IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Review On Anti-Tubercular Drugs

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Abstract: Tuberculosis (TB), caused by Mycobacterium tuberculosis, remains a critical global health issue, with an estimated 1.7 billion people infected and 10 million new cases in 2020. TB is a leading cause of death worldwide, outpacing HIV/AIDS, and is increasingly complicated by drug resistance. Current treatment for drug-sensitive TB involves a combination of isoniazid, rifampicin, ethambutol, and pyrazinamide. However, multidrug-resistant (MDR-TB) and extensively drug-resistant TB (XDR-TB) require more complex regimens, incorporating newer agents such as bedaquiline, delamanid, and pretomanid. Despite historical advancements, including the discovery of the TB pathogen by Dr. Robert Koch in 1882, TB continues to challenge global health systems. In India, a high-burden country, TB remains a significant issue with a high mortality rate. The Revised National TB Control Program (RNTCP) and the WHO's END TB strategy aim to drastically reduce TB deaths by 2035. Addressing TB effectively requires ongoing research, innovative treatment approaches, and improved diagnostic and treatment strategies to overcome the persistent challenges of this disease.

Index Terms –Tuberculosis, Mycobacterium tuberculosis, Multidrug-Resistant TB, Extensively Drug-Resistant TB.

I. INTRODUCTION

A class of pharmaceuticals known as antitubercular medications is used to treat tuberculosis. Mycobacterium tuberculosis (M-TB), an acid-fast aerobic bacterium that can grow on gram stain as either gram-positive or gram-negative, is the pathogen that causes tuberculosis (TB). Mycobacterium tuberculosis (MTB), the infectious agent that causes tuberculosis (TB), is ranked higher than HIV/AIDS among the top 10 causes of death in the world. The World Health Organization (WHO) has released research estimating that 1.7 billion people globally have M. tuberculosis infections, of which 5–10% develop tuberculosis over their lifetime [1]. Tuberculosis is a serious obstacle to human progress in health care systems and the widespread use of TB control programs as weapons. 10.4 million people were thought to have TE, according to the World Health Organization (WHO), but only 6 million cases had been documented. India has a rising incidence of extrapulmonary tuberculosis, or EPTB. One of the most common responses to underdiagnosis is papulation FPTB. The World Health Organization's 2020 Global Report on Tuberculosis states that 1.4 million people died from the disease in 2019 and that 10 million newly diagnosed cases were reported globally. The

Southwest Asian region has the highest incidence of tuberculosis cases (44%), followed by the African region (25%) and the Western Pacific region (18%). India, Indonesia, China, Philippines, Pakistan, Nigeria, Bangladesh, and South Africa are the eight nations that account for two-thirds of the new cases of tuberculosis. The bacterial disease known as tuberculosis is contracted by breathing in microscopic droplets from an infected person's cough and sneeze. Though it can affect any region of the body, it primarily affects the lungs. encompassing the neurological system, bones, and glands. The chance of getting active tuberculosis is further increased by smoking, alcohol use, undernourishment, and diabetes [2]. Drug resistance is one of the ongoing issues in the treatment of tuberculosis [3]. For instance, in 2016 there were reports of 490000 instances of multidrug-resistant TB (MDR-TB) and an additional 110 000 cases of isoniazid-susceptible TB cases that were resistant to rifampicin (RR-TB), the most potent first-line anti-TB medication. Currently, isoniazid, rifampicin, ethambutol, and pyrazinamide are used as a four-drug combination for two months of therapy for drug-sensitive tuberculosis, followed by isoniazid and rifampicin for an additional four months [4].People who do research in the field of TB treatment are encountered by the following challenges amongst others: the new drug must be more active than existing drugs in order to shorten the duration of treatment, it must be active against both active and latent bacteria, it must act by a new mechanism of action or to a new target especially for the treatment of MDR TB and XDR-TB, it must not interfere with antiretroviral drugs since many patients with TB also suffer from HIV/AIDS and it must also be compatible with other anti-TB drugs so that at least an active three-drug regimen can be constituted [5,6].

