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Multidrug-resistant tuberculosis (MDR-TB)

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Abstract

Tuberculosis (TB) is caused by *Mycobacterium tuberculosis* (Mtb), which is transmitted through the air from person to person. TB is curable, but inappropriate treatment can lead to multidrug-resistant TB (MDR-TB), which is resistant to the two most effective anti-TB drugs and extensively drug-resistant TB (XDR-TB), which is resistant to many anti-TB drugs. MDR-TB is significantly more difficult and expensive to treat than drug susceptible TB. Rapid drug-susceptibility tests are a pressing public health and diagnostic need because of the rise in multidrug-resistant and extensively drug-resistant tuberculosis (MDR/XDR-TB) globally. Timely diagnosis and effective treatment are the prerogatives for a favorable outcome. Care must be taken in terms of isolation procedure and infection control in MDR-TB. Although the diagnosis is made microbiologically, there are certain factors that predispose to the emergence of MDR-TB, notably a history of previous treatment for TB, particularly if that treatment was inadequate or incomplete. Medicinal plants have been used to cure different common as well as lethal diseases by ancient civilizations due to its virtue of variety of chemical compounds which may have some important remedial properties. In the present review, we have addressed medicinal plants effective against MDR-TB and herbal plants described for MDR-TB across the world. These herbal plants can serve as promising candidates for developing novel medications to combat MDR-TB.

Keywords: MDR-TB, Diagnosis, Multidrug-Resistant Tuberculosis, Prevention, Tuberculosis, Natural Remedies, Medicinal Plants

Introduction

Often considered a 'disease of the past', TB has had resurgence in some parts of the world in recent years. The World Health Organization (WHO) estimates that there are now 10.4 million new TB cases in the world. In 2016, it reported that the epidemic was larger than previously estimated, owing to new data from India, and increased its India figures from 2.2 million in 2014 to 2.8 million in 2015. Six countries account for 60 percent of the total number of TB cases, with India leading the list, followed by Indonesia, China, Nigeria, Pakistan and South Africa.

TB is as old as the mankind [1-3]. TB is the most common cause of death due to a single infectious agent worldwide in adults [4]. In 1993, the World Health Organization (WHO) took an unprecedented step and declared TB to be a global emergency [4-6]. TB is principally a disease of poverty, with 95 percent of cases and 98 percent of deaths occurring in developing countries. Multidrug-resistant (MDR) tuberculosis (TB) has a relevant epidemiological impact, with 480,000 cases and 190,000 deaths notified in 2014; 10% of them meet the criteria for extensively drug-resistant (XDR)-TB [MDRTB with additional resistance to any fluoroquinolone, and to at least one injectable second-line drugs (SLDs)] (capreomycin, kanamycin or amikacin) [7, 8]. The fight against MDR-TB is one of the eight core interventions to target TB elimination [9, 10]. In spite of the progresses achieved, no more than 60% among MDR-TB cases, 40% among XDR-TB cases and< 20% among cases with resistance patterns beyond XDR-TB achieve treatment success [11, 12]. Furthermore, in its 2015 report , WHO underlined as out of 480,000 MDR-TB cases, only 25% have been detected [123,000] and 50% cured. Anti-MDR/XDR-TB regimens are still very long, toxic and expensive, although recently shorter regimens have been recommended [13, 14].

The recent spread of drug-resistant TB (DRTB) is particularly difficult to treat using currently available medicines. In some countries, it is becoming increasingly difficult to treat MDR-TB. Treatment options are limited and expensive, recommended medicines are not always available, and patients experience many adverse effects from the drugs. In some cases even more severe drug-resistant TB may develop. Extensively drug-resistant TB, XDR-TB, is a form of multidrug-resistant TB with additional resistance to more anti-TB drugs that therefore responds to even fewer available medicines. The DOTS programme was reassessed and a revised version - DOTS Plus - was rolled out in 2000 taking into account drug resistance TB. But implementing this has had its own set of challenges. The drugs needed are often very expensive and difficult to obtain. Drug resistance can be detected using special laboratory tests which test the bacteria

