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The Significance of Flavonoids as a Potential Anti-Tuberculosis Compounds

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Review Article

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ABSTRACT

Mycobacterium tuberculosis, an agent of tuberculosis (TB), causes serious health problems such as multi drug resistance (MDR-TB), and extensive drug resistance (XDR-TB). According to WHO, 490,000 cases of MDR-TB and 40,000 cases of XDR-TB occur every year. There are several reasons to investigate a new class of antimicrobial drugs and the flavonoids represent a novel set of possibilities. Flavonoids display remarkable growth inhibitory activity against *M. tuberculosis*. Flavonoids and their derivatives might play a role in overcoming multidrug resistance. In this study, we attempted to review the subject under the subtitles below; a) The problems about chemicals regarding TB, MDR-TB or XDR-TB, b) Why TB drug investigation is needed, c) The current availability of anti-tuberculosis drugs, d) Properties of flavonoids, e) Antimycobacterial effects of flavonoids, f) Recent advances in anti-tubercular natural flavonoids.

Introduction

Tuberculosis (TB) infects approximately one third of the world population and 8.9–9.9 million new and recurrent cases of TB are declared each year [1]. Multidrug-resistant TB (MDR-TB) is known as tuberculosis whose bacteria are resistant to isoniazid (INH) and rifampicin (RIF). Extensively drug resistant TB (XDR-TB) is a form of tuberculosis whose bacteria are resistant to INH and RIF along with any fluoroquinolone [2]. At present, a million children die from this disease every year [1]. The disease appears to be especially prevalent among immune-suppressed patients such as those with Human Immunodeficiency Virus (HIV) because *Mycobacteria* are resistant to several chemicals, disinfectants, antibiotics and chemotherapeutic agents [3-5] and TB causes many more human deaths than any other microbial disease [6].

The problem about chemicals regarding TB, MDR-TB or XDR-TB

MDR-TB resistance is a problem of acquired drug resistance. This phenomenon is responsible for taking compounds (chemicals) that may have different structures and mechanisms of action from cell to cell, which has formed a variety of mechanisms that are not fully understood [7,8].

Microorganisms respond to compounds in different ways. Some of the mechanisms they employ include:

a) Increased activity of the efflux pumps [9]

b) Detoxification by stage II conjugating enzymes such as glutathione S-transferases [10]

c) Disturbed expression of target enzymes or altered target enzymes [11]

d) Provision of DNA repairs [12]

e) Changing the target for drug activation or degradation [13,14]

f) Mutations in drug target genes [15]

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Why TB drug investigation is needed?

According to WHO [16], 490,000 cases of MDR-TB and 40,000 cases of XDR-TB occur every year. To treat extensively drug resistant TB is more difficult than to treat multi drug resistant TB, and outcomes for patients are much worse [17]. In this respect, the viewpoints for the development of active constituents on *M. tuberculosis* are essential. An effective drug compound should contain some essential points; to develop existing treatment, to assure the successful treatment against multidrug resistant species, and to prevent the re-emergence of suppressed tuberculosis.

In this review, we attempt to discuss available drugs, the properties of flavonoids, some flavonoids that are thought to be efficient on *M. tuberculosis*, and recent advances in anti-tubercular natural flavonoids. In recent years, several published articles have reported the chemical profile of plant extracts, which include different kinds of chemical groups such as flavonoids, alkaloids, steroids, terpenoids, anthraquinones, saponins etc. These chemicals have different kinds of biological properties against microorganisms including mycobactericidal efficacy [18,19].

