Original Article

Bulletin of Pure and Applied Sciences.
Vol.37A (Zoology), No.2, Jul-Dec 2018: P.65-74
Print version ISSN 0970 0765
Online version ISSN 2320 3188
DOI 10.5958/2320-3188.2018.00009.8

A Study on Recent Trends in Therapy of Air Borne Communicable Disease Caused by *Mycobacterium tuberculosis*: The Tuberculosis

Parveen Kumar[1], Sushil Kumar Upadhyay[2*], Raj Singh[3]

Authors Affiliation:
[1]Department of Chemistry, Meerut College, Meerut, Uttar Pradesh, India.
[2,3]Department of Biotechnology, Maharishi Markandeshwar (Deemed to be University), Mullana-Ambala (Haryana), 133207, India

***Corresponding address:**
Dr. Sushil K. Upadhyay, Assistant Professor, Department of Biotechnology, Maharishi Markandeshwar (Deemed to be University), Mullana-Ambala (Haryana) 133207, India.

E-mail:
sushil.upadhyay@mmumullana.org

Received on 05.07.2018
Accepted on 12.11.2018

Abstract

The tuberculosis (TB) caused by a bacterium *Mycobacterium tuberculosis,* is a transmissible air borne disease. The primary infection as latent TB becomes active when the bacteria enormously multiplied in lungs. The active TB diagnosed with the symptoms of pneumonia along with chest ache, prolonged cough and coughing up blood. The unexplained weight loss, tiredness, fatigue, shortness of breath, fever, night sweats, chills, and loss of appetite has been noticed in the patients of active TB. The punctual and effectual management of TB disease is critical to put off enduring transmission of TB. Most of the TB patients having cure by directly observed therapy (DOT), and only one third of TB patients expected a combination of DOT and self-administered therapy. When TB is an inactive phase (Latent TB), monotherapy supposed to be adequate for the cure and patients at this time suggested to take a six months continuous dose of an antibiotic called isoniazid (INH). However, the active TB is treated with multi drug therapy (MDT) with a combination of 4 (Isoniazid, Rifampicin, Pyrazinamide and Ethambutol) or more drugs for a prolonged period. There are some chemical compounds, such as Thiolactomycin, Ethambutol, Mefloquine, Deazapteridines, Moxifloxacin, Nitromidazole, Pyridomycin and its analogues etc. are used for the treatment of tuberculosis effectively. A drug baseed upon pyridine structure, the 1,4-dihydropyridines (DHP) and its derivatives are well known chemical in pharmacology and are equipotent anti-tuberculosis drugs to Moxifloxacin and Gattiflaxocin. The Nanotechnology employed drug delivery systems have considerable potential for the treatment of TB, and allowed sustained and target specific release of drugs from the matrix. These properties of Nanotechnological approaches enable the improvement of the bioavailability of drugs, can reduce the dosage and frequency of administration, and may solve the problem of non-adherence to prescribed therapy, which is a major obstacle to the control of TB. Thus the purpose of this study is to systematically represent the recent trends and their advantages in treatment of air borne communicable disease i.e. TB.

Keywords: Tuberculosis (TB), *Mycobacterium tuberculosis,* Communicable disease, Monotherapy, MDT, DOT, Anti-tuberculosis.

1. INTRODUCTION

An air borne communicable disease caused by bacterium, *Mycobacterium tuberculosis* is known as Tuberculosis (TB). The foremost organ affected in this disease is lungs, but others like: organs of the central nervous system, lymphatic, reproductive and circulatory system also found to be infected. The disease was famous as 'consumption' in the past years because of the way it would consume from within anyone who became infected (Breitenbucher and Figiozz, 2000; David, 2007). The Medilexicon's medical dictionary defined tuberculosis as "a specific disease caused by the tubercle bacillus, and can affect almost any tissue or organ of the body but the most common site of the disease being the lungs." It has been noticed that during infection, the bacteria multiplied in lungs and symptomized to pneumonia along with chest ache, prolonged cough and coughing up blood. As the TB tries to extend to other parts of the body, it is habitually interrupted by the body's immune system. The immune system synthesizes scar tissue or fibrosis periphery to the TB bacteria, and this prevents spreading of disease all over the body and to other people. In the person with inefficient or weak immune system, the disease turns to an active state with pneumonia and may damage kidneys, bones, meninges of spinal cord and brain (Love et al., 1974). TB is a chief ground of poor health and death worldwide, principally in Africa and Asia, and kills about 2 million human beings (Bassert et al., 1981).