for sensitivity to the drugs or detect resistance patterns. These tests can be molecular in type (such as Xpert MTB/RIF) or else culture-based. Molecular techniques can provide results within hrs and have been successfully implemented even in low resource settings. “Treatment as prevention” has been emphasized for other infectious diseases (e.g. HIV and malaria) and increasingly for TB overall [15]. For MDR-TB, however, strategic discussions have largely focused on clinical outcomes [16] and cost [17]. Potential outcomes of completed treatment include cure, suppression of disease with ongoing risk for relapse and treatment failure with or without acquisition of resistance. Better TB and MDR-TB prevention strategies and future research should be explored as integral part of TB and MDR-TB prevalence reduction and ultimate elimination.

The medicinal properties of plants have been well known from ancient times and plants offer a new source of potent antimicrobial agents in the form of secondary metabolites [18]. Anti-tuberculosis activity has been reported in number of higher plants [19]. In Ayurveda tuberculosis is known as Rajayakshma, Yakshma, Shoosha, Kshaya [20]. Drug resistance is developed only against purified chemical compound. Any single purified compound will produce resistance in pathogens. The Mycobacteriae are trained themselves to digest the drug by modifying their receptor structure according the chemical structure of the drug. Thus the Mycobacteriae slowly adapt and develop resistance against modern drugs. Herbal drug whether extract or decoction used against any pathogen will not induce drug resistance. Hence an effective and alternative anti tuberculosis drug preferably herbal based drug has to be developed.

Drug resistance

Primary resistance is that which has not resulted from the treatment of the patient with the drug concerned. It includes resistance in wild strains which have never come into contact with the drug (natural resistance) and the resistance occurring as a result of exposure of the strain to the drug but in another patient. It includes primary resistance and resistance to previous treatment concealed by the patient or of which the patient was unaware [21, 22]. The term “acquired resistance” has often been used with the implication that resistance has developed due to exposure of the strain to antituberculosis drugs and the consequent selecting out of resistant mutant bacilli. In the strict sense, the term “acquired resistance” can be used to refer to strains proven to have drug resistance in a reliable laboratory which were subsequently isolated from a patient in whom initial susceptibility testing was done to document the presence of a drug susceptible strain earlier [23, 24]. Resistant strains differ from the sensitive strains in their capacity to grow in the presence of higher concentration of a drug.

Previous TB treatment is a strong determinant of drug resistance [25], and previously treated patients comprise a significant proportion (13%) globally. Of all the forms of drug resistance, it is most critical to detect multidrug resistance (MDR) because it makes regimens with first-line drugs much less effective [26] and resistance can be further amplified [27]. Prompt identification of MDR and initiation of MDR treatment with second-line drugs gives a better chance of cure and prevents the development and spread of further resistance.

Diagnosis of drug-resistant TB

A multidrug-resistant organism requires treatment with second-line drugs. While treatment of MDR-TB is more complicated, expensive and longer than treatment with first-line drugs, it has been proven efficacious. Patients who are identified early with MDR-TB can have greater than an 85% chance of cure. The treatment is also feasible in low-resourced areas. It is extremely important to treat MDR-TB patients both to prevent their deaths and to prevent those who remain infectious from spreading drug-resistant TB in the community.

Good history taking is essential when people present with TB symptoms to determine previous TB treatment, its length and the drugs used. In addition, during history taking, the patient may reveal contact with someone who suffered from drug-resistant disease. This patient’s sputum should be examined by Xpert MTB/RIF or cultured for drug sensitivity testing when risk factors for MDR-TB are detected. In some areas there are no resources for culture and sensitivity testing, but in those settings, a history of inadequate treatment, or past treatment with only one drug, or a past default on treatment, followed by a return of symptoms, may be considered as reasonable suspicion that one is dealing with MDR-TB.

Drug-resistant TB can only be defined through laboratory confirmation of *in vitro* resistance to one or more anti-TB drugs. In well-resourced settings all specimens are sent for culture and drug-sensitivity testing, in areas where there are fewer resources, specimens of high-risk cases may be sent for further investigation but in some areas it is not possible to offer any culture and sensitivity testing. Results are defined according to the pattern of resistance as follows:

Mono-resistant TB: TB in patients whose infecting isolates of *M. tuberculosis* are confirmed to be resistant to one first-line anti-TB drug.

