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Review Article

AN OVERVIEW ON TUBULARCULOSIS TREATMENT IN CURRENT SCENARIO

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ABSTRACT

The causative agent of tuberculosis (TB) is *Mycobacterium tuberculosis*, which mainly infects lungs and causes severe, fever, weight loss, chest pain, etc. It is an extremely transmittable disease spreaded throughout the world as per the WHO. It has emerged as new threat and drug resistance strains of *Mycobacterium* are emerging throws a challenge to human's health like Covid-19 in current scenario. TB is now come in the form of bone TB, which is very difficult to diagnosis due to very slow-growing characteristics of *Mycobacterium*. This review highlights the history, drug development, current treatment both allopathic and Ayurvedic, as well as novel drugs available for the treatment of drug resistance *Mycobacterium*.

Keywords: Tuberculosis, Nix-tuberculosis, Extensively drug-resistant-tuberculosis, *Mycobacterium tuberculosis,* Ayurvedic.

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INTRODUCTION

In 1882, Dr. Robert Koch has discovered *Mycobacterium tuberculosis* which causes tuberculosis (TB). Mycobacteria are transition forms between bacteria and fungi. These bacteria are non-motile and non-sporulating rods that resist decolorization with acidified organic solvents, that is, acid fast bacteria. The treatment for TB is linked with noncompliance to therapy because it consists of long-term treatment with a multidrug combination and is associated with the appearance of several side effects [1-3].

HISTORY AND DRUG DEVELOPMENT OF TB

The history of TB starts from early 1902 with discovery of para-aminosalicylic acid. The drug development of drugs against TB is shown in Figs. 1 and 2. [4-8].

EPIDEMIOLOGY

About one-fourth of the world's population is infected through TB. In 2018, an estimated 26.9 million new TB cases occurred worldwide. Most new cases reported in Southeast Asia (45%), Africa (25%), and the Western Pacific (17%). In 2019, total 1,725,920 cases reported in India, in which the most infected states are Uttar Pradesh, Madhya Pradesh, Maharashtra, Gujarat, Delhi, Bihar, and Andhra Pradesh.

ETIOLOGY

The main causative agent of TB is *M. tuberculosis*. Other similar causative agents are *Mycobacterium bovis*, *Mycobacterium africanum*, and *Mycobacterium microti*. TB infection occurs exclusively due to the breathing of airborne particles holding *M. tuberculosis.* Particles disperse primarily through coughing, sneezing, talking, etc., of patients with pulmonary infection or whose sputum possess a considerable number of bacteria are mainly infectious due to the presence of large number of bacteria [9,10].

Tubercle bacilli droplet nuclei having diameter <5 μ may stay suspended in air currents of room for several hours and increases the risk of spread. Although when these droplets settle down on surface of floor, it is hard to resuspend the bacteria due to its too large size. Contact with fomites (e.g., contaminated surfaces, food, and personal respirators) does not appear to facilitate spread. Environment also plays an important role in transmission of tubercle bacilli and this is increased by regular contact to patients, in the crowded area spreading large numbers of bacilli, poorly ventilated enclosed spaces are particular at high risk. Health-care practitioners who have close contact with active cases have increased risk.

TREATMENT

Single drug is not effective for the treatment of TB due to the emergence of drug-resistant bacteria. Therefore, recent treatment includes the combination therapy described below. The mechanism of action of anti-tubercular drugs is shown in Fig. 2 [11,12].

COMBINATION THERAPY

1. Multidrug-resistant TB: Isoniazid and rifampicin-resistant *M. tuberculosis* strains can be treated by Cornerstone medicines.
2. Extensively drug-resistant-TB (XDR-TB): Fluoroquinolone and capreomycin, kanamycin, and amikacin resistance *M. tuberculosis* can be treated with XDR-TB along with multidrug resistance therapy.
3. Nix-TB: The long treatment duration of TB is the key cause of the emergence of drug-resistant bacteria. Therefore, it is a trial to make the treatment shorter, oral, and affordable doses which do not require drug at injectable form. It is a combination of pretomanid, bedaquiline, and linezolid.