Tuberculosis may be either latent or active. The latent TB occurs when the pathogens are present in body of victim but the state is inactive without any symptoms of disease and non-contagious. However, active TB is contagious with sickness and disease symptoms. The people with active TB infection were symptomized with unexplained weight loss, tiredness, fatigue, shortness of breath, fever, night sweats, chills, and loss of appetite. The symptoms specific to lungs comprise coughing that lasts for three or more weeks, coughing up blood, chest pain, and pain with breathing and coughing (Boer and Gekeler, 1995; Briukhanov et al., 1998). As tuberculosis is an air borne communicable disease and spread among population from side to side by minuscule droplets of contaminated sputum during coughing, sneezing, talks or shouts and spits to uninfected people who breathe bacteria into their lungs (Sunkel et al., 1990). Although anyone can turn out to be infected with TB but some people are more prone to comparatively higher risk (David and Triggle, 1999), namely to those who living with patients having active TB, persons below poverty line and homeless, foreigners come from countries with endemic TB, aged and immune deficient people, alcoholics and intravenous drug users, persons with diabetics, cancer and HIV patients, and health-care workers as well as workers in refugee camps or shelters. Tuberculosis incidence has been on the increase in Africa, mainly as a result of the burden of HIV infection. Definitive diagnosis of tuberculosis based on culture for *M. tuberculosis* is classical and time consuming method, but rapid diagnosis of infectious tuberculosis by simple sputum smear for acid fast bacilli remains an important tool, at the same time as more rapid molecular techniques are being developed. Treatment with several drugs for six months or more can cure more than 95% of patients. Direct observation of treatment, a component of the recommended five-element DOTS (Directly Observed Therapy Short course) strategy, is judged to be the standard of care by most authorities. Currently only a third of cases worldwide are treated using this approach. There may be need to modify the treatment modalities especially with the choice of drugs and duration of therapy when TB infection occurs in special situation like pregnancy, liver disease, renal failure or even in coexistence with HIV/AIDS or the drug resistant state (Bello and Njoku, 2005).

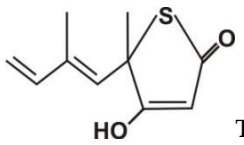
The international targets for tuberculosis control, framed within the United Nations Millennium Development Goals (UNMDGs), were to ensure the declining of global TB incidence, prevalence and death rates halved of the 1990 (Dye et al., 2006). These targets are to be achieved by implementing World Health Organization's (WHO's) Stop TB Strategy (STBS), central to which is the prompt diagnosis of patients with active disease followed by supervised, short-course, combination chemotherapy (Raviglione and Uplekar, 2006). The STBS sets the standards for case management today, as it is widely recognized that prompt treatment with the right drug regimens can cure almost all TB patients and save lives. However, combination chemotherapy has been widely available for at least 40 years and has thus affected TB transmission, incidence and mortality rates in industrialized

countries since before the DOTS era. The variables studied were readily available measures of specific aspects of the economy, the population, behavioral, biological and social risk factors, health services and the intensity of TB control (Styblo, 1991). It was conjectured that if TB diagnosis and treatment (including DOTS programs) are having a greater effect in countries where they have been most widely implemented, then conventional indicators of program performance, including case detection and treatment success rates, should emerge as dominant explanatory variables in an ecologic or correlation analysis. Conversely, if diagnosis and treatment are not yet the principal drivers of TB epidemics, then other factors should be more strongly associated with inter-country variation in TB incidence trends, both within regions and globally (Dye et al., 2009). TB is the ninth leading cause of death worldwide and the leading cause from a single infectious agent, ranking above HIV/AIDS. In 2016, there were an estimated 1.3 million TB deaths among HIV-negative people (down from 1.7 million in 2000) and an additional 374 000 deaths among HIV-positive people. An estimated 10.4 million people fell ill with TB in 2016: 90% were adults, 65% were male, 10% were people living with HIV (74% in Africa) and 56% were in five countries: India, Indonesia, China, Philippines and Pakistan (Shivangi and Meena, 2018).

