The Exploration of Phytomedical Compounds as a Novel Approach for Therapeutics in Tuberculosis

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Background: Tuberculosis (TB) caused by *Mycobacterium tuberculosis* (*Mtb*) remains a major global health challenge. With the rising emergence of drug-resistant strains in addition to the long duration and frequent side effects associated with existing treatment regimens, the need for innovative strategies to combat the disease has never been greater. Besides gaining recognition for extensive medicinal properties, plant-derived bioactive compounds have long been studied for their antimycobacterial activity. Literature associates phytocompounds with the advantages of flexibility and a multi-target approach, leaving little likelihood of resistance development. Notable medicinal-plant-based studies have been conducted at The Foundation for Medical Research (FMR), with an aim of identifying the most effective natural anti-TB agents. Six plants, namely *Acorus calamus* (rhizome), *Alpinia galanga* (tubers), *Andrographis paniculata* (leaves), *Ocimum sanctum* (leaves), *Piper nigrum* (seeds), and *Pueraria tuberosa* (tubers), were tested for their anti-TB activity using axenic cultures of *Mtb* reference strain (*Mtb* H37Rv), and clinical strains (drug-sensitive and drug-resistant), followed by intracellular assay systems. Among the six plants, *A. galanga, A. paniculata,* and *P. nigrum* were found to be most promising as they exhibited anti-TB activity against all strains including drug sensitive and resistant clinical strains, through multiple modes of action. The *Mtb* genome houses several noncanonical deoxyribonucleic acid (DNA) structures that are crucial in regulating replication and transcription processes. Recent studies have implicated the formation of these structures in regulating the expression of key bacterial genes responsible for survival, virulence, and drug-resistance. Researchers have been successful in targeting these structures using synthetic and natural ligands. Plant-derived flavonoids, alkaloids, and polyphenols are reported to show binding interactions with noncanonical DNA that can be exploited for developing therapeutic strategies. The binding and stabilization of noncanonical DNA structures formed in key *Mtb* genes, by quercetin and kaempferol has been successfully validated in the preliminary studies conducted at FMR.

Methods: In the future, assessing the role of phytomedical compounds in binding and targeting noncanonical DNA of *Mtb* through *in silico*, biophysical, and *in vitro* studies could provide insights into their potential in inhibiting *Mtb* growth, reducing cytotoxicity to the host, and modulating drug resistance. This can generate comprehensive evidence to support them as prospective drug candidates for therapeutic interventions.

Results: The expected outcomes would include the identification of phytocompounds as novel drug candidates or adjuncts to conventional therapy, capable of combating drug-resistant TB and contributing to the development of effective, phytomedicine-based therapies in the future.

Conclusion: Phytomedicine may hold promise for exerting a synergistic pharmacological effect through multiple modes of action including targeting of noncanonical DNA. This avenue warrants deep investigation, both with crude extracts and single/multi- phytocompounds.

Keywords: Noncanonical deoxyribonucleic acid, phytomedical compounds, tuberculosis

Conflicts of interest

There are no conflicts of interest