RECENT ADVANCEMENT

a) Bedaquiline: Chemically, it is a diarylquinoline inhibits mycobacterial adenosine triphosphate (ATP) synthase leads to intracellular ATP diminution [13]. It works on both aggressively replicating as well as dormant mycobacteria, which maintains ATP synthase activity [14].
b) Delamanid: It is metronidazole and nitroimidazopyran (nitro-dihydro-imidazooxazole, 6-nitro-2,3-dihydroimidazo(2,1-b) oxazole) derivative. It is a pro-drug, requires activation, and acts by inhibiting the biosynthesis of mycolic acid.
c) Pretomanid: This drug is a pro-drug and requires intracellular activation by a F420-dependent glucose-6-phosphate-dehydrogenase pathway. Activation produces a des-nitro metabolite that generates reactive nitrogen species, leading to a decrease in intracellular ATP and anaerobic killing [15,16].
d) Sutezolid: It is a linezolid analog and has better *in vivo* activity with less toxicity in comparison with linezolid [17].
e) AZD5847: Like linezolid, AZD5847 is an oxazolidinone that inhibits mycobacterial protein synthesis by binding to the 50S ribosomal

Fig. 1: History and drug development of anti-tubercular drugs

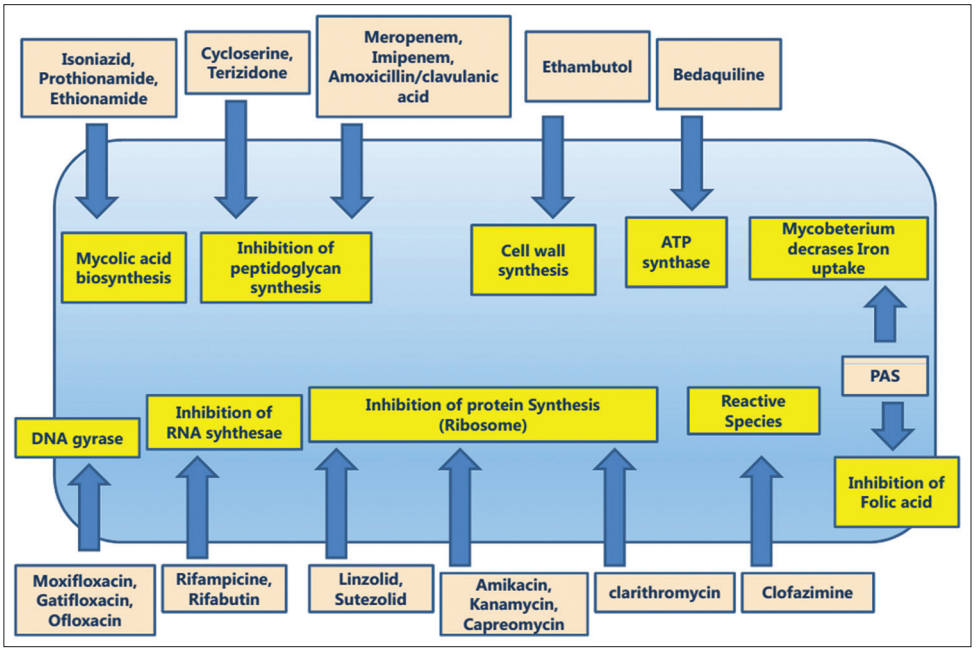

Fig. 2: Mechanism of action of anti-tubercular drugs

subunit; it's *in vitro* bactericidal activity is superior to that of linezolid [18].

f) SQ109: Structurally related to ethambutol, SQ109 is a 1,2-ethylenediamine with a different mechanism of action. It targets the transmembrane transporter encoded by the mmpL3 gene, SQ109 interferes with cell wall assembly [19].

g) The nitroimidazoles: OPC-67683 (Delamanid) and PA-824 are under development as potential TB drugs.

h) AZD5847: AZD5847 is a potential new TB drug being developed by AstraZeneca. In December 2012, it was announced that the first patient had been enrolled in a Phase 2a trial of the drug in South Africa to assess the effectiveness of the drug for patients with TB, including patients with TB and HIV infection.

i) The fluoroquinolones: Moxifloxacin and gatifloxacin are currently being developed for the treatment of drug-sensitive TB.

j) TB drug combinations: The combination of moxifloxacin and pyrazinamide had the greatest early bactericidal activity. One advantage of this drug combination is that it does not involve either isoniazid or rifampicin. It is, therefore, suitable for use with patients who are resistant to these drugs. A regimen without rifampicin would greatly simplify the provision of TB treatment alongside HIV antiretroviral therapy [20-44].