2. RECENT TRENDS IN TB THERAPY

Identification and treatment of Latent TB Incidence (LTBI) can substantially reduce the risk of development of active disease (by as much as 60%), and is an important TB control strategy in low-TB incidence settings where reactivation disease usually accounts for the majority of non-imported TB disease. The goal of testing for LTBI is to identify individuals who are at an increased risk for the development of active TB; these individuals would benefit most from treatment of LTBI. There is no diagnostic gold standard for LTBI and all existing tests are immunological tests that provide indirect evidence of sensitization of the host to TB antigens. There are two available tests for identification of LTBI: Tuberculin skin test (TST) and interferon-gamma release assays (IGRA). TST is usually performed using the Mantoux skin test method (MSTM), and purified protein derivative (PPD) antigen injected intra-dermally (Pai and Rodrigues, 2015). The treatment of TB depends on condition of disease whether active or latent. If TB is inactive in state (LTB), an antibiotic called isoniazid (INH) is prescribed for six to twelve months. The active TB is treated with INH by using the drugs of currently recommended treatment regimens for active pulmonary TB (MDT) are both lengthy and cumbersome. The treatment duration is a minimum of six months, with 4 drugs (Isoniazid, Rifampin, Pyrazinamide and Ethambutol) (Tarasenko et al, 2000). These drugs typically given daily for the first 2 months and with 2 drugs (isoniazid and Rifampin) administered for your additional months in part because of this lengthy and complex treatment regimen, the world health organization (WHO) in year 1993 introduced a global strategy for TB control known as Directly Observed Therapy, Short-course (DOTS) (Burdriesi and Pierfranco, 2008). There are some chemical compounds, such as Thiolactomycin, Ethambutol, Mefloquine, Deazapteridines, Moxifloxacin, Nitromidazole, Pyridomycin and its analogues etc. are used for the treatment of tuberculosis (Kumar et al., 2006) are given below:

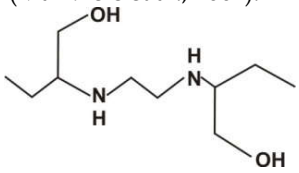
1. Thiolactomycin: Thiolactomycin is an antibiotic of considerable interest because of its selective activity in disrupting essential fatty acid synthesis in bacteria. This is expected that it is also used in the treatment of malaria, trypanosomiasis and various bacterial indications including TB (Kumar et al., 2006).



Thiolactomycin

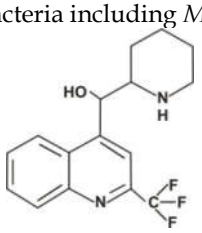
2. Ethambutol: Ethambutol is one of the main drugs used in TB treatment and in most countries it has now replaced streptomycin and thiacetazone. Although about the mode of action of ethambutol is

scarce till date but it is supposed to ethambutol interferes with construction of the arabinogalactan layer of *Mycobacterium* cell wall (Markhele et al., 2007).



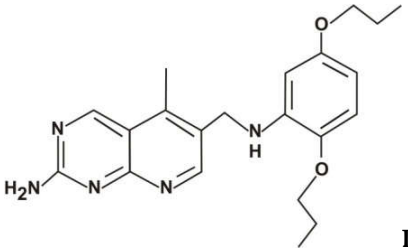
Ethambutol

3. Mefloquine: The antimalaria drug Mefloquine and its several analogues have been reported to have activity against a variety of bacteria including *Mycobacterium* (Mustafa et al., 2009).



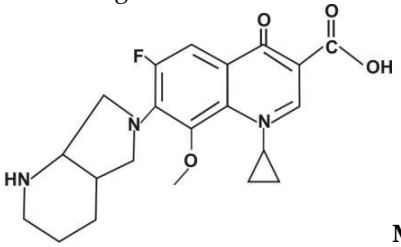
Mefloquine

4. Deazapteridine: A series of 2, 4-diamino-5-deazapteridine derivatives synthesized at Southern Research Institute (SRI), London and this drug highly active against *M. tuberculosis* when tested against albino mice.