II. History of Tuberculosis Disease:

From ancient times, reports of TB or diseases similar to it have been made from various civilizations. The first mention of TB is found in the Vedas, where the disease was referred to as Yakshma, which means wasting illness. Arabic, Greek, and Chinese literature also mentions tuberculosis like an illness [7]. The term "tuberculosis" was first used in 1834 by Johann Schonkein. Nevertheless, the estimated evolutionary history of Mycobacterium TB extends up to 3 million years. In the Middle Ages, TB affecting the neck and lymph nodes was referred to as "Scofuld." Scofuld was thought to be a distinct illness from pulmonary TB.Dr. Robert Koch declared the discovery of mycobacterium tuberculosis (TB) on March 24, 1882. The tuberculosis-causing bacterium at this time. In the US and Europe, tuberculosis claimed the lives of one in seven individuals.Towards the control and eventual eradication of this fatal illness, Dr. Koch's finding was the most significant move.TB Day won't be a notable event unless tuberculosis is eradicated globally. Nonetheless, it's a great chance to inform people about the terrible effects of tuberculosis. World TB Day was established on March 24, a century later.

History of Tuberculosis in India:

Approximately 2.5 million people in the nation needed treatment, according to the 1946 Bhore Committee study, despite there being only 6000 beds available. In Tilaunia, close to Ajmer and Almora in the Himalayas, the first open-air facility for the isolation and treatment of tuberculosis patients was established in 1906. It closed in 1908. The TB Association of India was founded in 1939, which gave the anti-TB fight in the nation a boost. In 1951, WHO and UNICEF expressed interest in offering support for the widespread, low-cost introduction of the BCG vaccination. Thiocetazone and isoniazid were launched in the 1950s, after the introduction of streptomycin and para-amino salicylic acid in the 1940s. The National Tuberculosis Control

Programme (NTP) was established in 1962 and was rolled out gradually. The Revised National TB Control Program (RNTCP) was created in 1963 when the NTP's shortcoming was discovered. The Indian government has committed to expanding RNTCP to encompass the entire nation by the year 2005.

III. Types of tuberculosis:

a) XDR TB:

TB that is highly resistant to drugs, including injectable drugs (Kanamycin, Capreomycin, or Amikacin) and at least one fluoroquinolone. [8] Isoniazid, Rifampicin, Ethambutol, and Pyrazinamide are the four medication combinations now used to treat drug-sensitive tuberculosis (TB). Ethambutol and Pyrazinamide are given for two months, followed by Isoniazid and Rifampicin for four months. [9,10] A recent pilot research using an oral combination of bedaquiline Pretomanid and linezolid demonstrated that after six months of treatment, there were no relapses and the patients' septum turned negative for XDR-TB.[11] This small-scale, ongoing study's results indicate that regimens have the potential to reduce the length of time patients receive XDR-TB medication.Treatment for all XDR-TB cases involve injections of capreomycin, doxorubicin (MIFX), PAS "High dose isoniazid (H), clofazimine (CF2), linezolid (L2d), and co-amoxcylav for six to twelve months during the intensive phase. The remaining drugs, with the exception of the injection, are then continued for eighteen months during the continuation phase.

b) MDR TB:

Drug resistance is a recurring issue in tuberculosis treatment. For instance, there are 49000 cases of multidrug-resistant tuberculosis (MDR-TB) and an additional 110 000 cases of isoniazid-susceptible tuberculosis (TB) that are resistant to both isoniazid and rifampicin, the two most potent anti-TB medications. This type of tuberculosis is known as MDR-TB. Another type of tuberculosis known as MDR TB. Isoniazid, Rifampicin, Ethambutol, and Pyrazinamide are currently used in combination therapy for drug-sensitive tuberculosis (TB). This treatment lasts for two months, after which isoniazid and Rifampicin are given for a further four months [9,10].