The current availability of anti-tuberculosis drugs

Active compounds affecting mycobacteria exhibit different modal structures among *Mycobacterium* species (Figure 1). In the history of anti-tubercular agents, many successful chemicals effective on *Mycobacterium* spp. were discovered towards the end of the 1940s, and RIF was found later [20]. Initially, these agents were influential and drug resistance did not emerge when this combination of drugs was used. However, in the course of time, the misuse of these drugs leads to the emergence of multiple drug resistant strains (MDR) [21]. MDR strains represent a major problem these days and the development of new effective drugs is imperative. Genotypic resistance to RIF is caused by target alteration due to non-synonymous single nucleotide polymorphisms in the majority of cases (90%) [22]. In addition, RIF resistance is caused by the occurrence of point mutations of the rpoB [23]. INH has an important key position among anti-tuberculosis drugs (Figure 1). Although activated INH causes a decrease of mycolic acids in the content of the cell wall by the enzyme NADH-specific enoyl-acyl carrier protein reductase [24], the clinical isolates show resistance to INH by reduced catalase activity. In addition, in virulence tests on guinea pigs, they showed a relative lack of virulence [25-27].

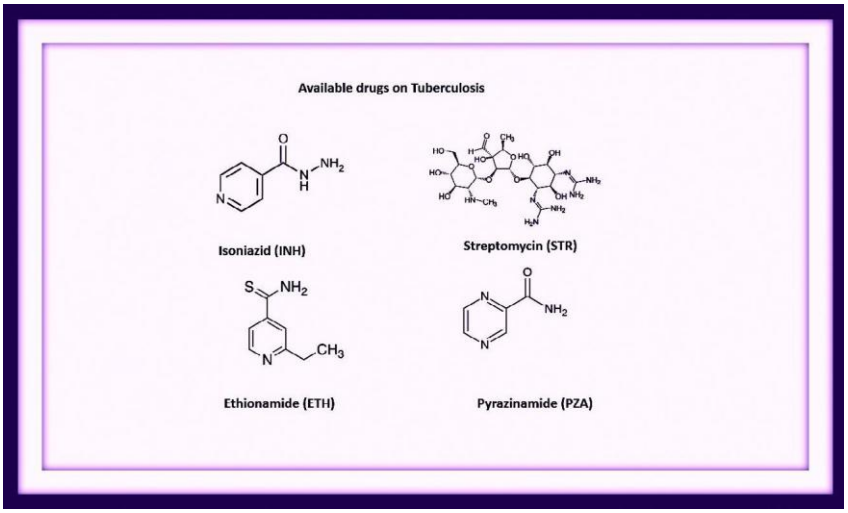

Figure 1: Active compounds affecting mycobacteria.

INH inhibits the synthesis of mycolic acids in all strains but mycolic acid production in resistant strains continues. Quemard et al. [28] and Hanoulle et al. [29] showed that in the existence of ETH, mycolic acid synthesis of the resistant and susceptible mycobacteria is damaged. Due to the resistance problems of MDR-TB, second line drugs such as ethionamide (ETH) with lower activity or increased toxicity are used. ETH affects the biosynthesis of mycolic acids by inhibiting NADH specific enoyl-acyl carrier protein reductase.

Pyrazinamide (PZA) is activated by pyrazinamidase encoded by the *pncA* gene [30] and PZA-resistant *M. tuberculosis* strains lose pyrazinamidase (PZase) activity. The action mechanism of PZA is decreasing intracellular pH and deactivating fatty acid synthase [27].

Streptomycin (SM), an aminoglycoside, affects ribosomes by misreading the genetic code inhibiting the initiation of translation of mRNA, and causing frame shifting in the process of proofreading. SM resistance is caused by the occurrence of missense mutations in the *rpsL* gene in some clinical isolates of *M. tuberculosis* [31-33].

Although early molecular studies reported *katG* (coded catalase–peroxidase) and *rpoB* (coded β-subunit of RNA polymerase) genes as the main goals for the acquired resistance of *M. tuberculosis* to INH and RIF, respectively, existing genes and drug target regions show that important genes of *M. tuberculosis* exhibit resistance to the first-line and some second-line anti-TB drugs [27]. INH is actually coded by the *katG* and exhibits activity against actively dividing *M. tuberculosis* via activated catalase–peroxidase.

