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Emerging tuberculosis risks and natural flavonoids: A cross talk

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Abstract

Flavonoids are a broad family of small molecular secondary metabolites that have the potential to act as antibiotic substitutes. Flavonoids have a wide structural diversity and show inhibitory activity against a variety of bacterial pathogens. Therefore, it stands out to be an ideal template for therapeutic development against a variety of chronic bacterial infections. There has always been a great demand for new drugs against many diseases among which tuberculosis may also be considered. Tuberculosis (TB) is the most common infectious cause of death worldwide. Several studies confirmed synergistic relationship between flavonoids and anti-microbial drugs. The goal of this work is to review the current tuberculosis research and development of flavonoids as prospective tuberculosis prevention drugs which may pave a new way for future tuberculosis treatment.

Key words : Infection; drug; *Mycobacterium tuberculosis*; flavonoids; cell wall.

Tuberculosis (TB) is one of the world's most lethal infectious diseases and major public health concern. *Mycobacterium tuberculosis,* the bacteria that causes tuberculosis, primarily infects the lungs and respiratory system, as well as other major organs[90]. According to the World Health Organization[90] (WHO) report 2017, around 10 million people were infected with this bacterium. Of these, 1.6 million people died as a result of inadequate treatment. Extensive investigation in the recent past showed the prevalence of worldwide diversity in TB case variation between different nations. India, Indonesia, Pakistan, Philippines, Nigeria, China, Bangladesh, and South Africa are among the top eight TB burdened countries (WHO Fact Sheet, Accesed 10.05.2019). The current TB treatment includes six months of antibiotic treatment, with the first two months (intensive

phase) consisting of ethambutol, isoniazid, pyrazinamide, and rifampicin. The latter four months (continuous phase) are treated with rifampicin and isoniazid[63]. Insufficient and improperly supervised therapeutic approach, dosage, or infection in the presence of other comorbidities is to be blamed for the evolution of multi-drug resistant strains of TB (MDR-TB). In most of the cases, MDR-TB variants show resistance against two frontline drugs *i.e.* isoniazid and rifampicin[51]. In these circumstances, the treatment term is extended to 20 (twenty) months with the second line of drugs such as amikacin, capreomycin, fluoroquinolones, and kanamycin[90]. MDR TB in its advanced form *i.e.* extensively drug-resistant (XDR) TB shows resistance against fluoroquinolone and second line of injectable drugs[28]. Furthermore, latent tuberculosis infection caused by the MTB (*Mycobacterium Tuberculosis*) does not manifest any symptoms[13]. It is estimated that over a quarter of the world's population was infected with MTB, with 5-15 percent developing active TB as a result of the MTB's longer latency period than other bacteria (Getahun *et al*.[33]; Houben *et al*.[43]). Although existing drugs for the treatment of tuberculosis are showing significant improvement, their availability to the world's population is a big concern due to their cost, toxicity and treatment length. Because all of the medications now approved are based on observational studies, there is considerable debate about the best treatment for MDR-TB patients in the absence of adequate randomized clinical trials[55].

Nature is the vast source of biologically active compounds[32]. Several published research in recent years has detailed the chemical composition of plant extracts, containing a variety of biological features that make them effective against bacteria, including mycobactericidal activity. As a result, worldwide TB medication research based on natural products is a promising avenue for the development of new anti-tubercular medicines that are well-tolerated, effective, and short-duration[62]. In this review, we attempt to discuss existing TB treatments, flavonoid characteristics known to be effective against *M. tuberculosis*, and breakthroughs in anti-tubercular research.

Pathogenesis :

Inhalation of as low as less than 10 bacteria may cause the disease[64]. The bacterium is passed from person to person through droplets released by active tuberculosis patients during sneezes, splits, and coughs[22]. Ninety percent of infected patients have latent tuberculosis infection (LTBI), whereas the other ten percent show the symptoms of an active TB disease[64]. It is well established that people with LTBI do not infect others; only untreated or partly treated tuberculosis patients transmit the bacteria[3]. First, the MTB reaches the alveolar air sacs and begins replicating inside the alveolar macrophage endosome[43]. With the help of the waxy coat cell wall of MTB, it escapes from the phagosome attack, the latter combines with lysosomes and becomes phagolysosomes (generally kills bacteria by the ROS and acid activity)[75]. The bacteria then adapt to the host phagosome environment through a process known as transcriptional reprogramming. MTB then switches to an anaerobic respiratory pathway, where aspartate and cholesterol are utilized as nitrogen and carbon sources,