IV. Treatment:

A diarylquinoline called bedaquiline is marketed as Sisturo and is used to treat tuberculosis. In December 2012 and May 2014, respectively, the Food and Drug Administration in the United States and the European Medicines Agency (EMA) approved bedaquiline for the treatment of multidrug-resistant tuberculosis [12,13].

Signs and Symptoms of TB:

a. Chest Pain, Or Pain with Breathing or Coughing.
b. Chills.
c. Coughing For Three Or More Weeks.
d. Coughing Up Blood or Mucus.
e. Fatigue
f. Fever.
g. Loss Of Appetite.
h. Night Sweats.
i. Unintentional Weight Loss.

V. Worldwide Scenario of TB (2020):

TB is the 13th most common cause of death worldwide. The first benchmark is a reduction of 35% from 2015. 2020 saw 1.5 million cases of tuberculosis-related deaths. Globally, 10 million persons contracted tuberculosis in 2020. of which men make up 5.6 million. There are 1.1 million children and 3.3 million women. 2020. Around the world, 1.1 million children and adolescents have contracted tuberculosis (TB). The disease is frequently misdiagnosed and treated with difficulty by medical professionals. In 2020, 86% of new cases of TB were found in 30 countries with high TB burdens. Two thirds of the total are made up of eight nations, with India at the top of the list. China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh, and South Africa are the other countries in order of importance. Public health still faces daily resistant tuberculosis. In 2020, only roughly one in three patients with drug-resistant tuberculosis received therapy. Between 2000 and 2020, it is predicted that 66 million lives were spared due to tuberculosis detection and treatment.

a) Multiday resistant tuberculosis (MDR-TB):

It is a kind of tuberculosis that arises from bacteria that are resistant to Isoniazid and Rifampicin, the two most potent first-line anti-tuberculosis medications. 2020 will see an increase in TB fatalities in the 30 nations with the highest TB burden. Only six nations with high rates of tuberculosis (TB) were able to reduce the disease by 35% between 2015 and 2020. These nations are Kenya, Mozambique, Myanmar, Sierra Leone, the United Republic of Tanzania, and Vietnam. The WHO African and South-East Asia areas accounted for approximately 84% of TB deaths among HIV-negative individuals and 85% of all TB deaths among HIV-positive individuals in 2020.

b) Indian Scenario (2020):

In 2020, the death rate from tuberculosis in India was 36 cases per 1,000 persons. India saw a moderate decline in the number of tuberculosis deaths per one million persons between 2001 and 2020, from 57 cases per one million in 2001.In 2020, TB killed almost 500,000 people in Indie. Following the two-year COVID-19 pandemic, there has been an increase in the death rate. According to medical specialists, people in India were too anxious to get tested during that period.

c) TB case notification 2020 in India:

1	Total new and relapse	1,629,301
2	% of tested with rapid diagnostics at time diagnosis	18%
3	% of with known HIV status	92%
4	% of Pulmonary	71%
5	% of bacteriologically confirmed	54%
6	% of children aged 0-14 years	6%
7	% of women	36%
8	% of men	58%
9	% of children	6%
	Total cases notified	1,812,643

Tuberculosis killed 5,04,000 people in India in 2020.

d) Indian Scenario (2021): The overall number of TB patients notified during 2021 was 19,33,381, compared to 16,28,161 in 2020. This is a 19% increase from the previous year.

e) India Scenario (2022): More than 68,000 people become Victims of TB in the India during the first five months.

VI. Treatment of TB:

Antibiotics are typically taken for several months as part of the treatment for tuberculosis (TB). Though TB is a dangerous illness that can be lethal if untreated, fatalities from the disease are uncommon when treatment is finished. The majority of patients don't require hospital admission while receiving treatment.

In the treatment of the tuberculosis the following drugs are used:

a) Bedaquiline:

- Mechanism of action: Inhibits the Proton pump of ATP Synthase. (14,15)
- Classification: Hydrolase
- Organism: Mycolic bacterium Smegmatis
- Mutation: No.
- Membrane protein: Yes.
- Resolution :3.40A°.