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The status of the anti-tuberculosis drugs used in the last ten years

From past to now, first-line drugs (isoniazid, rifampin, ethambutol and streptomycin) followed up by second-line drugs. Recently, we know that re-emerge of MDR-TB and XDR-TB have increased resistance to the second-line drugs such as para-aminosalicylic acid, [34], capreomycin which is found extremely high mutations in XDR-TB isolates in Africa [35], ethionamide, alterations in ethA and point mutations acquired ETH resistance [36], kanamycin and capreomycin, approximately of 10% patients acquired resistance [37-39], and amikacin, prevalent high-level resistance with the A1401G mutation in rrs region [40].

One-third of MDR isolates were resistant to ofloxacin. Cross resistance is also a factor for MDR or XDR resistance. Cross resistance of low level ISO and ETH associated with an inh - A mutation. This gen is important for ethionamide and prothionamide resistance [41].

Related with amikacin resistance, mutations in *rrs* were the well-known mechanism. Wang et al. [42] found that in 28.6% of MDR strain resistant to amikacin were carried no mutation in *rrs* region. Their results let them to believe that it could be a new unknown mechanism associated with amikacin. Moxifloxacin and gatifloxacin, contain fluoroquinolone, were unsuccessful in the short-term treatment [43]. Sitafloxacin were effective on ciprofloxacin (CIP)-resistant *M. tuberculosis* [44].

Recently identified new promising compounds

The development of new drugs has been inevitable due to increased MDR cases. In recent years, some of the new promising compounds developed against *M. tuberculosis* H37Rv were those; delamanid, the dihydro-nitroimidazole class, has effective in vitro activity against *M. tuberculosis* (Mt) isolates and no cross-resistance to first line drugs [45]; several synthesized coumarine hyrazides, designed molecular diversity seems to be a suitable structure for a new and effective chemicals [46]; tuberculostatic drugs which are pro-drug of first-line drugs such as rifapentin, alternative for rifampine [39]; studied on celecoxib derived compounds, identified five compounds were effective against *M. tuberculosis* [47]; the compound, 4-(adamantan-1-yl)-2-quinolinecarbohydrazide with the MIC_{99} values within the range of 3.125 to 6.25 mg/mL was a prominent antimycobacterial compounds [48]; hydroquinoline derived vanadium complexes, identified as alternative for STR [49]; pyridine-2-thiol-1-oxide complexes derivatives verified as being a desirable effective compounds against *M. tuberculosis* [50].

Drug metabolism

In order to develop new drugs, well-understanding of drug metabolism is essential. P450 is the most important element of drug metabolism. Drug metabolism (xenobiotic metabolism) is a series of metabolic reactions which changes drug compounds to hydrophobic compounds. Drug metabolism composed of three phases. In the phase-I, enzymes identify and modify some groups in their substrates. Some of the reactions in the phase-I are oxidations, reductions, and hydrolysis. Hydroxylation is, one of the well-known reactions in the phase-I, catalyzed by cytochrome P450 dependent oxidase system which is responsible for drug metabolism [51-53]. Then metabolites are fallowed by other reactions such as reduction.

The phase-II is known as conjugation phase. Metabolites conjugated with species such as glutathione and glucuronic acid. Glutathione S-transferases are the best well-known enzyme in glutathione conjugation. This enzyme catalyzes the conjugation of glutathione [54]. Therefore, compound (drug) is inactivated in this phase, the polarity of agent is increased and the agent is removed in this phase to keep the cell [55]. Conjugation reactions occur with the groups such as carboxyl, hydroxyl, and sulfhydryl but conjugation reactions not much produce active agents.

Other drug metabolizing enzymes are intracellular phosphamide mustard which causes damage on host DNA or cause detoxification process via glutation S-transferase. Ifosfamide are also used CYP-based pathway and form alkylating agent such as ifosfamide mustard by activating CYP3A4 (forms N-dechloroethylation of CPA) and CYP2B6 (forms hydroxylation of CPA) [53].