There are various side effects in TB drugs such as itchy skin, bruising or yellow skin, skin rashes, stomach upset, nausea, vomiting, diarrhea or loss of appetite, lack of feeling or tingling in the hands or feet, changes in your eyesight, particularly changes in red or green color vision, dark colored urine, and yellow eyes. Although several drugs are in the market, thrust of new drug is always there, so an alternate Ayurvedic drug therapy was developed in the treatment of TB due to side effects [45-54].

AYURVEDIC DRUGS USED IN TB

In Ayurveda, TB is known as *Kshayaroga* or *Rajyakshma*. Ayurvedic treatment procedures that are recommended for TB include *Snehana* which means *oleation*. It basically involves massage with warm medicated oils infused with the properties of herbs to treat the aggravated *doshas* and helps in liquefying and dislodging toxins from the smallest channels of the body, *Swedana* which means sudation or sweat therapy (it is three types, *Tapa,* that is, fomentation, involves the use of a metal object, heated cloth or warm hands to provide heat to the body, *Upanaha* involves the use of a hot poultice consisting of various herbs based on the aggravated dosha, *Ushma* refers to the use of warm steam created by boiling the appropriate herbs depending on the dosha that need to be balanced, and *Dhara* involves pouring of warm medicated liquid over the body), *Vamana* which means medical emesis and *Virechana* which means purgation (commonly used herbs for virechana are senna, aloe, and rhubarb).

Although, these procedures are only effective in individuals with aggravated *doshas* and in those who are strong enough to tolerate these therapies. *Shodhana karma* which means purification therapies, which should not be used in weak individuals, and they should be very mild even when used in strong individuals with TB. This is because there is *kshaya* which means depletion of all seven *dhatus* in TB. Hence, nourishing the treatment should be given to strengthen the body. However, care should be taken that *dhatu agni* is not affected [55-59]. Various drugs used in TB are as following:

Ayurvedic drugs used in TB are as – *Acalypha indica* (family – Euphorbiaceae) commonly known as Kuppi, *Adhatoda vasica* (family – Acanthaceae) commonly known as Vaasa, *Allium cepa* (family – Liliaceae) commonly known as Palaandu, *Allium sativum* (family – Liliaceae) commonly known as Lashuna, *Aloe vera* (family – Liliaceae) commonly known as Ghritkumaarika, *Vitex negundo* (family – Verbenaceae) commonly known as Nirgundi, *Trichosanthes dioica* (family – Cucurbitaceae) commonly known as Patola, *Tinospora cordifolia* (family – Menispermaceae) commonly known as Guduuchi, *Caesalpinia pulcherrima* (family – Caesalpiniaceae) commonly known as Padangam, *Prunus armeniaca* (family – Rosaceae) commonly known as Peetaalu, *Ocimum sanctum* (family – Labiatae) commonly known as Tulasi, *Morinda citrifolia* (family – Rubiaceae) commonly known as Ashyuka, *Myrtus communis* (family – Myrtaceae) commonly known as Muurad-daan, *Canscora decussata* (family – Gentianaceae) commonly known as Daakuni, *Piper species* (family – Piperaceae) commonly known as Pippali, *Vitex trifolia* (family – Verbenaceae) commonly known as Sinduvaara, *Mallotus philippensis* (family – Euphorbiaceae) commonly known as Kampillaka, *Colebrookea oppositifolia* (family – Lamiaceae) commonly known as Binda, *Rumex hastatus* (family – Polygonaceae) commonly known as Katambal, *Mimosa pudica* (family – Mimosaceae) commonly known as Laajavanti, and *Kalanchoe integra* (family – Crassulaceae) commonly known as Parnabija.

Medicines that are described in Ayurveda for the management of TB are *Eladi churna*, *Sitopaladi churna*, *Chitraka Haritaki*, *Mahalaxmivilasa Rasa*, *Chyawanprashavaleha*, *Draksharishta*, *Dhanvantara Gutika*, *Bhringrajasava*, *Swarna Malini*, *Vasanta*, *Madhumalini Vasanta,* and *Vasanta Kusumakar* [60-73].

CONCLUSION

In today's world, there has been an increase in demand of phytopharmaceuticals in all over the world because more side effects of allopathic drugs. The main aim of this review article is to compile various anti-tubercular drugs of both allopathic as well as Ayurvedic sources.

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