Poly-resistant TB: TB which is resistant to more than one first line drug, other than isoniazid and rifampicin.

Rifampicin-resistant TB (RR-TB): Active TB resistant to rifampicin, with or without resistance to isoniazid or other anti-TB drugs. This is a newer description following the rollout of the Xpert MTB/RIF rapid molecular diagnostic test.

Multidrug-resistant TB (MDR-TB): Active TB which is resistant to at least both isoniazid and rifampicin, the two most

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powerful anti-TB agents; an MDR-TB strain can be resistant to more than these two antibiotics and in many cases patients are resistant to other first-line drugs as well. Extensively drug-resistant TB (XDR-TB): Active TB resistant to at least rifampicin and isoniazid, in addition to any fluoroquinolone (FQ), and to at least one of the three following injectable drugs used in anti-TB treatment: capreomycin (Cm), kanamycin (Km) or amikacin (Am).

Patients with MDR-TB require prolonged treatment with drugs that are less effective and more toxic. Therefore, it is necessary to distinguish MDR-TB from mere drug-resistant tuberculosis by performing mycobacterial culture and sensitivity testing because the therapeutic implications are different.

Traditionally, Lowenstein-Jensen (LJ) culture has been used for drug sensitivity testing using (i) absolute concentration method; (ii) the resistance ratio method; and (iii) the proportions method [21, 22]. With the conventional methods, 6-8 wk time is required before sensitivity results are known.

Radiometric methods have been developed for rapid drug-susceptibility testing of *M. tuberculosis*. In the BACTEC-460 (BectonDickinson) radiometric method, 7H12 medium containing palmitic acid labelled with radioactive carbon (14C-palmitic acid) is inoculated. As the mycobacteria metabolize these fatty acids, radioactive carbon dioxide ($14CO_2$) is released which is measured as a marker of bacterial growth. The proportions method has been modified by incorporating the BACTEC technique in place of the conventional Lowenstein-Jensen culture. With this modification, sensitivity results will be available within 10 days [28-30].

The DOTS strategy and drug-resistant tuberculosis

Effective TB control based on the DOTS strategy is the first step in the fight against drug resistance. Second-line drugs should only be used by a project that follows the published WHO protocols for standardized or individualized DOTS treatment regimens for MDR-TB [31, 32].

Choice of drugs

New antituberculosis drugs are needed for three reasons: to shorten or otherwise simplify treatment of tuberculosis caused by drug-susceptible organisms, to improve the treatment of patients with MDR tuberculosis, and to provide more effective and efficient treatment of latent tuberculosis infection (LTBI) [33]. Although treatment regimens for drug-susceptible tuberculosis are effective, they must be administered for a minimum of 6 months to achieve optimal result. Nonadherence to this relatively lengthy course of treatment remains a major problem. To address the problem of nonadherence, DOT (as a component of the DOTS strategy) is recommended as a standard of care worldwide.

The choice of drugs is based on their efficacy and toxicity. Based on this principle, the 2008 and then the 2011 WHO guidelines proposed a range of drugs [34]. First-line anti-tuberculosis drugs are isoniazid, rifampicin, ethambutol, pyrazinamide and second-line anti-tuberculosis drugs are moxifloxacin, high dose levofloxacin (fluoroquinolones), linezolid, delamanid, bedaquiline (newer drugs with increased evidence), amikacin, capreomycin, kanamycin (injectables), clofazimine, ethionamide/prothionamide, carbapenems (imipenem, meropenem, ertapenem) and cycloserine, para-amino salicylic acid, amoxicillin/clavulanate.

Of the approved drugs isoniazid (INH), rifampin (RIF), ethambutol (EMB), and pyrazinamide (PZA) are considered first-line antituberculosis agents and form the core of initial treatment regimens. Rifabutin and rifapentine may also be considered first-line agents under the specific situations. Streptomycin (SM) was formerly considered to be a first-line agent and, in some instances, is still used in initial treatment; however, an increasing prevalence of resistance to SM in many parts of the world has decreased its overall usefulness. The remaining drugs are reserved for special situations such as drug intolerance or resistance.

