International Journal of Advanced Research in Biological Sciences
ISSN: 2348-8069
www.ijarbs.com
(A Peer Reviewed, Referred, Indexed and Open Access Journal)
DOI: 10.22192/ijarbs Coden: IJARQG (USA) Volume 10, Issue 1 -2023

Review Article

DOI: http://dx.doi.org/10.22192/ijarbs.2023.10.01.008

DNA G Primase: A potent target for the development of anti-tuberculosis therapeutics: A review study

Asif Iqbal*

Research Scholar, Post Graduate Department of Biotechnology,
Tilkamanjhi Bhagalpur University, Bhagalpur, Bihar, India 812007
* Correspondence: Email: *asifiqbal2010@rediffmail.com*; Tel: +91-8969243689

Abstract

A promising but understudied target for novel antimicrobial development is the bacterial primase, which is an essential component of the replisome. Bacterial primase differ greatly from human primase in structure and modelling. Halting DNA replication has a bacteriocidal effect, according to growing research. As a result, DNA primase inhibitors could be used as an antibiotic. Different approaches have been used to create compounds that inhibit bacterial DNA replication mechanism by using different bioinformatics techniques such as molecular docking, simulation, ligand-target selection and identification of the active site in Protein. Antibiotics efficacy, which has revolutionized medicine and saved millions of lives, is in jeopardy due to the increasing rise of resistant bacteria around the world. Bacterial illnesses have resurfaced many decades after the initial patients were treated with antibiotics. The threat of Antibiotic resistance is due to the overuse and misuse of antibiotics, as well as lack of new drug discovery by the Research and Development sector. It's all due to limited economic incentives and difficult regulatory requirements. Tuberculosis remains one of the major horrible infectious diseases for mankind since time immemorial. The prime organ for Tubercle bacilli infection is the lungs, especially the upper ventilated lobe. Tb bacteria are characterized as slow-growers, acid-fast bacilli with a thick covering of mycolic acid. This paper provides an overview of bacterial primase and the possible inhibitors so far documented in varied literature, but still we are in a search for more potent inhibitors which could change the treatment strategy in tuberculosis therapy.

Keywords: Antimicrobial, Tuberculosis, Chemotherapy**,** Primase, Inhibitors

1. Introduction

The laborious and time-consuming processes of selecting compounds exhibiting antibacterial activity starts with the selection of potential therapeutic targets in the Bacteria (Akbar et. al., 2020). It must be playing a critical role in an organism survival and growth and are very specific over Human homology. The optimized target in Bacteria should be drug sensitive, precise and pose a low tendency of becoming resistance (Reiche et. al., 2017). The bacterial cell contains a vast number of different genes, but unfortunately only a limited of these gene have been explored to become a possible drug targets (Lewis, 2013). DNA replication is a very important process in

both Eukaryotes as well as Prokaryotes, it is the root of Central dogma as formulated by Sir Watson and Crick (Cobb, 2017). The DNA replication process requires different sets of enzyme along with Primer and Probes. Replisome is a group of enzymes that aid in the continuous synthesis of DNA on the leading strand and the discontinuous synthesis of DNA on the lagging strand. (Marrians, 2008).DNA primase being an important constituent helps in the synthesis of small RNA primers which are later used by the enzyme DNA polymerase in the formation of "Okazaki fragments" from 5' → 3'onto the lagging DNA strand (Frick and Richardson, 2001). The RNA component of the primer is removed by the enzyme "RNase H" and the nick is annealed by the enzyme "DNA polymerase I" after primer extension (Randall et. al., 2019). The hindering of enzyme Primase could be an important way of ceasing the mechanism of DNA replication, which results into stopping the cell from growth, reproduction, survival and ultimately results in death (Berdis, 2017). The DNA primase has the capability of becoming a novel target for different Ligands. This review provides an insight of how Dna G could be a new drug target for bacterial disease especially *Mycobacterium tuberculosis* (L). The DNA Replication process in Bacteria is achieved by Replisome which in-turn is made by different individual components which work together in a very co-ordinated fashion (Marrians, 2008).The critical involvement of replisome in the DNA replication process has been documented in model organisms such as *Escherichia coli* and *Bacillus subtilis* (Kelman and Donnell, 1995).