In the fallowing process, phase-III, supply further modification and excretion occurs in the anionic groups, play a role such as label or sign for membrane transporters (ATP binding cassette transporters) of the multidrug resistance proteins. Therefore, phase-II metabolites carried to the extracellular area for further metabolizing by catalyzing ATP-dependent transport of hydrophobic anions [51].

The importance of cytochrome P450 enzymes and drug metabolism

Compounds (drugs) are metabolized by drug-metabolizing enzymes. Cytochrome P450 (CYP) enzymes, exist all domains, which are bound to the membrane, catalyzed lots of reactions and of great importance. All compounds are detoxified and excreted from the cell by bioactivation. Mostly oxidation process supports the change of C-H bound to C-OH through oxidizing process in the metal containing enzymes such as cytochrome P450 and methane monooxygenases [56,57]. Therefore, pharmacologically inactive compounds turn into pharmacologically active compounds “a prodrug”, a precursor of a drug [58]. CYP act as mono-oxygenases and play an important role on drug targets as biocatalysts. Recently, cytochrome P450 of microorganisms attracts great attention. It is reported that 40 varieties of CYPs occur in *Mycobacterium* [59].

Properties of flavonoids

Flavonoids, natural phytochemicals, are polyphenolic secondary plant metabolites, can be found in various parts of the

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plant such as fruit, seeds, leaves, stem, and flowers. Flavonoids contain diverse biological properties. Based on the structure, they consist of two benzene rings (A and B) connected through a heterocyclic pyran ring [60]. A phenol B ring (e.g. naringenin, apigenin) has been shown to contain prooxidants reducing NADH and increasing NAD radicals when metabolized by peroxidase in vitro [61-63].

Flavonoids are divided into eight classes according to changes in their C rings and their molecular structure [64] and categorized as flavones, anthocyanidines, flavans, flavanones, flavonolignans, isoflavones, isoflavanones, and chalcones [65-66]. Structures of flavonoid skeletons are given in (Figure 2).

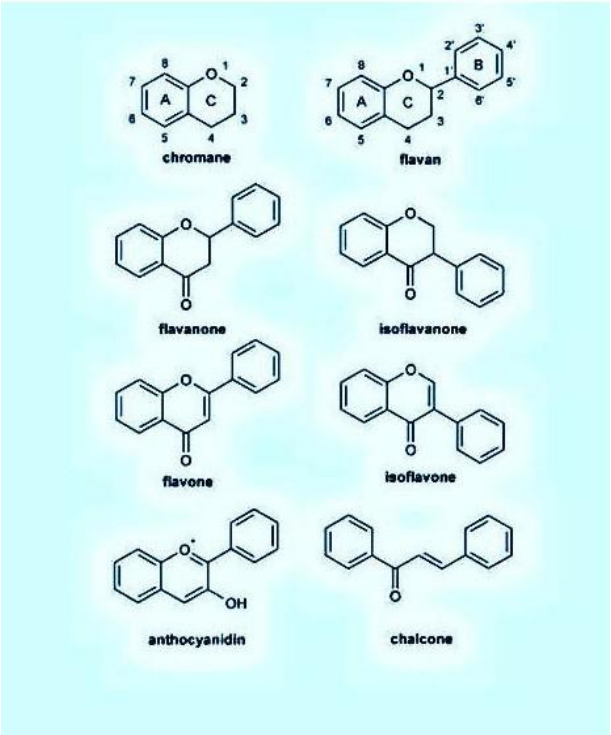

Figure 2: Structures of flavonoid skeletons (Hodek et al., 2002).

Antimycobacterial effects of flavonoids

Biflavonoids consist of flavone/flavone, flavanone/flavone and flavanone/flavanone component connections. After the isolation of gingetin in 1929, it was followed by the discovery of more than 100 biflavonoids in plants [67-68]. The identification of biflavonoids as new compounds of TB effective agents seems hopeful for the future. New type linkages, entering methoxy or nitro substituents to the structure, and/or high lipophilic properties are essential for the inhibitory activity of compounds [69,70].

