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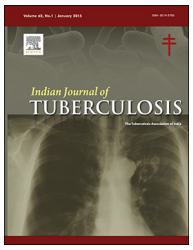

Review Article

Drug development against tuberculosis: Past, present and future

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ABSTRACT

Infection of *Mycobacterium tuberculosis* (MTB) was observed as early as 5000 years ago with evidence, which is a primeval enemy of the humanoid race. MTB is the pathogen which is responsible for causing the infectious disease tuberculosis; it remains a major cause of morbidity and mortality in poor low-income countries as well as in developing countries because of non-availability of reliable laboratory facilities. The current treatment for drug-resistant tuberculosis (TB) is lengthy, complex, and connected with severe harmful side effects and poor outcomes. The present cure against tuberculosis has substantial restrictions, in terms of their efficiency, side-effect outline, and complication of handling.

Furthermore, the emergence of multi-drug resistant tuberculosis (MDR-TB) outbreaks during the 1990s and additionally in recent times the vast deadly strains of extensively drug-resistant tuberculosis (XDR-TB) and totally drug resistance tuberculosis (TDR-TB) is hampering efforts to control and manage tuberculosis (TB). As a result, novel methodologies for the treatment of multi-drug-resistant and extensive drug-resistant tuberculosis (TB) are severely desired. A number of new potential anti-tuberculosis drug candidates with novel modes of action have been entered in clinical trials in recent years. These agents are most likely to be effective against resistant strains. The treatment landscape is beginning to shift, with the recent approvals by Food and Drug Administration to the new TB drugs bedaquiline and delamanid. Also, the pipeline of potential new treatments has been fulfilled with several compounds in clinical trials or preclinical development with promising activities against sensitive and resistant MTB bacteria. An additional new chemical entity is also under development. The already existing drugs with their suggested mode of treatment as well as new probable anti-tuberculosis drug moieties which are at present in the pipeline has been summarized in this review.

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Abbreviations: TB, tuberculosis; MTB, *Mycobacterium tuberculosis*; MDR-TB, multi-drug resistant tuberculosis; XDR-TB, extensively drug resistant tuberculosis; TDR-TB, totally drug resistant tuberculosis; INH, isoniazid; WHO, World Health Organization; RIF, rifampicin; PZA, pyrazinemide; EMB, ethambutol; ETH, ethionamide; CDC, Centers for Disease Control and Prevention; CBC, Complex Blood Count; GI, gastrointestinal; LFT, liver function test; PO, per os; *katG*, *catalase-peroxidase*; NADP, nicotinamide adenine dinucleotide phosphate; MRC, Medical Research Council; rRNA, ribosomal RNA; FQs, fluoroquinolones; FDA, Food and Drug Administration; MIC, minimum inhibitory concentration; CYP, cytochrome; GLP, Good Laboratory Practice.

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1. Introduction

The human tuberculosis are established over 6000 years of age which is proposed from another DNA investigation of a tuberculosis genome reproduced in southern Peru, in 2014. Analysts conjecture that humans initially acquired tuberculosis in Africa around 5000 years ago.[1] It was concluded by Gutierrez and her colleagues that in East Africa an early progenitor of *Mycobacterium tuberculosis* (MTB) was present as early as 3 million years ago, and it was suggested by them that, at that time it may have infected early humanoids.[2] MTB, the bacteria that cause tuberculosis (TB) was discovered by Dr. Koch on March 21, 1882. In the United States and Europe, TB killed one out of every seven people during that time. Dr. Koch's discovery was the most important step taken toward the control and elimination of this deadly disease.[3] After a century of Dr. Koch's discovery, World Health Organization (WHO) and the International Union declared the first World TB Day in 1982.[3] The timeline history of tuberculosis is represented in Fig. 1.

