin & soft tissue infection, eye problems, infection of neural tissues	Tuberculosis-likes signs in pulmonary disease, cystic fibrosis	(Boudehen and Kremer, 2021; Griffith and Daley, 2022)
10.	*M. xenopi*	African frogs, Toads, and immunocompromised Human	Nontuberculous pulmonary disease	The less symptomatic disease of the lungs	(Hassan and Berenson, 2022)
11.	*M. simiae*	Rhesus Monkey, Human	Nontuberculous pulmonary disease	Non-specific signs, cough, dyspnea, and weight loss	(Zare *et al.*, 2022)
12.	*M. phlei*	Human, Cattle	Cutaneous tuberculosis	Redness and swelling of the skin. Lymphadenitis, bone destruction	(Basri *et al.*, 2022)
13.	*M. marinum*	Fish, Human (occasional)	Marine non-tuberculosis skin infection	Cutaneous necrosis, granulomas, mortalities	(Hendrikx *et al.*, 2022)
14.	*M. fortuitum*	Human	Mycobacteria abscesses and skin disease	Local Swelling and Inflammation	(Gharbi *et al.*, 2021)

proper identification of these species (Cheng *et al.*, 2021; Dávalos *et al.*, 2021). Among the molecular techniques, 16s rRNA is a very much important technique that can help us differentiation of multiple species (Ehtisham-ul-Haque *et al.*, 2021) (Fig. 1).

Mycobacterium spp. have been a problem of zoonotic, veterinary and human medicine since long period (Borrás *et al.*, 2022; González-Barrio, 2022; Lekko *et al.*, 2022; García-Díez *et al.*, 2023). *Mycobacterium* spp. have been a problem of great concern because they are resistant to multiple drugs (Rabaan *et al.*, 2022). *Mycobacterium* spp. have a thick external layer of peptidoglycans, mycolic acids, and phospholipids (Gründling and Collet, 2021) which is resistant to multiple drugs and stops entry of drugs into the cell making the pathogen resistant to multiple drugs (Borah *et al.*, 2021; Xu *et al.*, 2021; Chiarello *et al.*, 2022) (Fig. 2). Multiple classes of antibiotics are used simultaneously to control *Mycobacterium* spp. infection (Cetuk *et al.*, 2021; Lee *et al.*, 2022). The problem becomes severe when they become resistant to available antibiotics (Terreni *et al.*, 2021). Multiple drug resistance has been reported by multiple scientists, indicating that chemical antibiotics are failing to control the disease in the normal dose ranges (Church and McKillip, 2021; Catalano *et al.*, 2022). The increased doses are responsible for multiple metabolic disorders (Fahed *et al.*, 2022), increased risk of heart failure, cancer development (Velikova *et al.*, 2021), disturbance in the normal microbiota of the body (Chen *et al.*, 2021) and increased chances of fungal growth (Fernández *et al.*, 2021; Sayyar *et al.*, 2021). Drug residues are a severe concern for public health and research data suggest that drug residues are among the major factors which disturb the natural balance of the ecosystem (Khan *et al.*, 2021a). These problems highlight the need for parallel control methods for the control of mycobacterial infections.