Studies done in the mice showed that bedaquiline has a long half-life with an extensive tissue penetration, including lungs and spleen, thus leading to a potent early bactericidal activity of the drug as a consequence of its prolonged effect after a single oral dose. It having the PDB code 7JGC.

b) Delamanid: Structure of Don, the Deazaflovin-dependent nitro reductase from Mycobacterium tuberculosis involved in bioeductive activation of PA-824, with co-factor f420.

- Mechanism of action: Inhibits mycolic acid biosynthesis. (16) Delamanid has specific anti mycobacterial activity but does not have activity against Gram-positive or Gram- negative bacteria or intestinal flora. (11) Protein data get in the PDB code 3R5R.
- Classification: OXIDOREDUCTASE
- Organism(s): Mycobacterium tuberculosis
- Expression System: Escherichia coli
- Mutation (s): No
- Resolution: 2-10 A°.

c) Pretomanid: Crystal structure of 7,8 diamino-pela organic acid synthase from Mycobacterium tuberculosis, complexed with on inhibitor optimized from HTS lead.

- Mechanism of action: Inhibition of mycolic acid Synthesis. Pretomanid or PA-824 is a nitroimidazole drug that is currently in clinical trials for its activity against drug- susceptible and drug-resistant TB.33 Pretomanid possesses activity against replicating drug susceptible and multi-drug resistant Mycobacterium tuberculosis as well as replicating microaerophilic Mycobacterium tuberculosis (24,25). It having the PDB code 4XJO.
- Classification: Transferase/transferase inhibitor
- Organism (s): Mycobacterium tuberculosis
- Expression system: Escheria coli.

- Mutation (s):NO
- Resolution: 1.50 A°.

d) Contezolid: Structure of the 50s subunit of the ribosome from Methicillin Resistant Staphylococcus aureus in complex with the antibiotic, contezolid.

- Mechanism of action: Inhibits protein synthesis. (17) Contezolid showed activity that was slightly higher or similar to the one of linezolid, the only oxazolidinone that is currently in clinical use against Gram-positive bacteria such as penicillin- resistant Streptococcus pneumoniae, methicillin-resistant Staphylococcus epidermidis, methicillin-resistant Staphylococcus aureus, vancomycin-resistant enterococci, and penicillin- Gener intermediate Streptococcus pneumonia (26). It having the PDB code 6WQN.
- Classification: RIBOSOME
- Organism(s): Staphylococcus aureus
- Mutation: Yes
- Resolution: 2.90A°

e) Delapazolid: Crystal structure of LC11-RNAse H1 in complex with RNA/DNA hybrid.

- Mechanism of action: Inhibits protein synthesis. In a single dose study done by Cho and colleagues, it was found that delpazolid was highly bioavailable and well tolerated for a dose of up to 800 mg (27). Protein data get in the PDB code 4H8K.
- Classification: Hydrolase /DNA/RNA.
- Organism: uncultured organism
- Expression System: E. coli
- Mutations: Yes
- Resolution: 2.30A°

f) Sutezolid: Caryo-EM structure of the large ribosomal subunit from Mycobacterium tuberculosis bound with a potent linezolid analog.

- Mechanism of action: Inhibits protein synthesis. Sutezolid was found more active than linezolid and its combination with first-line and second line anti-TB drugs showed great bactericidal activity with the potential to shorten the treatment time in a murine model (29,30). Protein data get in the PDB code 5V7K.
- Classification: RIBOSOME
- Organism (s): Mycobacterium Tuberculosis.
- Mutations: NO
- Resolution:3.70A°.

g) Macozinone: Crystal structure of Mycobacterium tuberculosis DprE1 in complex with PBTZ169.

- Mechanism of action: Inhibits cell wall synthesis by covalently binding to a cystine residue (18). In a study done by Lupine and colleagues, macozinone I was showed no synergism nor antagonism with first line drugs Toler-(ethambutol, isoniazid and rifampicin) or the second line manly drugs (28). Protein data get in the PDB code 4NCR.
- Classification: Oxidoreductase/ oxidoreductase inhibitor.