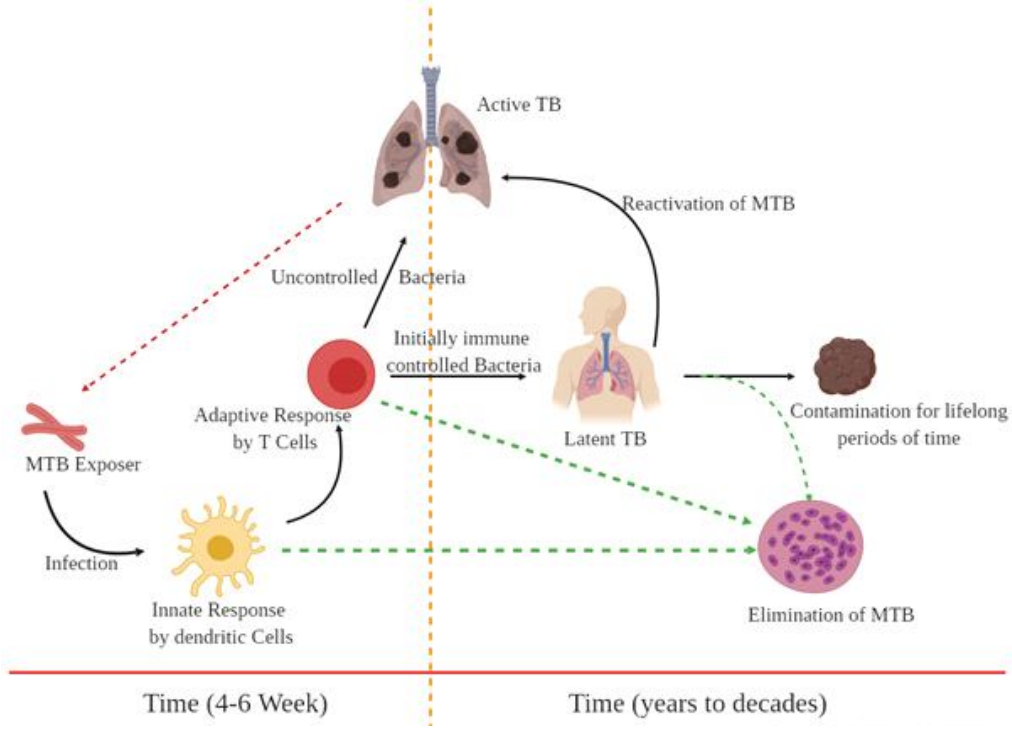

Fig. 1. Mycobacterium tuberculosis infection cycle and stages with treatment time

respectively, via modifying the iron scavenging mechanism[12]. During the process of infection, MTB secretes ESX-1 and ESAT6 to kill the host cell macrophages followed by apoptosis[84,91]. Efferocytosis and emancipation of bacteria into the extracellular space stimulate bacterial multiplication and onward transmission to other hosts when the host macrophage dies. During this phase, the MTB bacteria is sometimes controlled by body immune cells (dendritic cells, T cells), and some of them get eliminated (Fig 1). However, in certain situations, these regulated bacteria persist in the body without damaging the host, resulting in latent tuberculosis infection, which can reactivate over time and lead to active tuberculosis infections[25].

Natural flavonoids as an important drug leads:

Secondary metabolites from plants are well-known for their potential to cure and prevent a variety of infectious diseases[80]. The phenolic compounds make up a large fraction of plant-derived secondary metabolites, with flavonoids being the most bioactive compound[23]. Natural flavonoids derived from plants have been thoroughly studied, with results supporting their usefulness in the treatment of a variety of human illnesses[71]. 88 percent of people worldwide rely on natural remedies for their primary health care. Based on these observations, phytochemical-based drug discovery has become a popular object of research, and it

has already made a substantial contribution to the development of leads against numerous pharmacological targets. Alkaloids, glycosides, polysaccharides, and terpenoids are the best-investigated plant-based active compounds[80]. Flavonoids have a wide range of biological properties that benefit human health and aid to reduce disease risk[31]. The solubility of flavonoids may be the most important factor for their medicinal effectiveness. Flavonoids with low solubility aglycones in water, short residence time in the colon, and limited absorption do not allow humans to structure immediate harmful effects from flavonoid ingestion[41]. Flavonoids are being examined extensively because of their anti-oxidant, anti-inflammatory, anti-cardiovascular disease, anti-bacterial, anti-mutagenic, anti-carcinogenic, and anti-viral properties[66].