Vaccination of humans and animals, prone to the *Mycobacterium* spp. is an ancient strategy to combat the *Mycobacterium* spp. infections (Pacheco *et al.*, 2020). The first vaccine developed against *Mycobacterium* spp. was the "Bacillus Calmette–Guérin" Vaccine (BCG vaccine), which was named after the scientists who developed it (Guallar-Garrido and Julián, 2020). BCG has been primarily developed to combat *M. tuberculosis,* but it was found effective against multiple other species of *Mycobacterium* (Fatima *et al.*, 2020; Jia *et al.*, 2022). Anti-mycobacterial vaccine has been compulsory in multiple countries and is still practiced (Gosavi and Marley, 2020). BCG vaccine has been limited because of its safety, side effects, and low efficacy (Buddle *et al.*, 2018). Vaccines can't be given to immunocompromised people and have no efficacy against the latent tubercles of previous infections (Cho *et al.*, 2021). Multiple other vaccines have been developed and they are being practiced against *M. tuberculosis* especially and other *Mycobacterium* spp. (Broncano-Lavado *et al.*, 2022). *Mycobacterium* induced infections are not successfully being prevented by the vaccines because of their immune system evasion mechanisms, altered inflammatory pathways, and several virulence factors giving them the ability to survive in the macrophages (Ferluga *et al.*, 2020). These issues are not only leading to current vaccine failures but put a question on future vaccines because of the rapid shift in the genetics of *Mycobacterium* (Foster *et al.*, 2021; Kaufmann, 2021; Carey *et al.*, 2022). *Mycobacterium* is a challenge for researchers to opt for a suitable control strategy for it.

Mycobacterium spp. are under consideration for a long time because of human tuberculosis and other diseases in humans and animals (Mohamed, 2020). The ancient methods primarily focused on botanicals for the