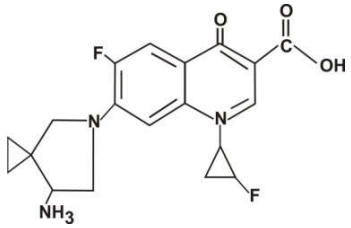


Deazapteridine

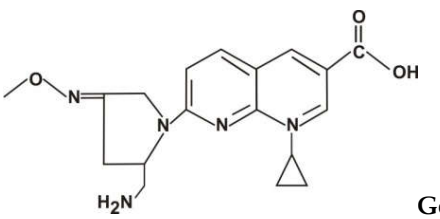
5. Moxifloxacin and derivatives: It is newest and 4th generation antibiotic used for the treatment of respiratory tract infections. In year 1999 US Food and Drug Administration (FDA) recommended moxifloxacin for the treatment of skin and soft tissue infection (Fassihi et al., 2009). This drug shows its activity against *M. tuberculosis in vitro* and *in vivo* too. Similarly other drugs like sitafloxacin, Gemifloxacin and Rifametane are also used as anti TB potent drug and used for the prevention and inhibit the growth of *M. tuberculosis* in human respiratory tract system (Amini et al., 2008).



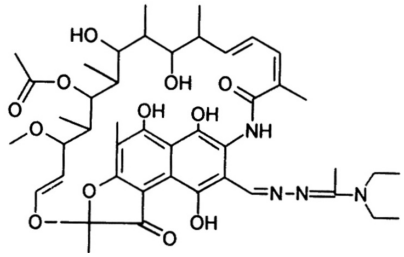
Moxifloxacin



Sitafloxacin

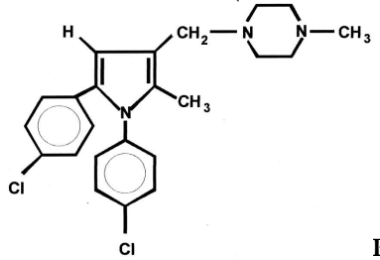


Gemifloxacin



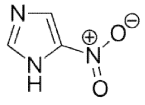
Rifametane

6. Pyrrole: Currently, the pyrrole is being developed by Lupin Pharma. The activity of Pyrrole against *M. tuberculosis* was reported and generally 1,5-diaryl-2-methyl-3-(4-methyl piperazin-1-yl)-methyl pyrrole is used to prevent the growth of *M. tuberculosis* (Shifi et al., 2008).



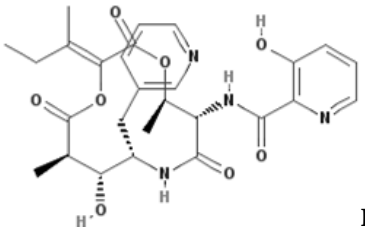
Pyrrole

7. Nitromidazole: Another class of compounds that has been the subject of considerable interest because of their in TB therapy is nitromidazole. Some imidazole derivatives like nitromidazole-oxazine, and dihydroimidazo oxazole can be used as potent anti TB agents (Dubey and Knaus, 1984).



Nitromidazole

8. Pyridomycin: Pyridomycin inhibits the growth of the tuberculosis pathogen *M. tuberculosis*, but it is degraded relatively quickly and is therefore ineffective. However, by using the structure of pyridomycin, a new molecule has been designed that has several advantages over the natural active substance. The new molecule is more stable and is easier to produce synthetically; it can also serve as a lead structure for the synthesis and biological testing of further modified versions of the active substance. Drugs could eventually be developed that work efficiently and are well tolerated (Oliver et al., 2013; Ruben et al., 2013).