Flavonoids can be found in a variety of plant parts, including the leaves, stems, roots, seeds, and flowers (major coloring compound). They are backboned by a 15-carbon compound composed of two benzene rings followed by a pyrene heterocyclic ring. Flavones are classified into flavons, flavonols, flavanones, flavonols, isoflavones, and flavan-3-ols based on their structure[48]. Furthermore, flavonoids are subdivided into the following classes based on changes in their C rings and molecular structure: flavones, anthocyanidins, flavans, flavanones, flavonolignans, isoflavones, isoflavones, and chalcones[10].

Anti-mycobacterial properties :

The antimicrobial actions of flavonoids are perhaps the well-studied and well-known biological effects of flavonoids. Many flavonoids have antimicrobial properties (Table-1). Several investigations have found a synergistic relationship between these phytocompunds and synthetic anti-tuberculous drugs. This interaction helps in decreasing the MIC value of the drug. Chrysin (5,7-dihydroxyflavone), for example, inhibits the growth of *E. coli* and *P.aeruginosa* at a rate comparable to streptomycin[6,17]. Synergistic interaction of anti-tuberculous drugs with cerulin and trans-cinnamic acid inhibited the growth of *Mycobacterium tuberculosis*[77]. Several investigations found that certain acetylated derivatives of quercetin, such as quercetin 3-arabinopyranoside-2"-gallate, were active against *E. coli*.[53,89]. The presence of hydroxyl groups at locations C-5 and C-7 support the action of lipophilic flavonoids against *B. Cereus*[94]. Another study using plumbagin and isoniazid found that isonicotinic acid hydrazide is approximately four times more effective against *Mycobacterium* sp. [58]. However, the toxicity profiles, as well as the pharmacokinetic features of these compounds, are under discussion.

Mode of Action of Flavonoids in Mycobacterium species :

The effects of flavonoids may be attributed to their capacity to resist microbial adhesions, transport proteins, *etc.* [48]. Flavonoids attack bacteria by binding to their cell walls and membranes. Key modes of action include bacterial enzyme inhibition, bacterial efflux pump inhibition, and biofilm eradication[29] (Fig. 2). Two flavonoids namely; chalcones (licochalcone A and licochalcone E) indicated inhibitory activity of bacterial infection by decreasing the expressions of bacterial genes, ultimately inhibiting the bacterial growth and

Table-1. List of bioflavonoids active against *Mycobacterium* species

Sl. no.	Compounds	Active against	Referencs
1	Isobachhalcone, Kanzanol C, 4-hydroxy-lonchocarpin, stipulin and amentoflavone	*Mycobacteria tuberculosis.*	Kuete *et al.*[47]
2	Cinnamic acid	*M. tuberculosis H37Rv* strain	Guzman *et al.*[38]
3	Cerulenin, trans-cinnamic acid strain, MDR-TB	*M. tuberculosis* H37Rv	Rastogi *et al.* [77]
4	5,4' -dihydroxy-3,7,8,3-tetramethoxy-flavone, 5,4' -dihydroxy-3,7,8-trimethoxyflavone	MDR-TB	Esquivel-Ferrino *et al.*[27]
5	3' -formyl-2',4' -dihydroxy-6'-methoxychalcone	*M.tuberculosis*	Prawat *et al.*[73]
6	Totarol, ferruginol, plumbagin	*Mycobacterium* sp.	Mossa *et al.*[58]
7	3-cinnamoyltribuloside, afzein and stilbin	*Mycobacterium* sp.	Christopher *et al.*[21]
8	Mombinrin, mombincone, mombinoate, and mombinol	*M. tuberculosis*	Olugbuyiro *et al.*[65]
9	7-hydroxy-6,8-dimethoxyflavanone	*M.tuberculosis*H37Ra	Prawat *et al.*[72]
10	Kenusanone F 7 methyl ether and sophoronol-7-methyl ether	*M. tuberculosis* H37Rv	Mutai *et al.*[6]
11	Flavones: Nevadensin, Isothymusin	*M.tuberculosis,*	Suksamrarm *et al.*[86]
12	Isosakuranetin, 4'-hydroxy-5,6,7-trime-thoxyflavanone, Acacetin and luteolin	H37Ra strain	Suksamrarm *et al.*[85]
13	Linaroside, Lantanoside	H37Rv strain	Begum *et al.*[11]
14	(2S)-5,7,2'-trihydroxyflavanone and (E)-2',4'-dihydroxychalcone	*M. tuberculosis*	Mativandlela *et al.*[56]
15	Cirsimaritin, eupatilin, eupatorin, salvigenin, 3'-o-methyl-eupatorin, 3'-7-dimethoxy-5, 6, 4-trihydroxyflavone, 7'-10'-methylapigenin, oleanolic acid	*M. tuberculosis*	Castellar *et al.*[19]
16	3-hydroxyxanthyletin, genistein, prunetin and (2S)-Naringenin	H37Rv strain	Chen *et al.*[20]
17	Ermanin	*M. tuberculosis*	Murillo *et al.*[59]
18	Licochalcone A	*M. tuberculosis*	Molina-Salinas *et al.*[57]
19	Licoisoflavanone, Phaseollidin, Erythbyssin II	*M. tuberculosis*	Shawar *et al.*[83]