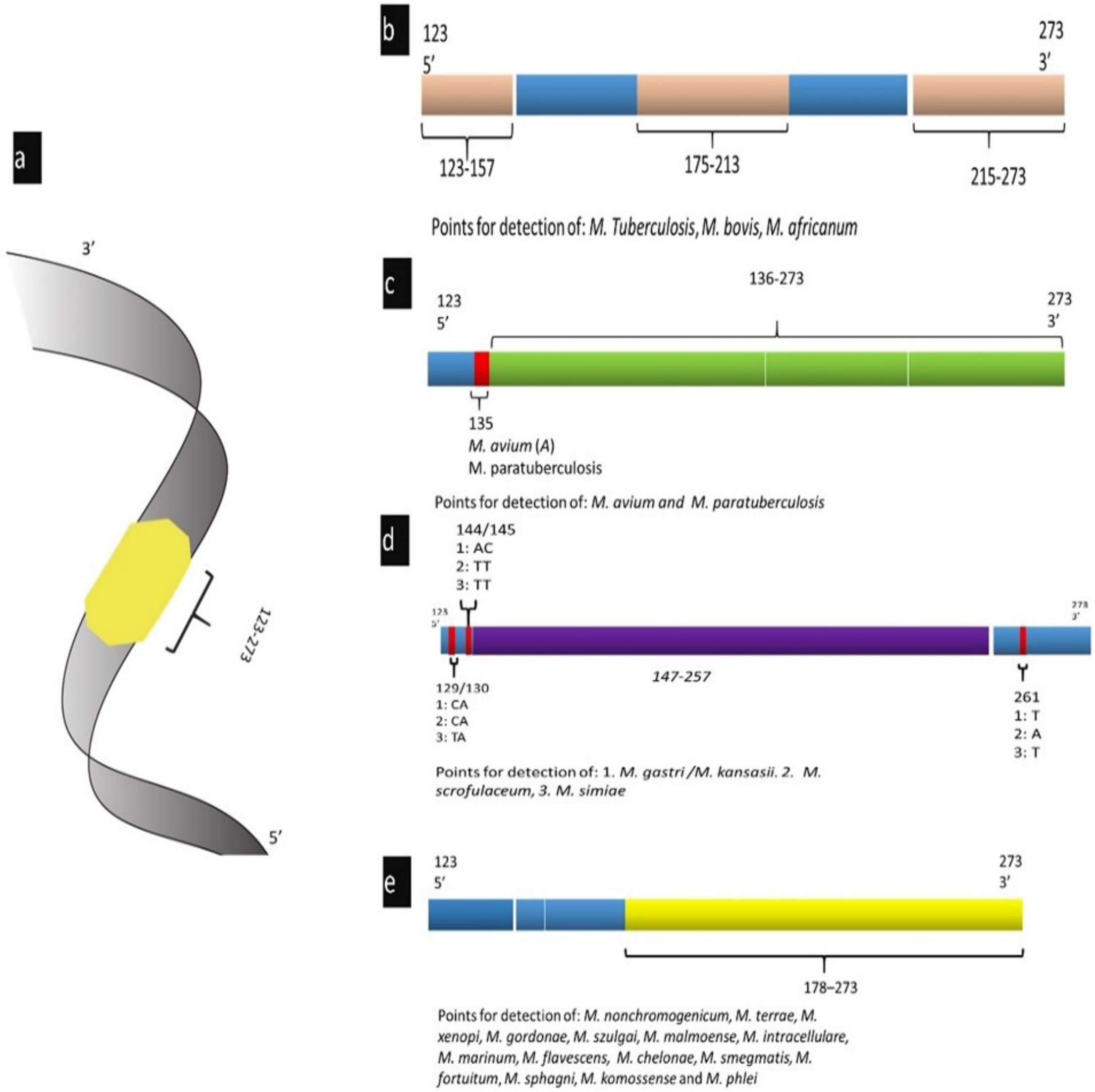

Fig. 1: 16S RNA is used for the differentiation of multiple species of *Mycobacterium* (*M.*). (a) There are several nucleotide sequences on the 16S RNA which can serve as distinction markers for the *Mycobacterium*, among them a region between 123-273 base pair (3' to 5' according to *E. coli* numbering) helps differentiation of multiples species. (b) *M. tuberculosis*, *M. africanum*, and *M. bovis* have three distinct base pair regions (i) 123-157, (ii) 175-213, and (iii) 215-273 which are common for these species and make them distinct from other species, however these species need microscopic techniques to be differentiated from each other. (c) *M. avium* and *M. paratuberculosis* have a similar arrangement for the 136th base pair to the 273rd base pair, they can be differentiated at the 135th base pair where *M. avium* has adenine which is not present in the *M. paratuberculosis*. (d) *M. gastri*, *M. sacrofulaceum*, and *M. simiae* have similar base pair arrangement from position 147-257 and they can be differentiated from each other at 129/130. 144/1145 and 261 positions where they have different nucleotide arrangements. (e) Multiple other species have their identification points from 178 to 273 base pairs, each having its differentiation points based on nucleotide arrangement.

control of *Mycobacterium spp.*, which were extracted from indigenous plants (Vaou *et al.*, 2021). Modern scientists suggest multiple strategies, but phytochemicals are still among the major substances which can be alternatives to antibiotics and vaccines, or they may be used as supportive agents to combat mycobacterial infections (Chowdhury *et al.*, 2023). Multiple botanical compounds have been proved to be effective antibiotic, antiparasitic, antibacterial, anti-inflammatory, antioxidant, and immunomodulatory agents (Giordano *et al.*, 2021; Radwan *et al.*, 2021; Sarwar *et al.*, 2021; Dahab *et al.*, 2022; Degla *et al.*, 2022; Ugwuoke *et al.*, 2022). These properties have forced researchers to discover their activities to combat mycobacterial infections. This review presents an overview of prominent groups of phytochemicals which can be used as anti-mycobacterial agents.

Review methods: Keywords were selected after reading multiple articles. The keywords included the title "Botanicals for the control of *Mycobacterium* spp."; where "phytochemicals", "Herbals", "plants", "essential oils", "Herbal compounds", and "Plant derived compounds" were used as synonyms with botanicals. Similarly, the names of botanical compounds like "flavonoids", "alkaloids" "tannins" "terpenes", "terpenoids" and were also used as alternatives for the botanicals. "*Mycobacterium*", and "*Mycobacteria*" were used as synonymous with the "*Mycobacterium* spp." while specific names of multiple pathogenic species were also used ResearchGate (www.researchgate.com), ScienceDirect (https://www.sciencedirect.com), Google Scholar (https://scholar.google.com/), and National Library of Medicine (https://www.ncbi.nlm.nih.gov/)