Linezolid, delamanid and bedaquiline might acquire a more prominent role in MDR-TB treatment both in adults and in children, given their 'core drug' profile. Under specific conditions delamanid and bedaquiline might be considered for combined use [35], although further randomized clinical trials evidence is necessary. Further studies are also necessary to establish if high dose moxifloxacin and rifabutin, might play a future role in the MDR-TB armamentarium.

Medicinal plants having anti-mycobacterial activity against MDR-TB

Prunella vulgaris L

Experimental animal model in rats was induced by MDR-TB. The extract of *Prunella vulgaris* L. can enhance the cellar immunological function in rats from up-regulation of the level of genetic transcription, accordingly provide the theory basis of healing of tuberculosis with it [36].

Celastrus vulcanicola

A series of natural and derivative dihydro-β-agarofuran sesquiterpenes have been tested against sensitive and resistant Mycobacterium tuberculosis strains. Among those tested, 20 exhibited promising anti-MDR TB activity. 1 α-Acetoxy-6β, 9β-dibenzoyloxy-dihydro-β-agarofuran (20) exhibited antituberculosis activity against the MDR TB strain with a MIC value of 6.2 μg/mL, comparable to or better than isoniazid or rifampin, two of the best first-line drugs commonly used in the treatment of TB [37].

Allium sativum

Researchers evaluated anti-bacterial activity of garlic against non-MDR and MDR isolates of *M. tuberculosis*. A total of 20 clinical isolates of MTB including 15 MDR and 5 non-MDR were investigated. Ethanolic extract of garlic was prepared by maceration method. Minimum inhibitory concentration (MIC) was performed by using 7H9 middle brook broth dilution

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technique. MIC of garlic extract was ranged from 1 to 3 mg/ml; showing inhibitory effects of garlic against both non-MDR and MDR M. tuberculosis isolates [38].

Aristolochia brevipes

Researchers evaluated the dichloromethane extract from *Aristolochia brevipes* (Rhizoma) and the compounds isolated from this extract against several mycobacterial strains, sensitive, resistant (monoresistant), and clinical isolates (multidrug-resistant), using the alamarBlue™ microassay. This study demonstrates that the dichloromethane extract (rhizome) of *A. brevipes* possesses strong *in vitro* antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv (minimum inhibitory concentration value [MIC], 12.5 µg/mL). The most active compound against all mycobacterial strains tested was the compound aristolactam I (**5**), with MIC values ranging between 12.5 and 25 µg/mL [39].

Tiliacora triandra

Bisbenzylisoquinoline alkaloids, tiliacorinine (1), 2'-nortiliacorinine (2), and tiliacorine (3), isolated from the edible plant, Tiliacora triandra, as well as a synthetic derivative, 13'-bromo-tiliacorinine (4), were tested against 59 clinical isolates of multidrug-resistant Mycobacterium tuberculosis (MDR-MTB). The alkaloids 1–4 showed MIC values ranging from 0.7 to 6.2 µg/ml, but they exhibited the MIC value at 3.1 µg/ml against most MDR-MTB isolates. The present work suggests that bisbenzylisoquinoline alkaloids are potential new chemical scaffolds for antimycobacterial activity [40].

Humulus lupulus

The antimycobacterial effect of this plant on rifampin sensitive and resistant strains of *Mycobacterium tuberculosis* was examined. Sensitivity and resistance of 37 Iranian isolates of *M. tuberculosis* to rifampin was determined by proportion method. Ethanolic extract of hops was prepared using maceration method. PCR-SSCP and direct sequencing were used for confirming existence of mutations in 193-bp *rpoB* amplicons related to the rifampin resistance in *Mycobacterium tuberculosis* isolates. Two different concentrations of hops alcoholic extract (4 and 8 mg/ml) were prepared and its effects against 21 resistant and 15 sensitive isolates was determinate using proportion method. Six different mutations in the 193-bp amplified *rpoB* gene fragments and seven distinguishable PCR-SSCP patterns in 21 Iranian rifampin resistant isolates were recognized. This study showed that the percentage of resistance and the type of mutations were correlated with the PCR-SSCP patterns and the type of mutations in *rpoB* gene (P<0.05). The results of hops antimycobacterial effect showed that different concentrations of hops ethanolic extract (4 and 8 mg/ml) had a remarkable inhibitory effect on rifampin sensitive and resistant isolates of *Mycobacterium tuberculosis* [41].