reducing the production of bacterial toxin[2,29]. Some of the antibacterial mechanisms of flavonoids as proposed by different researchers earlier are as follows: Inhibition of nucleic acid synthesis, alteration in cytoplasmic membrane function, inhibition of energy metabolism, porin inhibition, reduction of cell attachment and biofilm formation, change in membrane permeability, weakening pathogenicity, damage of cytoplasmic membrane, *etc*.[24,29].

The bacterial plasma membrane is important for numerous vital processes, and its disruption can lead to bacterial death either directly or indirectly[40]. Flavonoids establish hydrogen bonds with the polar head groups of lipids and the more hydrophilic flavonoids at the membrane interface, interacting with the more non-polar substances in the hydrophobic interior of the membrane[88]. Flavonoid's interaction with phospholipids may modify the activity of membrane proteins, influencing the pharmacological characteristics of flavonoids[9]. Catechin triggers an oxidative burst by producing reactive oxygen species (ROS), which alters membrane permeability and damages the membrane, resulting in bacterial death[5]. It also ruptures the bacterial membrane by binding to the lipid bilayer and by inactivating or inhibiting the synthesis of intracellular and extracellular enzymes[79]. Many additional flavonoids have been reported to have membrane-disrupting properties[35].

Many acute and chronic illnesses in people are caused by bacterial biofilms[1,44]. Flavonoids have been demonstrated to decrease bacterial growth by blocking the aggregation process[8]. Furthermore, research suggests that they may play a role in preventing the formation of bacterial biofilms[74]. The ability of the hydrophilic flavonoids to interact with the membrane surface provides protection against a variety of harmful substances as well as the formation of biofilms. Aside from blocking efflux pumps, efflux pump inhibitors have been confirmed to prevent biofilm formation[81].

Mycolic acid is a key component of the bacterial cell wall and serves a crucial function in bacterial survival[54]. FAS-I and FAS-II are two types of fatty acid synthases found in MTB that are vital for the synthesis of mycolic acids. Elmasri *et al*;[26] discovered two flavones as promising drugs against bacterial growth through inhibiting the malonyl CoA-acyl carrier protein transacylase, which controls bacterial FAS-II [26]. Enoyl-ACP-reductase, beta-ketoacyl-ACP reductase, *etc* shows activity against FAS-II [15]. A number of flavonols as well as flavones have been reported to inhibit FAS-I such as quercetin, kaempferol, morin, fisetin, baicelin, luteolin *etc*[50]. Conventional medicines and flavonoids both work by inhibiting peptidoglycan production. Catechin inhibits the development of the bacterial cell wall by attaching to the peptidoglycan layer. Following induced structural disruption, naringenin and quercetin were found to have the highest binding affinity for MTB-MurI and decrease racemization activity[68]. Many inhibitions of cell wall synthesis have been linked to the combinatorial actions of different flavonoids[36].