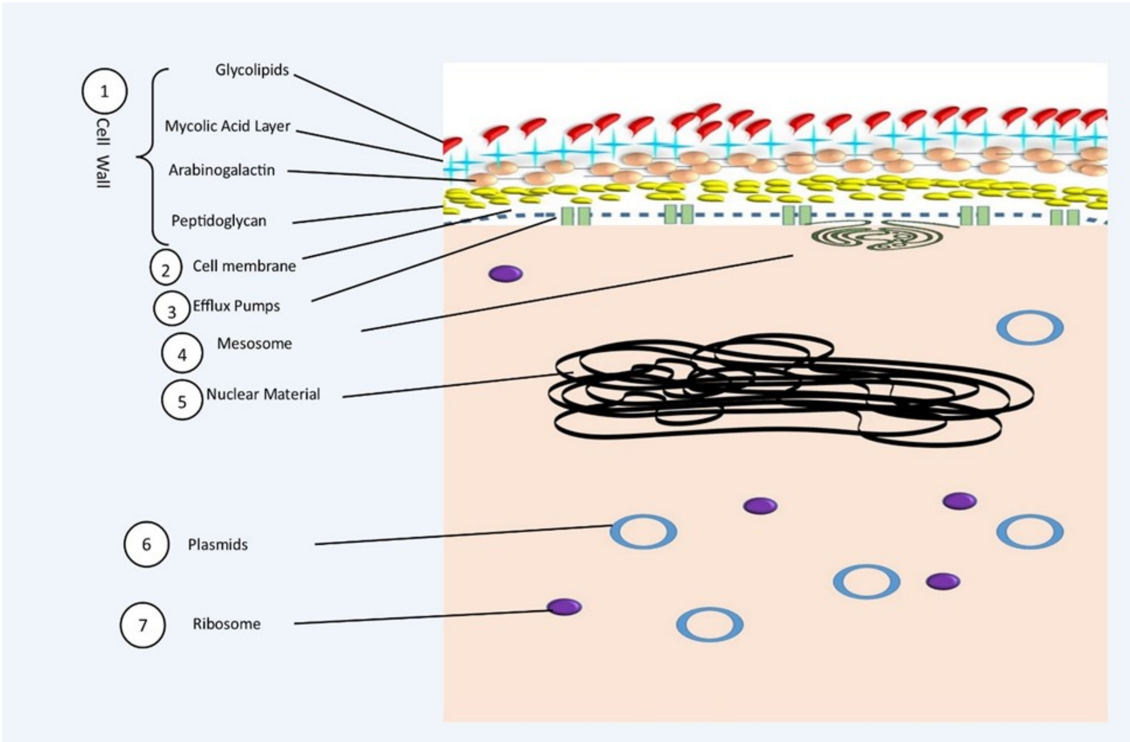

Fig. 2: Bacterial cell outlook presenting a cross-section of the cell wall and intracellular contents. This helps us to understand the control point to destroy mycobacterial cells. 1. Cell wall is the primary checkpoint because the thick multilayered cell wall protects *Mycobacterium* spp. targeting it makes the immune system and antibacterial botanicals. 2. Cell membrane is another critical point to destroy the cell structure of *Mycobacterium* because the permeability of materials depends upon the cell membranes as well as the cell membrane is the site of energy production for the *Mycobacterium.* 3. Efflux pumps which control the elimination of toxic materials from the cell. 4. Mesosomes are involved in DNA synthesis and cell division, disabling them can disturb cell maintenance and replication. 5. Nuclear material contains basic information for the cell its destruction or mutation disturbs the cell's existence. 6. Plasmids are important non-nuclear circular DNA, they can be targeted to limit the *Mycobacterium* spp. 7. Ribosomes help in protein synthesis; they can be targeted to disturb cell maintenance and functioning.

were used as research engines (Saeed and Alkheraije, 2023). The table was constructed on qualitative data and quantification however; statistical meta-analysis was not performed.