Kuete et al. [71] studied with *Dorstenia barteri* crude extracts and compounds such as isobachhalcone, 4-hydroxylonchocarpin, stipulin, and amentoflavone and they determined the best activity on isobachhalcone (MIC 2. 44 µg/mL) [71]. They reported that crude extracts and compounds were effective in preventing *Mycobacteria* sp. at MIC < 10 µg/ml.

Cinnamic acid is much more efficient against *M. tuberculosis* H37Rv with an MIC value 270-675 µM. They indicated that it was essential to have free carboxylic acid and α,β-unsaturation together to assure the anti-TB activity [72]. It is reported that synergistic activities of anti-tuberculous drugs with cerulenin and trans-cinnamic acid showed inhibition against *M. tuberculosis* with the MIC value as 675 µM against *M. tuberculosis* H37Rv strains and the range of 337-1.4 µM for MDR-TB [73].

Favela-Hernández et al. [74] investigated flavonoids (5,4′-dihydroxy-3,7,8,3-tetramethoxyflavone; 5,4′-dihydroxy-3,7,8-trimethoxyflavone; 5,4′-dihydroxy-7-methoxyflavone; 5,8,4′-trihydroxy-3,7-dimethoxyflavone) from *Larrea tridentate.* They reported the activity of flavonoids 5,4′-dihydroxy-3,7,8,3-tetramethoxyflavone and 5,4′-dihydroxy-3,7,8-trimethoxyflavone against MDR-TB at MIC 25 and MIC 25-50 µg/ml, respectively [74].

Prawat et al. [75] isolated a new flavonoid (3′-formyl-2′,4′-dihydroxy-6′-methoxychalcone), which is effective (MIC 6.25 µg/mL) on *M. tuberculosis.* On the other hand, Lechner et al. [76] showed that the It was shown that flavonoids butein and isoliquiritigenin have an inhibitory effect on fatty acid and spoil the mycolic acid biosynthesis [76,77]. Although plant originated antibacterials have less activity and are less potent, when used with synthetic antibiotics they are capable of showing synergy and inhibiting the targets. Some flavonoids have a synergistic interaction with the drugs given below. This interaction helps to decrease the minimum inhibitory concentration (MIC) value of the drug. There are several studies on the existence of synergy between plant compounds and synthetic drugs against bacteria in the literature. Some of the samples of this interaction are that the synergy between plumbagin and INH increases the efficacy of isonicotinic acid hydrazide fourfold against *Mycobacterium* sp. [78]. The synergy between carnosic acid and tetracycline causes inhibition of the MDR pumps in *Staphylococcus aureus* [79]. Carnosol and

erythromycin inhibit β-lactamase [80]. Epigallocatechin-gallate and penicillin inhibit penicillinase from penicillinase producing *S. aureus* [81].

However, the numbers of synergetic interactions between plant antibacterials and synthetic drugs against *M. tuberculosis* are few. Therefore, more study is needed into the mechanism of action of flavonoids and drugs. One of them, myricetin, was reported as the most effective compound that reduced the MIC value. Quercetin and luteolin are part of the 3-hydroxy group, which improves their antimycobacterial activities and synergistic interaction. Kaempferol also has an active compound involved next to the hydroxy groups in ring B, providing potentiation activity of flavonoids. Mossa et al. [78] reported that totarol, ferruginol and plumbagin increased the potency of isonicotinic acid hydrazide four-fold against *Mycobacterium* sp. Combinations of a naphthoquinone with isoniazid or RIF resulted in a reduction in the minimum inhibitory concentration of each compound [82]. Chemical structure of some of effective antimycobacterial compounds were given in the (Figure 3).