Pyridomycin

3. MONOTHERAPY *VS* MULTYTERAPY IN TUBERCULOSIS

The World Health Organization (WHO) in 1993 declared TB as a global emergency due to a large increase in number of cases. TB is the single largest cause of death by infection among adults, mainly in developed countries. The WHO estimated that one third of the world's population is infected by *M. tuberculosis*. Despite the availability of treatments that can cure over 90% of cases, TB remains the second leading cause of death from an infectious disease worldwide after the human immunodeficiency virus (HIV), which caused an estimated 1.7 million deaths in 2011 (Koul et al., 2011). In recent years, the number of patients with TB has rapidly increased due in part to the appearance of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains. Another factor that contributes to the problem is the fact that approximately one third of the world's population is infected with the bacillus in its latent form. Of these, approximately 10% will develop clinical manifestations (characterized as TB disease), especially in individuals co-infected with HIV. Finally, TB is associated with HIV; this association is a major cause of death in co-infected patients (Maciel et al., 2010).

The use of specific anti-TB drug combinations is always necessary in all the regimens of treatment to avoid the development of drug-resistant TB. A monotherapy (the use of one anti-TB drug alone) must never be used in any stage of treatment. Once a choice is made to treat TB, it is the health care

provider's responsibility to assure that the patient is notified and finishes the full course of treatment. Due to the great increase in the number of TB cases, patients should not be treated in hospitals except those TB patients who are seriously ill or MDR or XDR carriers. All the patients diagnosed with TB must be entitled to free anti-TB drugs. The only effective treatment of TB consists of an appropriate combination of anti-TB drugs, given in the right dosages, taken daily and continuously by the patient, under supervision, throughout the treatment period and there are five drugs available for first-line anti- TB treatment (Pavan et al., 2013).

Nearly 30 years ago, the WHO recommended a combined regimen of three drugs, rifampicin (RIF) + isoniazid (INH) + pyrazinamide (PZA), for the treatment of TB and recommended a treatment with four antituberculosis drugs, RIF+INH+PZA+ethambutol (ETB). The adverse effects that are caused by the first-line tuberculostatics may result in the interruption of treatment and have serious consequences for control of the disease. The occurrence of risk factors, morbidity and mortality of the adverse effects related to INH (particularly its hepato-toxicity) is well documented in the literature; the adverse effects related to RIF, PZA and ETB treatment are also well-reported. In general, the main adverse effects include irritative, allergic and toxic reactions. The allergic reactions can be mild (hives, rash, itching, cholestatic jaundice) or severe (anaphylactic shock, blood dyscrasias, vasculitis, interstitial nephritis) (Shishoo et al., 2001). The great potential of Medicinal Inorganic Chemistry (MIC) as a tool for the development of possible anti-tuberculosis drugs has been observed. It is also known that many metal ions play an important role in living systems (Zarghi et al., 2003). The metal ions are deficient in electrons and that the majority of biological molecules such as proteins and DNA are rich in electrons, the attraction of these opposite charges causes an interaction between metal ions and biological molecules within biological systems. New ruthenium(II)/ phosphine/ diimine complexes, lichexanthone derivates, 1,2,3-triazole derivates of carbohydrate, cobalt(II) sulfonamide complexes, and Ag(I) and Au(I) complexes with 2-(2-thienyl) benzothiazole have shown low cytotoxicity good *in vitro* activities against *M. tuberculosis* (Micheletti et al., 2013; dos Santos et al., 2013). Other metallic complexes have excellent *in vitro* and *in vivo* activities against *M. tuberculosis* like ruthenium complexes containing phosphines/diimines and picolinate. These compounds are active *in vitro* against susceptible and resistant strains, and have low cytotoxicity and good intracellular activity. These are also active against non-replicating persistent *M. tuberculosis*, and are not mutagenic or antagonistic. The *in vivo* toxicity analysis showed that these compounds had no or limited toxicity. More recently, pharmacokinetic studies of these compounds have been performed, and unfortunately, these compounds were degraded by the digestive system or they were not absorbed (Pavan et al., 2010, 2011).