Aristolochia taliscana

In animals infected with drug-sensitive or MDR strains, (–)-Licarin A isolated from *Aristolochia taliscana* produced a significant decrease of pulmonary bacillary burdens at day 30 of treatment, and a significant pneumonia reduction at days 30 and 60 of treatment. Regarding subacute toxicity, (–)-Licarin A administration during 21 days showed no abnormalities in main-organ macro- and microarchitecture. Biochemical and hematological parameters analyzed showed no statistical differences between control and treated groups. (–)-Licarin A reduces pneumonia of mice infected with both mycobacterium strains. Also, subacute toxicity of (–)-Licarin A exhibits no major signs of damage [42].

Hypericum species

Extracts from 15 Hypericum species were screened for its antimicrobial activities against 2 Gram− and 2 Gram+ bacteria, 4 non-tuberculous Mycobacterium species, a reference strain H37Rv and 4 drug-resistant strains of *Mycobacterium tuberculosis*, as well as 4 drug-resistant clinical isolates. *H. elodes* and *H. hircinum* subsp. majus extracts were the most active against MDR-TB strains and isolates, with MIC of 25–100 µg/mL and both exhibited significant effect against MDR-TB clinical isolates [43].

Rhoeo spathacea

The proportion of inhibition of aqueous extract (2.5 mg/ml) of *Rhoeo spathacea* was 100% against *M. tuberculosis* H37Rv and MDR strain [44].

Croton tonkinensis

All the di-terpenoids showed activity against susceptible and resistant strains. ent-1b,7a,14b-triacetoxykaur-1 6-en-15-one showed highest activity, MIC-3.125 - 6.25 µg/ml for MDR and XDR strains [45].

Kaempferia galangal

The compound ethyl p-methoxycinnamate (EPMC) isolated from the traditional medicinal herb *Kaempferia galanga* L. was shown to be active against sensitive and drug resistant strains of *Mycobacterium tuberculosis*. By resazurin microtitre assay (REMA), EPMC was shown to inhibit *M. tuberculosis* H37Ra, H37Rv, drug susceptible and multidrug resistant (MDR) clinical isolates (MIC 0.242–0.485 mM). No cross resistance was observed to any standard anti-TB drugs in the MDR strains. The compound did not inhibit any prototype bacteria tested. EPMC seems to be a potential anti-TB lead molecule [46].

Vetiveria zizanioides

The essential oil of *Vetiveria zizanioides* showed significant antimycobacterial activity against the drug-resistant strains of *Mycobacterium smegmatis*, which on activity guided fractionation afforded four bioactive fractions Vz-2, Vz-7, Vz-8, and Vz-9. Further purification of these bioactive fractions over preparative thin layer chromatographic resulted in the characterization of six compounds: 5, 10-pentadecadiyn-1-ol (1), α-curcumene (3), hydroxy junipene (4), (+)

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cycloisosativene (5), valencine (6), and selino 3,7 (11)-diene (7). All these compounds showed significant antimycobacterial activity against the drug-resistant strains (MDR-R and MDR-40) of *M. smegmatis* and their MIC was in the range of 31.25–62.5 µg/ml [47].

Cassia sophera and *Urtica dioica*

Cassia sophera and *Urtica dioica* plant extracts exhibited promising anti-mycobacterial activity against MDR strain of *M. tuberculosis*. Hexane extract of *U. dioica* (HEUD) and methanol extract of *C. sophera* (MECS) produced inhibition zone of 20 mm in disc diffusion assay and MIC of 250 and 125 µg/mL respectively in broth dilution assay against *Mycobacterium semegmatis*. Semipurified fraction F2 from MECS produced 86% inhibition against clinical isolate and 60% inhibition against MDR strain of *M. tuberculosis*. F18 from HEUD produced 81% inhibition against clinical isolate and 60% inhibition against MDR strain of *M. tuberculosis*. Phytochemical analysis indicated that anti-mycobacterial activity of MECS may be due to presence of alkaloids or flavonoids and that of HEUD due to terpenoids [48].