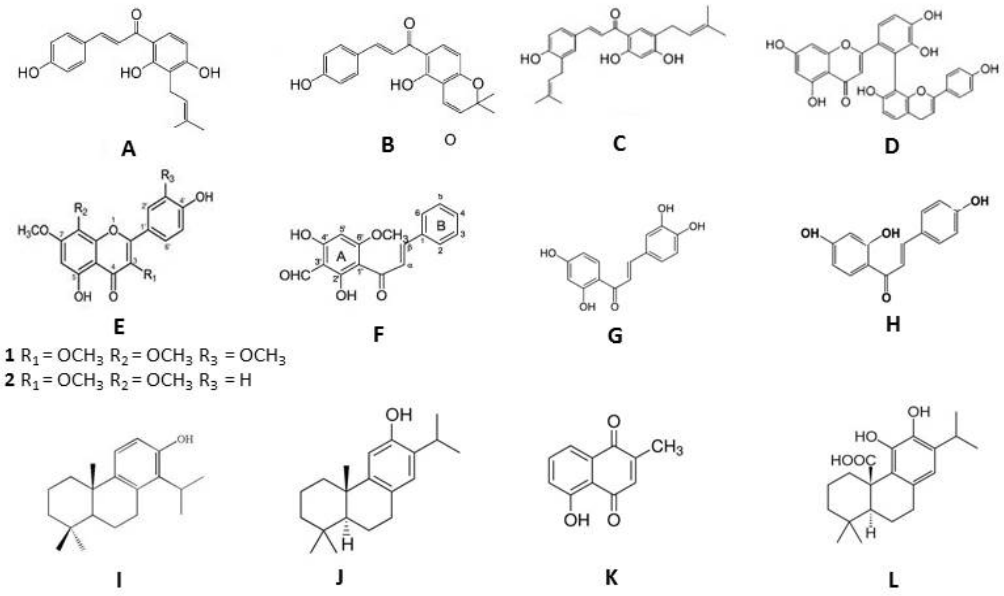

Figure 3: Chemical structure of some of effective antimycobacterial compounds A) Sobachalcone; B) 4-hydroxylonchocarpin; C) Stipulin; D) Amentoflavone (Kuete et al. 2010), E) 1, 5,4′-dihydroxy-3,7,8,3′-tetramethoxyflavone; 2, 5,4′-dihydroxy-3,7,8-trimethoxyflavone (Favela-Hernández et a., 2012); F) 3′-formyl-2′,4′-dihydroxy-6′-methoxychalcone; G) Butein; I) İsoliquiritigenin; J) Ferruginol; K) Plumbagin L) Carnosic acid.

Chemical structure of some of effective antimycobacterial compounds

A) sobachalcone;

B) 4-hydroxylonchocarpin;

C) stipulin;

D) amentoflavone (Kuete et al., 2010),

E) 1, 5,4′-dihydroxy-3,7,8,3′-tetramethoxyflavone; 2, 5,4′-dihydroxy-3,7,8-trimethoxyflavone (Favela-Hernández et a., l 2012);

F) 3′-formyl-2′,4′-dihydroxy-6′-methoxychalcone;

G) butein;

I) isoliquiritigenin;

J) ferruginol;

K) plumbagin

L) Carnosic acid.

Although many drugs have been developed for the treatment of TB in the past 40 years, none of the new molecules has achieved success [83]. Investigations into anti-TB agents are currently being continued on the multi-directional pathways to affect different targets such as the cell wall, membrane energy production and protein synthesis [84]. The treatment success rate still struggles to reach the target of 85% [85]. Villemagne et al. [83] reported that at least ten compounds that are still in clinical trials and various modes of action such as ATP synthase inhibitors, cell wall synthesis inhibitors, DNA gyrase inhibitors, and protein synthesis inhibitors [83].

Modes of flavonoid actions

Flavonoids harm to the bacteria cells in different ways. Their effects on bacteria might be related to ability against microbial

adhesins, cell-wall or transport proteins [86]. Some of the modes of flavonoids action well-known in the past are that they restrict expression activation of phase I enzymes in drug metabolism. In this section, we reviewed the new researches on the mode of flavonoid action that are made between the years of 2007-2015.