- Organisms: Mycobacterium Tuberculosis H37Rv
- Expression system: E. coli BL21 (DE3)
- Mutations: No
- Resolution: 1.88 A°.

h) Clofazimine: The fibrinogen like domain human Ang ptl4.

- Mechanism of action: Its mechanism of action is not yet clear but might involve the production of reactive oxygen species upon its metabolism by Mycobacteria (19). Clofazimine the riminophenazine which was originally known as B.663 and has the trade name Lamprene, was shown to have anti tuberculous activity as early as in 1957 (31,32). Two awkward features of clofazimine are that it has a very long half-life (65 days) and that it causes skin and internal organs discolouration (33). Clofazimine have PDB code 6EUB.
- Classification: Signalling Protein
- Organisms: Homo sapiens
- Expression System: F. coli str. K-12 Substrate MD542
- Mutations: NO
- Resolution: 2.30 A°

i) Linezolid: The structure of the antibiotic Linezolid bound to the large ribosomal subunit of HALOARCULAMARISMORTUT. PDB code 3CPW.

- Mechanism of action: Inhibit translocation by binding to the 50s subunits of ribosomes.
- Classification: Ribosome
- Organisms: Haloarcula marismortui.
- Mutation: Yes
- Resolution: 2.70 A°

j) Levofloxacin: Quinolone (levofloxacin) DNA clevage complex of type TV. topo-isomerase from s. pneumoniae.

- Mechanism of action: Inhibit DNA gyrase subunit (Gyrase A & Gyrase B) topoisomerase iv subunit (Par C &Par E) (20,21,22). Levofloxacin is an orally administered fluo- roquinolone antibacterial agent developed in Japan and is the L-isomer of the D, L-racemate ofloxacin (34,35). Protein data get in the PDB code 3RAE.
- Classification: Isomerase /DNA/ANTIBIOTIC
- Organisms: Streptococcus pneumon
- Expression system: E. coli
- Mutations: No
- Resolution: 2.90A°

k) Moxifloxacin: 2.95 A Structure of moxifloxacin with S. aureus DNA gyrase and DNA. (PDB-5CDQ).

- Mechanism of action: Inhibit DNA gyrase subunit (Gyrase A & Gyrase B) topoisomerase iv subunit (Par C &Par E) (20,21,22).
- Classification: HYDROLASE
- Organisms: Staphylococcus aureu subsp. aureus N315 Synthetic construct.

- Expression system: Escherichia toli
- Mutations: No
- Resolution: 2.95A°

l) Nitrozoxanide: X-ray structure of Beta catenin in complex with Bcg19.

- Mechanism of action: Inhibit pyruvate ferredoxin oxidoreductase (23). Nitazoxanide is a nitrothiazolyl sold under the brand name of Alinia for the treatment of a range of intra- cellular and extracellular protozoa, anaerobic, micro- aerophilic bacteria, viruses and helminths (36). It having PDB code 3SL9.
- Classification: Signalling Protein, Protein Binding
- Organisms: Homo sapiens.
- Expression Systems: E. coli BL210
- Mutations: NO
- Resolution: 2.20A°.

m) Rifampicin: Crystal structure of rifampin mono-oxygenase from streptomyces venzeualae, complexed with Rifampicin and FAD

- Mechanism of action: Inhibit RNA polymerase (40,41,). Rifampicin came first into clinical use in the late 1960 for the treatment of patients with chronic drug-resistant pulmonary TB. (37) WHO recommends a rifampicin dose of 8-12 mg/kg of body weight even if this is known to be suboptimal especially among HIV infected patients and in children (38,39). Rifampicin has the PDB code 6BRD.
- Classification: Oxidoreductase.
- Organisms: Streptomyces venezue Lige ATCC 107/2
- Expression system: E. coli BL21(DE3)
- Mutations: No
- Resolution: 3.32 A°.

n) Isoniaziade: Crystal structure & function of the Isoniazid target of Mycobacterium Tuberelosis. PDB code of the Isoniazide is 1ENY.