Inhibition of bacterial nucleic acid synthesis is another mode of action of flavonoids.DNA gyrase, essential for DNA replication has been reported to be inhibited by quercetin, apigenin, and 3,6,7,3',4'-penta

hydroxyl flavones[82]. The study confirmed that quercetin binds to the B subunit of gyrase and the corresponding blockage of ATP binding pocket by the formation of hydrogen bonds[70]. Another mechanism supported by insilico studies indicated that flavonoids inhibit the DNA supercoiling by competitively interacting with the ATP binding site of the DNA gyrase B subunit. When flavonoids bind to DNA, it stabilizes the DNA-gyrase complex, ultimately leading to DNA cleavage induction[70]. Furthermore, it was observed that many flavones and flavonols inhibit the replicative helicases, DNA and RNA polymerases as well as viral reverse transcriptases[37]. Dihydrofolatereductase (DHFR), an important enzyme for folic acid synthesis, provides a precursor of pyrimidines and purines. Epigallocatechingallate (EGCG) has been found to inhibit DHFRs from *M. tuberculosis, E. coli,* and other species. It also has synergistic effects with other inhibitors of the folic acid pathway[61]. Some flavonols act on the bacteria by depolarizing the bacterial membrane, others by inhibiting oxygen consumption[14]. Many causes inhibition of NADH-cytochrome c reducates activity in the membrane fraction[39]. Flavonoids inhibit F_1F_o ATPase of *E. coli*and lead to the blockage of clockwise or anticlockwise rotation of the γ-subunits[35]. Polyphenol binding pocket residues are highly conserved across species such as humans, bovines, rats, and *E. coli* [34]. Overall a decline in bacterial metabolism can lead to the indirect arrest of the biofilm formation[26]. Flavonoids can chelate transition metal ions, which inhibits bacterial metal enzymes[46]. Flavonoid chelation sites are made up of two proximal hydroxyl groups: the C ring's 3-hydroxy-4-keto group or the A and C rings' 5-hydroxy-4-keto location. Many studies suggest that flavonoids form 1:2 complexes with metal ions and that their binding effectiveness is linked to the metal ion's transition state[78].

Bacterial hyaluronidases, a key virulence factor directly interact with host tissues. In Streptococcus sp., flavonols including myricetin and quercetin are well-known hyaluronic acid lyase inhibitors. Flavonoids, particularly catechin and proanthocyanidins, have been suggested to neutralize bacterial toxic factors originating from different species of bacteria[1,76]. Drug efflux pumps in bacteria can efflux a wide range of novel chemical treatments, and they play a key role in the development of antimicrobial resistance in bacteria[30]. Biochanin A and its metabolite genistein can have a moderate effect on the NorA MDR efflux pump[49,93]. According to molecular dynamics research, quercetin can bind to the *M. tuberculosis* Mmr and *E. coli* EmrE efflux pumps, downregulating drug efflux, and acts as a non-antibiotic adjuvant[87]. A study on antibacterial activity of EGCG and quercetin against drug-resistant *M. tuberculosis* and *K.pneumonia* showed that both flavonoids have antimicrobial properties[67]. Overall, these findings suggest that flavonoids function as efflux pump potentiators rather than inhibitors and that the link between effluxes pumps and biofilm formation requires further studies.

Gene expression regulation :

Sixty percent of all polyphenols are flavonoids[69]. By blocking the Sp1 transcription factor, epigallocatechin-3-gallate, a key component of green tea polyphenols suppresses the expression of TACO gene in human