Plumeria bicolor

The *in vitro* anti-mycobacterial activity of chloroform extract of *P. bicolor*, plumericin and isoplumericin were tested against *M. tuberculosis* (H37Rv) and four multi-drug resistant (MDR) clinical isolates by measuring the minimum inhibitory concentration (MIC) using MTT (Tetrazolium bromide [3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide]) assay. Plumericin showed better activity against all the four sensitive as well as MDR strains. Interestingly, both isolated active compounds showed an advantage over rifampicin (80 times) and isoniazid (8 times) by being highly active against the MDR strains [49].

Punica granatum

Therapeutic potential of pomegranate juice, extracts of non-edible peel prepared with methanol/water, and its four polyphenolic constituents, namely caffeic acid, ellagic acid, epigallocatechin-3-gallate (EGCG) and quercetin was evaluated against drug-resistant clinical isolates. The peel extracts exhibited greater antimycobacterial activity (MIC 64–1024 µg/mL) than the potable juice (MIC 256>1024 µg/mL). EGCG and quercetin exhibited higher antitubercular (MIC 32–256 µg/mL) and antibacterial (MIC 64–56 µg/mL) potencies than caffeic acid and ellagic acid (MIC 64–512 µg/mL). The pomegranate fruit peel and pure constituents were active against a broad panel of *M. tuberculosis* and β-lactamase producing *K. pneumoniae* isolates [50].

Challenges

The global challenge of eliminating TB in all its forms can be overcome with increased investments in innovative health technologies and patient-centered approaches to care; broader involvement of health-care providers from both the public and private sectors in the most affected communities and better preventive, diagnostic, and treatment options. Strengthening basic TB control programs to improve access to diagnosis and care and to ensure successful treatment of patients with drug-susceptible TB is critical to preventing the development of drug-resistant TB. Early and accurate diagnosis and effective treatment of MDR-TB will reduce the spread of MDR-TB and prevent the development of XDR-TB. New products for the diagnosis, treatment, and prevention of TB are urgently needed to accelerate control of drug-resistant and drug-susceptible TB. Faster and more accurate tests to diagnose TB and determine its susceptibility to available drugs would allow more timely and effective treatment of drug-resistant TB. Shorter regimens and new drugs that are effective against all forms of TB, including TB that is caused by strains of Mtb that are resistant to the currently available drugs and could cure TB within days or weeks, rather than months or years, would make it more likely for patients to complete therapy and decrease opportunities for the emergence of drug resistance. Finally, the development of an effective vaccine against TB could have a significant impact around the world by preventing all forms of drug-susceptible and drug-resistant TB. There is a need for greater research into developing more effective antituberculous medications and immunotherapy may play an adjunctive role in future management.

Conclusion

Drug-resistant strains of TB arise when an antibiotic fails to kill all of the bacteria that it targets. The surviving bacteria become resistant to that particular drug and often to other antibiotics as well. Multidrug-resistant TB (MDR-TB) occurs when bacteria become resistant to at least the two first-line drugs, isoniazid and rifampin. Under current practices, in which the majority of individuals with MDR-TB remain untreated, the proportion (and likely the absolute number) of MDR-TB cases in many countries is expected to increase over the next decade and beyond. Expanding MDR-TB detection and treatment will require investments in infrastructure and safeguards against second-line drug resistance, but it is key to effectively preventing MDR-TB transmission and reversing the tide of existing MDR-TB epidemics. To meet the challenge of preventing, controlling and ultimately eliminating TB and MDR-TB, healthcare and treatment of TB and MDR-TB patients should not only be appropriate but also effective. Thus, new drugs that would permit significant shortening of treatment are urgently needed, as are drugs that could enable effective treatment to be given at dosing intervals of 1 week or more.

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