- Mechanism of action: inhibit of mycolic acid.
- Classification: Oxidoreductase
- Organisms: Mycobacterium tuberculosis
- Expression System: E. coli
- Mutations: No
- Resolution: 2.20A°

o) Pyrazinamide: Urate Oxidase under 18 MPa/18 bars pressure of equimolar mixture Xenon: nitrous oxide. It having PDB code 3PLI.

- Mechanism of action: Inhibit the growth of bacteria.
- Classification: Oxidosredite fase.
- Organisms: Aspergillus flavus.
- Expression system: Saccharomyces cerevisiae.
- Mutations: Yes
- Resolution:1.68 A°.

p) Ethambutol: Crystal Structure of the C-terminal extracellular domain of Mycobacterium tuberculosis EmbC. (PDB-3PTY).

- Mechanism of action: Inhibit of arabinosy transferase.
- Classification: Transferase
- Organisms: M. tuberculosis.
- Expression system: E. coli
- Mutations: NO
- Resolution: 2.00 A°.

q) Para Amino Salicylic Acid: Homo sapiens dihydrofolate reductase complexed with beta-NADPH & 3'-[(2R)-4-(2, 4 diamino-6-ethylphenyl but-3yn-2-yl)-5'-methoxy- [1.1'-biphenyl]-4-carboxylic acid. It having PDB codes 4FQS, 6DE4.

- Mechanism of action: Inhibit of folic acid synthesis.
- Classification: oxidoreductase/ oxidoreductase
- Organisms: Homo sapiens.
- Expression System: Escherichia coli
- Mutations: No.
- Resolution: 2.41A°.

VII. Conclusion:

From the above the study, we conclude that tuberculosis infection and disease remain common in populations characterized by poor housing conditions, drug use, and HIV infection. Linking a major medical provider with community-based organizations is an effective means to provide highly targeted screening services to a population at serious risk for disease acquisition and transmission. Tuberculosis continues to challenge physicians, pathologist and microbiologists in every possible way and dilemma persists till today in early diagnosis and treatment of every form of it. WHO END TB strategy wishes to achieve 95% reduction in absolute number of tuberculosis deaths by 2035 which needs thorough understanding of tuberculosis and systemic filling of gaps in TB detection and treatment. The war is set on a platform of real knowledge; mankind equipped with experience of past and armed with present medicine to win against this ancient foe in its all forms.

REFERENCES

[1] WHO.Global tuberculosis report 2019. Geneva: World Health Organization; 2019. http://www.who.int/tb/publications/globa

[2] World Health Organization. Global Tuberculosis Report. 2018 ISBN 978-92-4-156564-6. Geneva, Switzerland

[3] World Health Organization. Global Tuberculosis Report. 2017.ISBN 978-92-4-156551-6. Geneva, Switzerland.

[4] Poce G, Cocozza M, Consalvi S, Biava M. SAR analysis of new anti-TB drugs currently in pre-clinical and clinical development. Eur J Med Chem. 2014; 86:335-351.

[5] Zumla A, Nahid P, Cole ST. Advances in the development of new tuberculosis drugs and treatment regimens. Nat Rev Drug Discov. 2013;12(5):388-404 https://doi.org/10.1038/ nrd4001.

[6] Marriner GA, Nayyar A, Uh E, et al. The medicinal chemistry of tuberculosis chemotherapy. In: Elliott R, ed. Third World Diseases. Topics in Medicinal Chemistry. Berlin. Heidelberg: Springer Berlin Heidelberg: 2011:47-124. https://doi.org/ 10.1007/7355_2011_13.

[7] Sharma SK, Mohan A. Tuberculosis: from an incurable scourge to a curable disease- journey over a Millennium. Indian J Med Res. 2013; 137:455-493.