Bacteria have acquired or developed several kind of mechanism to resist the effects of drugs such as drug efflux transporters [87]. Multidrug resistant bacteria have devised capability against chemotherapeutic agents. Efflux pumps are recently known to source of resistance for antibiotics. Lots of efflux pomp mechanisms activated extrusion were displayed such as Rv1258c efflux pump in *M. tuberculosis* responsible for tolerance to rifampicin and virulence factor for pathogenic mycobacteria [88,89]; TetA, TetB, and TetM family of efflux pumps, resist the tetracyclines [90,91].

MdfA, belongs to multidrug efflux pump family, a bacterial membrane transporters such as Rv0783c, multidrug resistance integral membrane efflux protein; Rv2333c, integral membrane transport protein; and Rv1410c, aminoglycosides/tetracycline-transport integral membrane protein, have a regulation and functional role in *M. tuberculosis* [92]. The resistance-nodulation-division proteins (RND) family gives a high resistance against a wide range of compounds [93]. While, other families of efflux pumps such as RND and the major facilitator superfamily accepted as secondary transporters, ABC family of multidrug efflux pumps, coupled with proton, accepted as a primary efflux pumps which is uses ATP for energy and others [92].

EmrD-3, related to the Bcr/CflA subfamily of membrane proteins, a multidrug efflux pump of *Vibrio cholera* [94]. and also common among the Gram-positive and Gram-negative bacteria; LmrS efflux pump of the MFS family from methicillin-resistant *Staphylococcus aureus* strain [95]; Mdt(A) efflux pump related plasmid-encoding from *Lactococcus lactis, Qac*A efflux pump related plasmid-borne genes, QacB efflux pump related plasmid-encoded from *Staphylococcus aureus,* and NorA chromosomally-encoded efflux pump from *Staphylococcus aureus* [87].

Why the risk of drug resistance development does not occur after using flavonoid?

Xiao et al. [96] showed inhibition properties of some flavonoids against efflux pumps. They reported drug accumulation and the effects of a multi-target bacterial topoisomerase inhibitor. They also declared that a complex fluoroquinolone hybridized with narigenin was being the most active.

These studies confirmed that, inhibition of the drug efflux transporters is of great important. Some of the flavonoids such as chrysin [97] and genistein have effective inhibitors on the multidrug transporters [98].

Chan et al., [99] showed that diosmetin and erythromycin together inhibit the growth of ABC pomp and reported antibacterial efficacy when shortage of ATP. This action might be one of the reasons of the mode of antibacterial actions of compound against bacteria.

Fukuda et al. [100] reported that catechins affected aryl hydrocarbon receptor activation pathway by suppressing the activity of CYP1As. Some flavonoids such as topoisomerase-I acted as poison on phase-II conjugative metabolism [101]. Quercetin and luteolin have been described as a poison DNA Topoisomerase-I and II enzymes, which are regulator for DNA supercoiling [102]. Two mechanism of flavonoids action, the inhibitory effect on cell membrane synthesis [103] and by inhibition of cell wall synthesis [104], have been reported. The mode of flavonoid action was given in (Figure 4).

Figure 4: The mode of flavonoid action.

Flavonoids may initiate the detoxification process which is formed the reactive intermediates that which has DNA binding potential. It is reported that the flavonoids has regulatory effect on drug metabolizing enzymes [105]. Some flavonoids show

antagonistic effect by activating aryl hydrocarbon receptor by increasing CYP1A1 transcription such as diosmetin [96,99,106]. quercetin, chrysin and genistein [107].

Difference in the structure, such as different derivatives of flavonoids, might cause different mechanism of action. For example, while myrecetin suppressed of the tumor necrosis factor (TNF-a) mediated NF-kB activity [108]; mode of flavones and flavanones action were depend on the methoxylation at the 5-position of the A-ring [63].

