European Journal of Medicinal Chemistry 137 (2017) 504–544

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Review article

Drug development against tuberculosis: Impact of alkaloids☆

Shardendu K. Mishra [a, b, 1], Garima Tripathi [a, 2, 1], Navneet Kishore [a, 3], Rakesh K. Singh [c], Archana Singh [a], Vinod K. Tiwari [a, *]

[a] Department of Chemistry, Institute of Science, Banaras Hindu University, Varanasi, 221005, Uttar Pradesh, India
[b] Department of Pharmacology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, 221005, Uttar Pradesh, India
[c] Department of Biochemistry, Institute of Science, Banaras Hindu University, Varanasi, India

ARTICLE INFO

Article history:
Received 4 April 2017
Received in revised form
26 May 2017
Accepted 2 June 2017
Available online 3 June 2017

Keywords:
Alkaloids
Tuberculosis
Mycobacterium tuberculosis
Antimycobacterial agents
Multi drug resistant tuberculosis
Natural products
Drug development

ABSTRACT

Despite of the advances made in the treatment and management, tuberculosis (TB) still remains one of main public health problem. The contrary effects of first and second-line anti-tuberculosis drugs have generated extended research interest in natural products in the hope of devising new antitubercular leads. Interestingly, plethoras of natural products have been discovered to exhibit activity towards various resistant strains of *M. tuberculosis*. Extensive applications of alkaloids in the field of therapeutics is well-established and nowday's researches being pursued to develop new potent drugs from natural sources for tuberculosis. Alkaloids are categorized in quite a few groups according to their structures and isolation from both terrestrial and marine sources. These new drugs might be a watershed in the battle against tuberculosis. This review summarizes alkaloids, which were found active against *Mycobacteria* since last ten years with special attention on the study of structure-activity relationship (SAR) and mode of action with their impact in drug discovery and development against tuberculosis.

Contents

☆ This manuscript is dedicated to Prof. (Dr) Rama P. Tripathi, Senior Scientist at CSIR-Central Drug Research Institute, Lucknow, India.

* Corresponding author.
E-mail address: Tiwari_chem@yahoo.co.in (V.K. Tiwari).
[2] Present address: Department of Chemistry, Indian Institute of Technology, Kanpur, India.
[3] Present address: Department of Plant Science, University of Pretoria, Pretoria-0002, South Africa.
[1] Author contributed equally.

http://dx.doi.org/10.1016/j.ejmech.2017.06.005
0223-5234/

1. Introduction

Since inception tuberculosis (TB) has been the most challenging disease in human era that is caused by *Mycobacterium tuberculosis* (*M.Tb*), an acid-fast bacillus, which persists in host body for the longer period without any indication of disease [1–3]. The primary cause for the survival of this bacillus is its unique property to develop resistance against the drugs discovered till today [4,5]. In immunocompromised patient, this bacillus start a silent warfare, which eventually transformed into an assault leading to the uncontrolled growth of bacteria (nearly 10^{13} organisms) [6,7]. The period of tuberculosis drug discovery and current researches in pipeline has been associated with multilateral agencies and various non-governmental organizations for technical assistance as well as pharmaceutical companies developed new strategy to alleviate tuberculosis [8–10].

It has been considered a sickness of death for many years with relatively rare cases in the developed countries. Tuberculosis remains a huge problem in economically weaker section (below poverty line) in developing countries [11]. This “White Plague” is a critical challenge not only for medical but also from the social point of view for the current situation, too. Virtually, every year about 1.5 million people dies all over the world, and around 9–9.5 million of new TB patient's registration are observed. Recently, World Health Organization (WHO) has declared as a worldwide catastrophe due to the sudden rise of new TB cases supported by the introduction of Human Immunodeficiency Virus (HIV) resulting in millions of deaths every year [12]. Around one-third of the world's population is presently informed to be infected with *M. tuberculosis*. World Health Organization, 2014 survey, revealed on TB patients that the estimated 85% cases happened in Asia (58%) and Africa (28%), while around 14% cases arised in the rest of the world [13–15]. According to the WHO (2016) annual report on TB, 2.84 million Indians contracted the disease in 2015 alone and thus India bears the maximum number of TB patients with an estimated 79,000 persons becoming sick with this disease each year [16].

Immuno deficiency due to HIV clears the path for tuberculosis persistence by leading towards an immunocompetent person transformation into a horrifying assault [17,18]. HIV prevalence with tuberculosis is marked increasing from last two decades and fueled tuberculosis outbreak. The available regimen for the tuberculosis was discovered in between 1950 and 1975 resulting in a drastic decrease in the disease, but the emergence of multi-drug resistant (MDR) leads to a sudden increase in disease graph which is alarming statistics [19,20]. Today's treatment is more problematic to the clinicians due to resistance to more than two antimycobacterial drugs leading to development of multi-drug resistant tuberculosis (MDR-TB) [21,22].

However, owing to the advent of drug-resistant TB strains, new drugs are immediately required and thus efforts have been twisted