[8] https://www.who.int/news-room/questions-andanswers/item/tuberculosis-extensively drug-resistant-tuberculosis-(XDR-TB)

[9] Extensively drug-resistant tuberculosis (XDR-TB): recommendations for prevention and control. Wkly Epidemiol Rec 2006; 81:430–432.

[10] Centers for Disease Control and Prevention (CDC). Emergence of Mycobacterium tuberculosis with extensive resistance to second-line drugs – worldwide, 2000–2004. MMWR Morb Mortal Wkly Rep 2006; 55:301–305.

[11] Ryan NJ, Lo JH. Delamanid: first global approval. Drugs 2014;74(9):1041-1045. https://doi.org/10.1007/s40265-014-0241

[12] https://www.cdc.gov/tb/publications/factsheets/treatment/bedaquiline.htm

[13] https://www.cdc.gov/tb/publications/factsheets/treatment/bedaquiline.htm

[14] Cohen J. Approval of novel TB drug celebrated – with restraint. Science. 2013; 339:130.

[15] Andries K, Verhasselt P, Guillemont J, et al. A diarylquinoline drug active on the ATP synthase of Mycobacterium tuberculosis. Science. 2005;307(5707):223-227. https://doi.org/ 10.1126/science.1106753.

[16] Fujiwara M, Kawasaki M, Hariguchi N, Liu Y, Matsumoto M Mechanisms of resistance to delamanid, a drug for Mycobacterium tuberculosis. Tuberculosis. 2018; 108:186-194. https://doi.org/10.1016/j.tube.2017.12.006.

[17] Jadhavar PS, Vaja MD, Dhameliya TM, Chakraborti AK. Oxazolidinones as anti-tubercular agents: discovery, development and future perspectives. Curr Med Chem. 2015;22(38):4379 4397.

[18] Makarov V. Lechartier B, Zhang M, et al. Towards a new combination therapy for tuberculosis with next generation benzothiazines EMBO Mol Med 2014;6(3):372-383. https://doi.org/10.1002/emmm 201303575.

[19] Yano T, Kassovska-Bratinova S. Teh JS, et al. Reduction of clofazimine by mycobacterial type 2 NADH: quinone oxidoreductase: a pathway for the generation of bactericidal levels of reactive oxygen species. J Biol Chem. 2011:286(12):10276-10287. https://doi.org/10.1074/ jbc.M110.200501,

[20] Wimer SM, Schoonover L, Garrison MW. Levofloxacin: a therapeutic review. Clin Therapeut. 1998;20(6):1049-1070.https://doi.org/10.1016/S0149-2918(98)80104-5.

[21] Langtry HD, Lamb HM. Levofloxacin. Its use in infections of the respiratory tract, skin, soft tissues and urinary tract. Drugs. 1998;56(3):487-515. https://doi.org/10.2165/00003495- 199856030-00013.

[22] Yamaba Y, Ito Y, Suzuki K, et al. Moxifloxacin resistance and genotyping of Mycobacterium avium and Mycobacterium intracellular isolates in Japan. J Infect Chemother. 2019:25:995-1000. https://doi.org/10.1016/j.jiac.2019.05.028.

[23] De LC, Lin G, Jiang X. Nathan C Nitazoxanide kills replicating and nonreplicating Mycobacterium tuberculosis and evades resistance J Med Chim, 2009,52(19) 5789-5792 https://doi.org/10.1021/jm9010719

[24] Stover CK, Warrener P, VanDevanter DR, et al. A small-molecule nitroimidazopyran drug candidate for the treatment of tuberculosis. Nature. 2000;405(6789):962 966.https://doi.org/10.1038/35016103.

[25] Singh R, Manjunatha U, Boshoff HIM, et al. PA-824 kills nonreplicating Mycobacterium tuberculosis by intracellular NO release. Science. 2008;322(5906):1392-1395. https://doi.org/ 10.1126/science.1164571.

[26] L i C-R, Zhai Q-Q, Wang X-K, et al. In Vivo antibacterial activity of MRX-1, a new oxazolidinone. Antimicrob Agents Chemother. 2014;58(4):2418-2421. https://doi.org/10.1128/194.6/AAC 01526-13.