In 1997, it was estimated that one-third of the human population (approximately 1.86 billion people) are infected with *M. tuberculosis* worldwide.[4] Tuberculosis, TB (tubercle

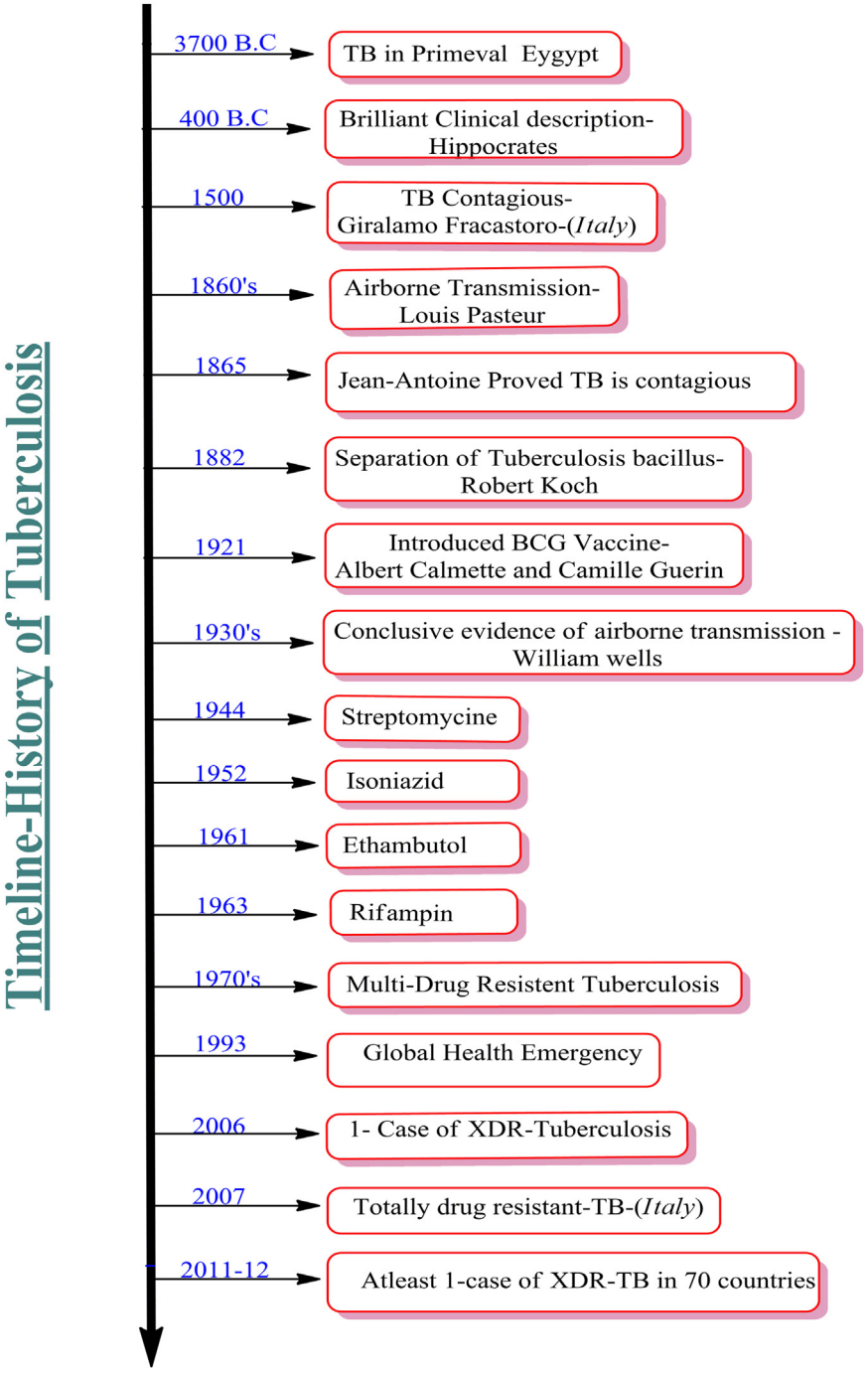

Fig. 1 – Timeline history of tuberculosis.

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