Review findings: A qualitative review was performed, so the data of the review is not presented statistically. After all, in this review, it is found that plants are being used in multiple forms, i.e., essential oils (El Omari *et al.*, 2019; Silva *et al.*, 2020), ethanolic extracts (Gibango *et al.*, 2020; Zodape *et al.*, 2021;), aqueous extracts and methanolic extracts (Jethva *et al.*, 2020) are in recent trend (2019-2023) being searched for their against *Mycobacterium*, but trend is now being shifted from complex mixtures to isolated compounds and their synthetic derivatives (Maiolini *et al.*, 2020). Multiple authors have used more than one plant and even one hundred plants have been used in a single study (Jethva *et al.*, 2020). Similarly, researchers used more than one species of *Mycobacterium* in their studies (Sari *et al.*, 2019). Most of the research was present on *M. tuberculosis* and it was the major species to be searched for control, other major species were *M. smegmatis, M. avium, and M. bovis* (Kapojos *et al.*, 2020). Major anti-mycobacterial botanical compounds included alkaloids, terpenes, flavonoids, and tannins (Table 2). For the proper understanding of the mechanism of actions of these botanical compounds, checkpoints for the control of mycobacterial infections are necessary.

Mechanism of antimycobacterial to control the *Mycobacterium* spp.: There are diverse mechanisms of actions of anti-mycobacterial substances major points of antimycobacterial are given below:

Cell wall: The cell wall has the primary role in the protection of Mycobacterium spp. from external agents including the immune system and drugs (Daffé and Marrakchi, 2019; Gondil *et al.*, 2020; Arrigoni *et al.*, 2022). The cell wall of *Mycobacterium* spp. is a complex structure comprising phospholipids, mycolic acids, peptidoglycans, and arabinogalactan (Daffé and Marrakchi, 2019) (Fig. 2). Disturbing production, assembly, and maintenance of these compounds can lead to the control of *Mycobacterial* infection (Xiong *et al.*, 2020; Holzheimer *et al.*, 2021). Multiple botanical compounds like flavonoids can target mycolic acid, peptidoglycans, and arabinogalactan leading to the destruction of *Mycobacterium* spp. (Maiolini *et al.,* 2020).

Cell membrane: The cell membrane is the biological barrier that controls the transport of ions, nutrients, and metabolites through it (Möller *et al.*, 2019). Prokaryotes like Mycobacterium spp. have their energy production mechanisms i.e., electron transport channels in the cell membrane (Han *et al.*, 2022). Energy production is the key factor to the cell's existence and maintenance. Targeting cell membranes leads to disturbance in the cell atmosphere, energy production and cell functioning

Table 2: Botanical compounds, their mechanism of action (MOA), and their effects against different species of genus *Mycobacterium*.