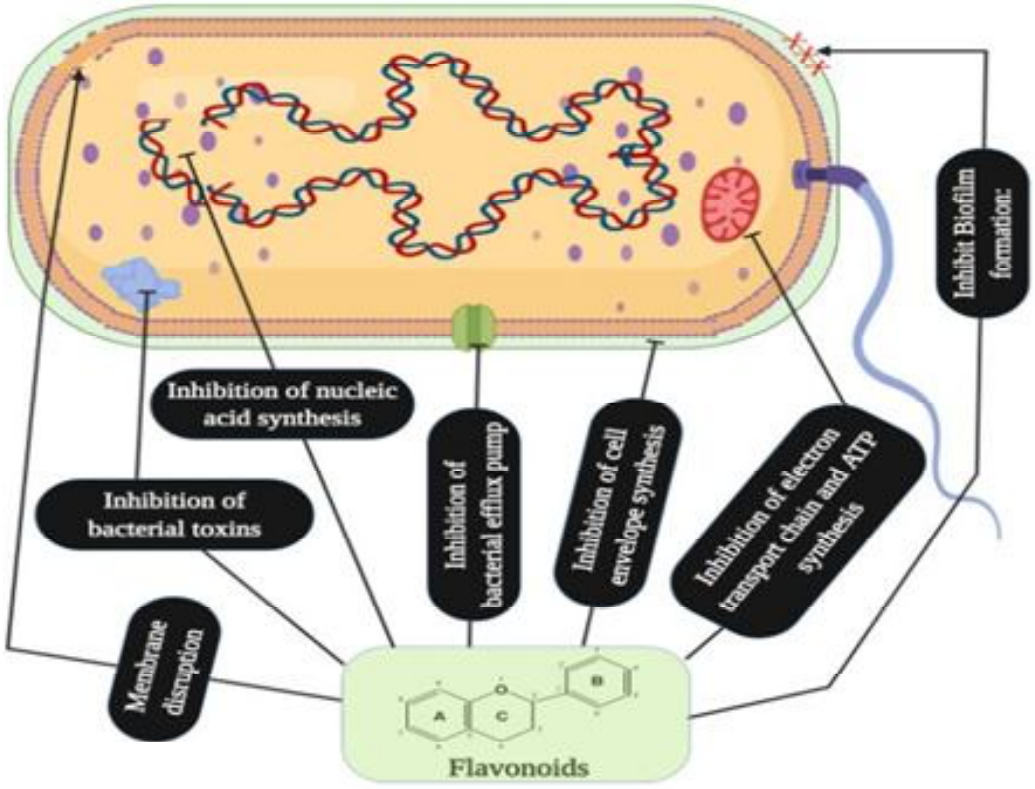

Fig. 2. Graphical representation of the mode of action of flavonoids

macrophages. This downregulation is accompanied by inhibition of mycobacterium survival within macrophages showing the importance of Epigallocatechin-3-gallate in the prevention of tuberculosis infection[7]. Cao *et al*.[18] found that mixed flavonoid supplementation reduced intracellular Mtb survival, increased cell density, aggregation, granuloma formation, and glutathione (GSH) levels, and elevated glutathione (GSH) levels. This research backs up previous findings on the use of flavonoids to treat tuberculosis. Isorhamnetin possesses anti-inflammatory and anti-cancer properties through suppressing the release of tumor necrosis factor (TNF)-α and interleukins[52]. A study involving lipopolysaccharide lung inflammation of mice showed that an anontoxic dose of isorhamnetin reduced the levels of IL-1β, IL-6, IL-12, and IFN-γ in lung tissue, indicating this flavonoid as a potent antituberculosis drug[45].

Several flavonoids have been discovered to inhibit both fungal and human FAS-I [16,35,92]. In 2007, Brown *et al*. discovered that flavonoids inhibit mycobacterial FAS-II, specifically Rv0636, which is a promising candidate for *M. tuberculosis* β-hydroxyacyl-ACP dehy-

dratase enzyme. Resistance to butein and isoliquiritigenin was imparted by overexpression of *M. tuberculosis* Rv0636 in M.bovis BCG; most likely due to flavonoid binding. Because of their activity, flavonoids could be exploited as possible antitubercular drugs as well as a technique for identifying undiscovered FAS-II dehydratases. The Mtb proteasome is responsible for virulence by mediating resistance to damage caused by reactive oxygen and nitrogen intermediates (ROI/RNI) as well as the macrophages' acidic environment. It also inhibits transcription factors that control the expression of anti-host defense genes. Flavonoids reduce Mtb proteasome activity by more than 65 percent. The hydroxyl at the flavonoid C ring C-3 or the hydroxyl/methoxyl at the flavonoid A ring C-6 is important in inhibiting proteasome activity[96].

Tuberculosis, particularly its drug-resistant variants, has posed a significant threat to global health. Several biological compounds have been studied in the last ten years for their potential to help fight tuberculosis. Amongst these compounds flavonoids are the best exploited due to their beneficial role in human health. Flavonoids are known to be rich in antioxidants and abundantly found in edible plants. A few reports confirm the synergistic relationship between flavonoids and anti-tuberculosis drugs. Flavonoids were discovered to have many modes of action by which they operate as bacterium inhibitors.

The present progress in discovering novel drugs for mycobacterial targets is still inadequate. There have been few studies on the synergistic effects of natural items and synthetic medications. The major cause for ineffectiveness is bacterial resistance, as well as unmet demands for novel drug combinations. It is necessary to get novel flavonoids from plants and explore their mode of action against micro-organisms in order to develop a better knowledge of synergistic behaviour and the mechanisms of action of flavonoids-drug combinations against tuberculosis. These compounds would pave the way for future flavonoid-based tuberculosis treatment strategies.

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Conflicts of interest

The authors declare that no conflict of interest exists for this work.

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