Recent advances in anti-tubercular natural flavonoids

Searches are ongoing on anti-tubercular natural flavonoids. New compounds, isobachalcone, kanzanol C, 4-hydroxylonchocarpin, stipulin and amentoflavone, isolated from *Dorstenia barteri* (Moraceae), showed antimycobacterial activity against *M. tuberculosis* H37Rv *and M. smegmatis* with the MIC values were the range of 2.44-30 μg/mL [71].

New cinnamolyglicoflavonoids 3-cinnamoyltribuloside and afzein and stilbin isolated from *Heritiera littoralis* (Sterculiaceae) ethanol leaf extracts showed antimicrobial activity against *Mycobacterium* species, *M. madagascarience* and *M. indicus pranii*. The MIC values were the range of 1.6-0.8 mg/mL for the pure compounds [109].

New flavonoids, isolated from *Spondias mombin*, (Anacardiaceae), mombinrin, mombincone, mombinoate, and mombinol, exhibited anti-tubercular inhibition against *M. tuberculosis* strain a lower dose of 40 M/mL concentrations [110].

A new flavanone, 7-hydroxy-6,8-dimethoxyflavanone, displayed antimycobacterial efficacy against *M. tuberculosis* H37Ra at the MIC value of 50 μg/mL [111].

Two new 3-hydroxyisoflavanones, isolated from stem bark of *Dalbergia melanoxylon* (Fabaceae), kenusanone F 7 methyl ether and sophoronol-7-methyl ether, showed inhibition against *M. tuberculosis* H37Rv strains [112].

There has been no development of new anti-tuberculosis drugs in the last 50 years. Recent advances on antimycobacterial drugs are categorized in three stages:

1) Re-dosing and re-engineering of known-drugs which have antimycobacterial efficacy.

2) Using non-antibiotic drugs possessing antimycobacterial properties such as efflux-pomp inhibitors. However, more evidence is needed before implementing these drugs [113].

3) Discovery of new, effective drugs. It is thought that instead of developing a unique drug or a combination of drugs, constituting of two or three drug combinations could be an available solution and should be an objective [114].

Conclusion

TB is a severe and sometimes lethal infectious disease. Nowadays, TB threatens millions of people regardless of their countries and continents. Drug resistant forms of TB have created additional and unacceptable dangers that include global security risks.

Unfortunately, over the last five years little progress has been made in the investigation of new natural products against mycobacterial targets. Studies on synergistic relations between natural products and synthetic drugs are very limited. For a better understanding of synergistic behavior and the mechanisms of action of flavonoids-drug combinations against TB, there is need to obtain new flavonoids from plants and to investigate their mode of action against microorganisms.

An attempt to find new drugs has accelerated in line with the increase in the global occurrence of MDR-TB and XDR-TB. It is vital to discover new molecules effective on resistance targets of *M. tuberculosis.*

To date, the favorite strategy for the treatment of MDR is to combine altered targets such as the inhibition of DNA gyrase activity and cell wall synthesis. However, in the future studies on the synergistic relations between flavonoids and synthetic drugs will be much more effective than conventional drugs.

There are several reasons to investigate a new class of antimicrobial drugs and the flavonoids represent a novel set of possibilities [115]. After revising the chemical profile of the flavonoids, the results should be analyzed to see whether they show the target sites for new drugs against extensively drug resistant TB (XDR-TB) and multidrug resistant TB (MDR-TB). The new class of drugs effective on TB might bring about a better understanding of flavonoids and structure–activity relationships. Thus, these compounds might be useful to cope with the resistance problem.

Although all these efforts are implemented by several pharmaceutical companies and research is being conducted on TB drug development projects, current development is not yet sufficient to overcome the resistance problem. The main reason for ineffectiveness seems to be bacterial resistance, and the demands that are not satisfied in terms of the requirements for the combinations of new molecules. New targets among the bacterial resistance mechanisms and research on new molecules are crucial for developing new anti-TB drugs.

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