[27] Cho Y-S, Lim H-S, Han S, et al. Single-dose intravenous safety, tolerability, and pharmacokinetics and absolute bioavailability of LCB01-0371. Clin Therapeut. 2019;41(1):92 106. https://doi.org/10.1016/j.clinthera.2018.11.009.

[28] Lupine A. Vocat A, Foo CS-Y, et al: Optimized background regimen for treatment of active tuberculosis with the next- generation benzothiazinone macozinone (PBTZ169) Antimicrob Agents Chemother 2018,62(11). https://doi.org/ 10.1128/AAC.00840-18, e00840-18

[29] Williams KN, Stover CK, Zhu T, et al. Promising antituberculosis activity of the oxazolidinone PNU-100480 relative to that of linezolid in a murine model. Antimicrob Agents Chemother. 2009;53(4):1314-1319. https://doi.org/ 10.1128/AAC.01182-08.

[30] Williams KN, Brickner SJ, Stover CK, et al. Addition of PNU- 100480 to first-line drugs shortens the time needed to cure murine tuberculosis. Am J Resp Crit Care. 2009;180(4):371 376. https://doi.org/10.1164/rccm.200904-06110C.

[31] Barry VC, Belton JG, Conalty Ml., et al. A new series of phenazines (Rimino-Compounds) with high antituberculosis activity. Nature. 1957,179(4568):1013. https://doi.org/10.1038/1791013a0.

[32] Reddy VM, Nadadhur G, Daneluzzi D, O'Sullivan JF, Gangadharam PR. Antituberculosis activities of clofazimine and its new analogs B4154 and 84157. Antimicrob Agents Chemother. 1996;40(3) 633-636

[33] Reddy VM, Nadadhur G, Daneluzzi D, O'Sullivan JF, Gangadharam PR. Antituberculosis activities of clofazimine and its new analogs B4154 and 84157. Antimicrob Agents Chemother. 1996;40(3) 633-636

[34] Wimer SM, Schoonover L, Garrison MW. Levofloxacin: a therapeutic review. Clin Therapeut. 1998;20(6):1049-1070.https://doi.org/10.1016/S0149-2918(98)80104-5.

[35] Davis R, Bryson HM. Levofloxacin. A review of its antibacterial activity, pharmacokinetics and therapeutic efficacy. Drugs. 1994;47(4):677-700. https://doi.org/10.2165/00003495 199447040-00008.

[36] de Carvalho LPS, Darby CM, Rhee KY, Nathan C. Nitazoxanide disrupts membrane potential and interbacterial pH homeostasis of Mycobacterium tuberculosis. ACS Med Chem Lett. 2011;2(11):849–854. https://doi.org/10.1021/ml200157f.

[37] Grobbelaar M, Louw GE, Sampson SL, van Helden PD, Donald PR, Warren RM. Evolution of rifampicin treatment for tuberculosis. Infect Genet Evol. 2019,74 103937, https://doi.org/10.1016/j.meegid 2019.103937

[38] Chirehwa MT, Rustomjee R, Mthiyane T, et al. Model-based evaluation of higher doses of rifampin using a semimechanistic model incorporating autoinduction and saturation of hepatic extraction. Antimicrob Agents Chemother 2015;60(1):487-494. https://doi.org/10.1128/ AAC.01830-15

[39] van Ingen J, Aarnoutse RE, Donald PR, et al. Why do we use 600 mg of rifampicin in tuberculosis treatment? Clin Infect

[40] Wehrli W. Rifampin mechanisms of action and resistance. Rev Infect Dis. 1983.5(supply 3) 5407-5411 http://doi.org/10.1093/clinids/5 supplement 3s407

[41] Munsiff 55, Kambili C, Ahuja SD. Rifapentine for the treatment of pulmonary tuberculosis. Clin Infect Dis. 2006,43(11):1468-1475. https://doi.org/10.1086/508278.