4. NANOTECHNOLOGICAL APPROACHES TO TB THERAPY

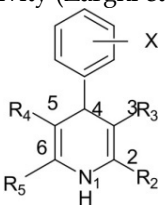
To minimize the side effects of treatment and, to protect and improve the bioavailability of these compounds, new strategies are being been investigated. Within this context, nanotechnology-based drug delivery systems have considerable potential for the treatment of TB. The technological advantages of these systems as drug carriers include their high stability, high capacity, the feasibility of incorporating hydrophilic and hydrophobic substances, and the possibility of varying the routes of administration, such as oral application and inhalation. These properties of nano-systems enable the improvement of drug bioavailability and a reduction in the frequency of administration and may solve the problem of non-adherence to therapy, which is a key obstacle in the control of tuberculosis epidemic (Kumar et al., 2011; da Silva et al., 2016). Using nanotechnology, it is possible to improve the liberation of water-insoluble drugs, the liberation of drugs in specific cells or tissues and even to affect the intracellular release of macromolecules (Farokhzad and Langer 2009). The basis of this technology is the use of nanostructured systems that have a variable maximum size (nanometer scale) being both important in the application of the medicine (Praba et al., 2013). The use of different nanotechnology-based drug delivery systems such as polymeric nanoparticles (PNs), solid lipid nanoparticles (SLNs), liquid crystal (LC) systems, liposomes (LIPs), microemulsions (MEs), nanomicelles (NMs) and metal-based nanoparticles (gold nanoparticles, silver nanoparticles, iron oxide nanoparticles) is an interesting approach to improve the most desirable properties of a drug formulation. Furthermore,

nanoscale particles represent a future where activity is ensured and the problems associated with the treatments of TB can be overcome (Lu et al., 2013).

The development of drug-resistant TB, drug delivery to the infected site through nanoparticles had been studied for long time. Nanoparticles indicate different sorts of association with the natural particles of the body. Nanoparticles can be used as controlled or specific drug delivery system. It can be achieved through temporal controlled or can be distribution controlled. Glucose polymer-based nanoparticles might play an important role as drug delivery system in case of targeted drug delivery in the infected site of the body or in infected macrophages. As these are biodegradable so there should not be any side effects of these particles in the body and also they show very slow immune response. CD4, Beta 1, IL-2 and IL-13 are the major biomarkers that are secreted after infection of this bacterium by the macrophages which can be used for targeted drug delivery in infected macrophages. As these markers can be used for delivery of drugs at destined position, they can be very beneficial in reducing toxicities of anti-tubercular drugs to the other uninfected sites and in operating only the infected macrophages (Shivangi and Meena, 2018).

5. DIHYDROPYRIDINE: A POTENT ANTITUBERCULOSIS AGENT

The 1,4-dihydropyridines (1,4-DHP) is a molecule based upon pyridine, and the parent of a class of molecules that have been semi-saturated with two substituents replacing one double bond. They are particularly well known in pharmacology as L-type calcium channel blockers, used in the treatment of hypertension. Compared with certain other L-type calcium channel blockers (phenylalkylamine namely verapamil) that have significant action at the heart, they are relatively vascular selective in their mechanism of action in lowering blood pressure. The 1,4-dihydropyridines is ever-growing due to their varied biological pharmaceutical applications. The 1,4-dihydropyridine is a six membered aromatic ring containing N at 1stposition, and saturated at 1st and 4th position. The most feasible position for substitution is 4th which exhibit various activities i.e., as the calcium channel antagonists (Devki et al., 1969) and the heterocyclic ring is the common feature for various pharmacological activities such as antihypertensive, antianginal (Mathew et al., 1995; Paramsivan, 1998; Paramsivan et al, 2000), antitumor (Mitchison, 1993), anti-inflammatory activity (Miyazaki et al., 2002; Gasling et al., 2003), anti-tubercular activity (Manfunatha et al., 2006), analgesic activity (Lee et al., 2003), antithrombotic (Mathew et al., 1993; Lee et al., 1996). It binds to L-type channel and also shows action by binding to N-type channel also (Cozzi et al., 1993) other activities like vasodilation (Harfenist et al., 1978), anticonvulsant (Miller and Tainter, 1994) stress protective effect (Misra et al., 1973), and cardio depressant activity (Zarghi et al., 2003).