Sr. No	Group	Compound/ preparation name	MOA	Plant name	*Mycobacterium* species	Results	References
	Alkaloids	Piperine	Inhibition of efflux pumps of ethidium bromide	*Piper nigrum* and *Piper longum*	*M. smegmatis*	Blocked the efflux pumps of *m. Smegmatis*	(Jin *et al.*, 2011)
		Ethanolic acetic acid extracts	Inhibition of efflux pumps, disturbance of cell membrane permeability, destruction of glucose pumps	*Combretum* (C.) *zeyhri, C. molle, C. apiculatum, C. platypetalum*	*M. smegmatis*	*C. Zeyhri* was the best among all. All showed antimycobacterial activities.	(Nyambuya *et al.*, 2017)
		Ethanolic extracts	Inhibition of efflux pumps, disturbance of cell membrane permeability, destruction of glucose pumps	*C. zeyhri, C. molle, C. hereroense, C. pletypetalum, C. alaegnoids*	*M. aurum, M. smegmatis*	*C. Zeyhri* was the best among all. All showed antimycobacterial activities	(Magwenzi *et al.*, 2014)
		Bisbenzylisoquinoline	Inhibiting the Protein synthesis in the bacteria	*Tiliacora triandra*	*M. tuberculosis*	Proved strong antibacterial agents	(Sureram *et al.*, 2012)
		Quinolones	Bactericidal agents	*Dicranostigma franchetianum*	*M. avium, M. aurum, M. kansasii M. smegmatis*	Showed antimycobacterial activities	(Wijaya *et al.*, 2022)
		Globospiramine	Bactericidal agents	*Voacnga globosa*	*M. tuberculosis*	Showed antimycobacterial activities	(Macabeo *et al.*, 2011)
		Vaccine acetate, 2-acetyl benzylamine	Bacteriostatic activity	*Adhatoda vasica*	*M. tuberculosis*	The strong antimycobacterial activity was observed	(Ignacimuthu and Shanmugam, 2010)
		Pyridine-N-oxide	Blocking of efflux pumps of cell membrane	*Allium stipitatum*	*M. tuberculosis*	Potent antimycobacterial activity was observed	(Amengor *et al.*, 2022)
	Flavonoids	Tirimethoxy flavanone compounds	Disturb nucleic acid formation. Disturb mycolic acid formation	*Chromolaena odorata*	*M. tuberculosis, M. avium, M. smegmatis, M. fortutum, M. aurum*	Sufficient to control the growth of infectious agents	(Omokhua-Uyi *et al.*, 2023)
		Linaroside, Lantanoside	Inhibition of growth of *Mycobacterium*	*Lantana camara*	*M. tuberculosis*	Linaroside was found effective for *mycobacterium*	(Begum *et al.*, 2008)
		Isoliquiritigenin	Possesses anti-inflammatory properties by stopping inflammatory factors	*Glycyrrhiza* spp.	*M. tuberculosis*	Successful stopped inflammation produced an immune response to mycobacterial infection	(Sun *et al.*, 2022)
		Quercetin	Efflux pumps of bacteria are blocked	*Allium cepa*	*M. smegmatis*	Sufficient antibacterial activity was observed	(Sharma *et al.*, 2019)
	Terpenes and derivatives	Terpene-rich ether extract	Destroy the structure and function of the cell wall and cell membrane	*Lantana camara*	*M. tuberculosis*	Showed anti mycobacterial activities	(Patil and Kumbhar, 2018)
		Essential oil	Cell membrane of bacteria is affected	*Micromeria barbata, Juniperus excelsa, Eucalyptus globulus*	*M. kansasii, M. gordonae, M. tuberculosis*	Proved strong antibacterial agents	(El Omari *et al.*, 2019)
		Essential alpha-pinene, Tricyclene	Cell wall damage and disturbing of the lipophilic structure of mycobacterial cell	*Zingiber officinale*	*M. tuberculosis, M. smegmatis, M. chlonae, M. abscessus* (subspecies: abcessus, bolletti, massiliense)	Strong antibacterial activities were observed	(Baldin *et al.*, 2019)
		Alpha-pinene, Beta pinene, and sabinene (Essential oil)	Biofilm formation of the bacteria. Coagulation of the cytoplasmic material.	*Juniperus communis*	*M. avium, M. intracellulare*	Essential oil was successful in restricting growth of *Mycobacterium* spp.	(Peruč *et al.*, 2022)
	Tannins	Condensed tannin (falavan-3-ols)	Improved immune efficiency to control the infection	*Diospyros kaki*	*M. avium*	The strong antimycobacterial activity was observed	
		multiple compounds (unspecified tannins)	Bactericidal and anti-inflammatory activities	*Schkuhria pinnata*	*M. smegmatis*	Sufficient to control the growth of infectious agents	(Masiphephethu, 2019)
		Extracts	Unspecified mechanism of action	*Uvaria afzelli, Tetracera alnifolia, Scott elliot*	*M. tuberculosis*	Sufficient to control the growth of infectious agents	(Lawal *et al.*, 2011)
		Ellagitannins	Multiple compounds present in extracts were responsible for bactericidal activities	*Combretum hartmannianum*	*M. smegmatis*	Linaroside was found effective for *mycobacterium*	(Salih *et al.*, 2018)
		Tannin rich extracts	inhibit mycobacterial enzymes, decrease the availability of essential ions for mycobacteria by chelate forming	*Anacardium occidentale*	*Mycobacterium smegmatis*	Successful stopped inflammation reduced in response to mycobacterial infection	(Santos *et al.*, 2011)