1,4-Dihydropyridine

a. Structure *vs* activity of Dihydropyridine: The activity of dihydropyridine essentially governed by the 1,4-DHP ring. The un-saturation of fundamental ring decreased the dihydropyrine activity. Substitution at N_1 position and oxidation or reduction in ring system greatly decreased or abolished the anti-bacterial activity. The substituent of 2 and 6 position in 1,4-DHP ring should be smaller alkyl with one NH_2 group can be tolerated (Shashikant et al., 2010). The ester groups at C_3 and C_5 position showed optimum activity. The presence of electron withdrawing groups showed decreased antagonistic activity and might be agonist activity (Isradipine), however, removal or replacement by CN greatly reduced activity. The ester substitution might be greatly maintain or even augmented activity because of bulk tolerance in the site of 1,4-DHP (Amlodipine, C-3-methyl, C-5-ethyl). The substitution of phenyl ring at C_4 position has optimum activity, however, substitution of small non planar alkyl or cyclo-alkyl group showed decreased activity. The compound with ortho or meta substitution posses optimum activity, while unsubstituted or a para substitution showed declining in activity according to their electronic and steric effect (Sabudhi and Panda, 2009). The synthesis of 1,4-

dihydropyridine was first reported by refluxing of aldehyde or ketoester and ammonia or ammonium salt in ethanol or methanol. The eminent workers have reported 1,4-dihydropyridines can be prepared using catalyst alumina sulphuric acid by condensing aldehydes, 1,3-dicarbonyl compounds, and ammonium acetate (Mishra and Mishra, 2007). In the yesteryears a new method has been proposed for synthesis of 1,4-DHP under ultrasound irradiation without solvent and catalyst and get higher yield at shorter time (Chhillar and Arya, 2006).

b. Antituberculosis activities of 1,4-dihydropyridine: Antituberculosis activity of some 4-substituted-2,6-dimethyl-3,5-bis-N-(heteroaryl)-carbamoyl-1,4-dihydropyridines have studied. It is found that such derivatives of 1,4-DHP are equipotent to Moxifloxacin and Gattiflaxocin (Sawarnalata et al., 2011). A series of symmetrical, asymmetrical and unsubstituted 1,4-dihydropyridines have studied for anti-tuberculosis activity against *M. tuberculosis* H_{37} strain. The highest activity was observed for the 4-(4-(Dimethylamino)phenyl) -1,4-dihydro-N^3,N^5-bis (2-methoxyphenyl) -2,6-dimethylpyridine-3,5 dicarboxamide and 4-(2-Hydroxyphenyl)- 1,4-dihydro- N^3,N^5-bis (3-nitro-phenyl)- 2,6-dimethylpyridine-3,5-dicarboxamide showed 93% and 92% of inhibition respectively, because of the presence of 2-methoxy and 3-nitro groups on the carbomoyl moiety. The other compounds like 4-(4-Chlorophenyl)- 1,4-dihydro-N^3,N^5-bis (3-chloro-4-fluorophenyl)- 2,6-dimethylpyridine- 3,5-dicarboxamide showed 88% of inhibition because of 3-chloro and 4-fluro substitution in the carbomoyl side chain. The 3,5-dicarboxamide showed 85% of inhibition because of 2-chloro substitution in carbomoyl side chain 4-chloro in phenyl ring (Tasaka et al., 2001). Similar studies have been performed for series of 4-substituted Phenyl-2,6-dimethyl-3,5-Bis-N-carbamoyl-1,4-dihydropyridines. The compounds substituted with NO_2 group or 2-Cl or OCH_3 at 3 and 4 position of phenyl carbamoyl ring exhibit >90% of inhibition against H_{37} in comparison with rifampicin (Mishra and Mishra, 2007). Some of the novel 4-substituted imidazolyl-2,6-dimethyl-N^3,N^5-bisaryl-1,4-dihydropyridine-3,5-dicarboxamides have studied for the anti-tuberculosis activity against *M. tuberculosis* H_{37} strain. The compound 4-(1-Benzyl-2-(methylthio)-1H-imidazol-5-yl)-2,6 dimethyl-N^3,N^5-bis(4-chlorophenyl) -1,4dihydropyridine-3,5-dicarbo-xamide is as potent as rifampicin and 4-(1-Benzyl-2-(methylthio)-1H-imidazol-5-yl)- 2,6-dimethyl- N^3,N^5-bis (pyridin-3-yl)- 1,4-dihydropyridine-3,5-dicarboxamide with potent activity (Chhillar and Arya, 2006). In the same way a new series of N^3,N^5-diaryl-4-(4,5-dichloroimidazole-2-yl)- 1,4-dihydro- 2,6-dimethyl- 3,5-pyridinedicarboxamides have screened for the anti-tuberculosis activity against *M. tuberculosis* (H_{37}) and the compound with 3-chlorophenyl group at 3,5 dicarbox-amide position was the most active compound and the compounds with 3-Nitrophenyl and 4-nitrophenyl compound are relatively active compared to rifampicin (Kumar et al., 2009). A series of N^3, N^5-Diaryl-4-(5-arylisoxazol-3-yl)-1,4-dihydropyridine-3,5-dicarboxamide have tested for same activity and the compound N^3,N^5-bis-(4-methoxy-2-nitrophenyl)-2,6-dimethyl-4-(5-phenylisoxazol-3-yl)-1,4-dihydropyridine-3,5-dicarboxamide exhibit good activity (Saponara et al., 2007).

6. RISK FACTORS FOR TB

The TB disease is most common among people who travel to or who were born in countries with high rates of TB. In 2016, a total of 68.5% of reported TB cases in the United States occurred among non-U.S. born persons. In Asian citizen the outbreak of TB was about 18 TB cases per 100,000 persons in 2016. The case rate among non-U.S.–born persons (14.7 cases per 100,000 persons) was approximately 14 times higher than among U.S.-born persons (1.1 cases per 100,000 persons) was also observed from a case study. The percentage of U.S. TB cases among non-U.S.–born persons who have been in the United States for 10 years or longer are about equal to those who have been in the United States less than 10 years (da Silva et al, 2016). It was also emphasized in the same report that out of total recovered TB cases, 16.4% reported having diabetes, 10.0% reported excessive alcohol use, 5.6% were co-infected with HIV, 6.8% reported using non-injectable drugs, 1.3% reported using injectable drugs, 4.9% reported being homeless in the past year and 4.0% were residents of correctional settings at time of diagnosis.

7. CONCLUSIONS

National TB control programs play a vital role in curing TB patients and preventing deaths. The diagnosis and treatment of active TB have significantly reduced disease transmission and incidence in some countries. However, treatment programs have not had a major, detectable effect on incidence on a large scale. The possible reasons are that: (i) patients are not diagnosed and treated soon enough to significantly reduce transmission; (ii) case detection, cure and TB incidence trends cannot be measured accurately; (iii) there has been insufficient time to see the effects of reduced transmission; and (iv) any effects on transmission are offset by a growing risk of developing TB following infection. This review presents, not definitive results, but a challenge: to show that early diagnosis and treatment can have a major effect on TB transmission and incidence worldwide, overriding or reinforcing other biological, social and economic determinants of TB epidemiology. The authors also conclude that TB diagnosis and treatment programs, pre- or post-DOTS, have not yet become the principal determinants of TB transmission and incidence trends, though they may do so in the future. Recent trends in TB incidence are, by contrast, more strongly associated with biological, social and economic determinants that differ among countries and regions. The regional differences explain why only three general measures of development were dominant worldwide: the human development index, child mortality and access to improved sanitation. The nanotechnology dependent drug delivery systems have remarkable potential for the treatment of TB. The technological advantages as drug carriers include their high stability, high capacity, the feasibility of incorporating hydrophilic and hydrophobic substances, and the possibility of varying the routes of administration, such as oral application and inhalation may contributed fabulous impacts on TB control.

ACKNOWLEDGEMENT

SKU is grateful to Dr. A. K. Sharma, Prof. & Head of the Department of Biotechnology, Maharishi Markandeshwar (Deemed to be University), Mullana, Ambala (Haryana), India for his incessant support to the mutual research work.

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