(Xiong *et al*., 2020) (Fig. 2). Research shows that botanicals like terpenes and essential oils can destroy phospholipid bilayer and efflux pumps in the cell of *Mycobacterium* spp. leading to cell death (Tariq *et al*., 2019; Wińska *et al.,* 2019; Gorlenko *et al.,* 2020).

Protein production: Protein synthesis is the key function of transferring genetic information into any living cell (Dong *et al*., 2020; Silverman *et al*., 2020). Proteins are responsible for the maintenance of cell structure, function, and division (Bertrand, 2019; Cassio Barreto de Oliveira and Balan, 2020). Disturbing in the translation of nucleic information i.e., protein synthesis can lead to faulty cell functions leading to cell death of *Mycobacterium* spp (Równicki *et al*., 2020; Baran *et al*., 2023). Multiple botanical compounds have been found to be effective in controlling protein production by different pathways (Sharma *et al*., 2019; Maiolini *et al*., 2020).

Disturbance in nuclear material: *Mycobacterium* has no definite nucleus, but their nuclear information is present as nuclear material found in the cytoplasm, plasmids, and in ribosomes (Haider *et al.,* 2022). Multiple drugs are available those target the DNA gyrase of the *Mycobacterium* (Shetye *et al*., 2020). Botanicals are effective in disturbing DNA assembly and DNA gyrase activities leading to the destruction of mycobacterial cell structure (Khameneh *et al*., 2021).

Botanicals compounds for control of Mycobacteria

Alkaloids: Alkaloids are a diverse group of botanical-driven compounds which contain Nitrogen in their structure (Chen *et al*., 2022b). Alkaloids are divided into multiple groups based on their structure and function (Gutiérrez-Grijalva *et al*., 2020). The alkaloids have vide reported antibacterial, anti-inflammatory, and antifungal activities (Doughari and Saa-Aondo, 2021). Alkaloids can cause disturbance in the DNA and protein synthesis of bacteria (Kasta, 2020). In the studies, it has been presented that alkaloids may attach to DNA during the transcription process and disturb the transfer of information from DNA to RNA and interrupt the protein and nucleic acid formation (Abookleesh *et al*., 2022). These changes can cause major issues in the bacterial cell structure and functioning hence the bacterial cell undergoes death (Deng *et al*., 2021). Alkaloids may cause disturbances in the cell wall and cell membrane structure altering these physical barriers and disturbing the transport of nutrients (Nourbakhsh *et al*., 2022; Nazarov *et al*., 2023). Likewise, alkaloids disturb the bacterial efflux pumps leading to the late excretion of antibiotic agents from the cell. Due to these properties, alkaloids have been the favorite substances to be searched for their medical use against the mycobacterium species. Multiple alkaloids have been used by the researchers and found effective to control multiple species of Mycobacterium including M. tuberculosis, M. bovis and non-tubercular Mycobacterium species (Daniel and Bhakta, 2022; Swain *et al.,* 2022; Thibane and Mudau, 2022).

Flavonoids: Flavonoids are among the phenolic compounds that have two phenolic rings in their structure along with an additional heterophilic ring in their basic structure (An *et al*., 2021; Scicutella *et al*., 2021). They are divided into various classes like flavones, isoflavones, flavonols, flavanones, etc. (Guven *et al*., 2019; Dias *et al.,* 2021; Khan *et al*., 2021b). Flavonoids are among the major substances which have been searched for their antibacterial activities (Adamczak *et al*., 2019; Murtaza *et al*., 2021). A wide range of flavonoids have been used in research trials to treat Mycobacterium infections. They can control Mycobacterium by multiple pathways (Sun *et al*., 2022). Flavonoids can cause the efflux pump blockage of Mycobacterium spp. leading to disturbed metabolite and drug regulations (Górniak *et al.,* 2019; Biharee *et al.,* 2020; Biswas *et al*., 2021) (Table 2). It has been reported that quercetins not only block the efflux pump but also affect DNA gyrase inhibition, leading to malfunctioning in the DNA replication, translation, and transcription of mycobacterial DNA. Quercetin and other flavonoids have been found to disturb the cell wall structure and synthesis of *Mycobacterium* spp. as they inhibit the Uridine 5'-diphopshategalactopyranosemutase (Gupta and Datta, 2019; Swain *et al*., 2022). Flavonoids also disturb fatty acid synthesis and mycolic acid formation (Dong *et al*., 2015; Bouyahya *et al.,* 2022). Because of these properties, flavonoids have been recommended by multiple researchers to be used against tubercular and non-tubercular *Mycobacterium* spp. (Bose *et al*., 2021).

Tannic acids and derivatives: Tannic acids and their derivatives are usually called tannins (Fabbrini *et al.,* 2022; Zeng *et al*., 2022). Botanical tannins are usually divided into hydrolyzable tannins, condensed tannins, and phlobatannins (Li *et al*., 2022). They are polyphenolic compounds with astringent properties. The tannins are known because of their chelating activities. Tannic acids can coagulate proteins and metals and can form chelates (Baldwin and Booth, 2022; Chen *et al.,* 2022a). They can reduce cellular nutrition by reducing the availability of nutrients for bacteria (Samtiya *et al*., 2020). They can potentiate immune response against the bacteria and lead to control of the *Mycobacterium* spp. Researchers have searched multiple tannins for the control of *Mycobacterium* spp. and have found them effective (Farha *et al*., 2020; Bolívar-Ramírez *et al*., 2022).

Terpenes and terpene derivatives: Terpenes are hydrocarbons with usually low molecular weight, also termed isoprene derivatives (Mahizan *et al.,* 2019; Zhang *et al.,* 2023). They are widely present in the plants, especially in conifers (Raza *et al*., 2022). Essential oils are the fraction of plants that are rich in terpenes and derivatives (Bhardwaj *et al.,* 2020). They are further divided into subclasses: monoterpenes, diterpene, and sesquiterpenes (Bahmani *et al*., 2022; Di Sotto *et al*., 2023). These compounds are lipophilic and have the potential to assimilate into the phospholipid membranes (El-Dawy *et al*., 2022). Terpenes can destroy the phospholipid assembly of the cell membrane of Mycobacterium and lead to destruction in the structure and function of the cell membrane (Tariq *et al*., 2019; Nourbakhsh *et al*., 2022). Research states that terpenes and essential oils rich in terpenes are effective against various Mycobacterium spp. (Bueno *et al*., 2011; Baldin *et al*., 2019).

Conclusions: Plants are the largest natural source of medicine provider. Since ancient times plants have been practiced to control several diseases. In this review, we have observed that the phytochemicals have the potential to control the *Mycobacterium* spp. multiple compounds extracted from plants showed promising results against various species of *Mycobacterium*. Various classes of compounds have shown effective antibacterial activities via diverse mechanisms of action. Further research is being done to find suitable derivatives which may potentiate their effects. The article shows that the botanical compounds ndividually and in combinations can control *Mycobacterium*. Data are scarce on their clinical use against clinical forms. There is a need to identify the obstacles limiting their commercialization. Their pharmacological interactions with other antimycobacterial compounds should also be determined so that we may control mycobacterial infections easily.

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