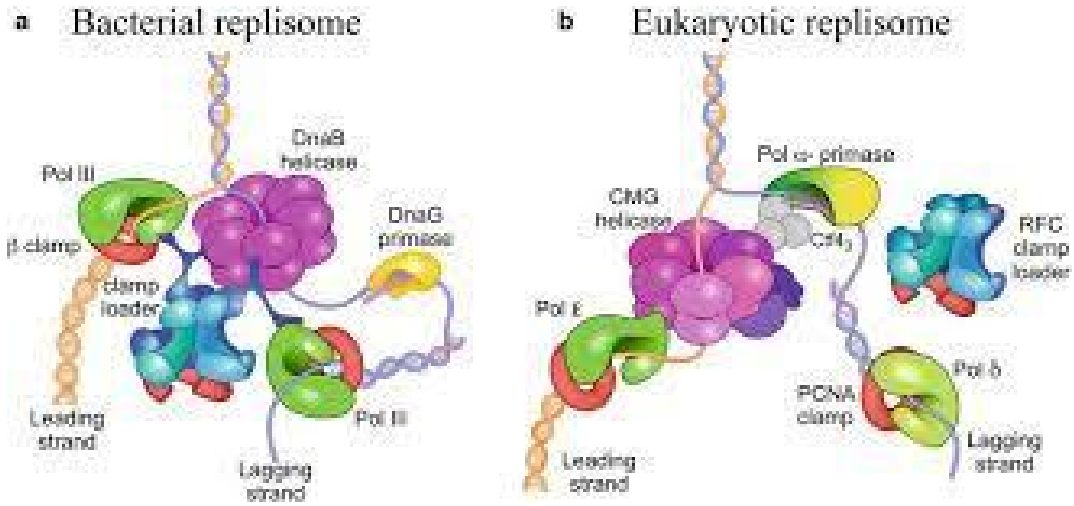

Fig showing 1: The Bacterial Replisome and the Eukaryotic Replisome (Bowmann, 2004)

2. *Mycobacterium tuberculosis*

Tuberculosis (TB) is an Infectious disease predominantly occurring because of Infection by members of mycobacterial species called as *Mycobacterium tuberculosis* complex (MTBC) (Gutierrez et. al., 2005). Each species of MTBC has the ability to cause TB independently. The global TB epidemic is mainly concerned with the transmissibility of pulmonary infection. Every year around 2 million people become prey of Tuberculosis and approximately 9 million people become newly infected (Sultana et. al., 2021). In the year 2020 a total of 1.5 million lost their life due to TB disease, comprising 2 lac 14 thousand people having HIV Co-morbidity (Mandalakas et. al., 2020). One-fourth of the entire globe population is already infected by the Tubercle bacilli but showing no sign and symptom also without transmissibility (Houben, 2016). Tuberculosis is also named as Koch's disease, named credited to Robert Koch who discovered the Tubercle bacilli. Tb bacteria can infect any body part, based on the occurrence of

Tuberculosis in the patient it is broadly classified into two types. Active tuberculosis infection and Latent tuberculosis infection (Carranza et. al., 2020). In Former infection the patient carrying the organism has prevailing symptoms and it could be transmitted to an healthy individual, whereas in Latent case the patient carries the bacteria in his body but it is non-transmissible to others and also the patient do not show any signs and symptom. Other form of Tuberculosis involve various organs of the body such as Pulmonary Tb, Skeletal Tb, Brain Tb, Pleural Tb, Gastro-intestinal Tb, Kidney Tb, Genito-urinary Tb, Miliary Tb (Sia and Weiland, 2011).

3.Bacteriology

Mycobacterium tuberculosis is a slow growing, obligate aerobic and facultative intracellular organism (Smith, 2003). The Pathogen primarily infects the lungs and secondarily other body parts except the hair and nail (Baykan et. al., 2022). Organisms are always present in the well-aerated upper lobes of the lungs in the classic form of tuberculosis. (Baykan et. al., 2022). The bacteria have a delayed growth time of 15-20 hours since it is a nonobligatory intracellular parasite of macrophages (Lin, 2010). Tubercle bacilli appear chains of cell in smear when made from colonies grown In-vitro and stained with the Z-N staining method (Chen et. al., 2012).

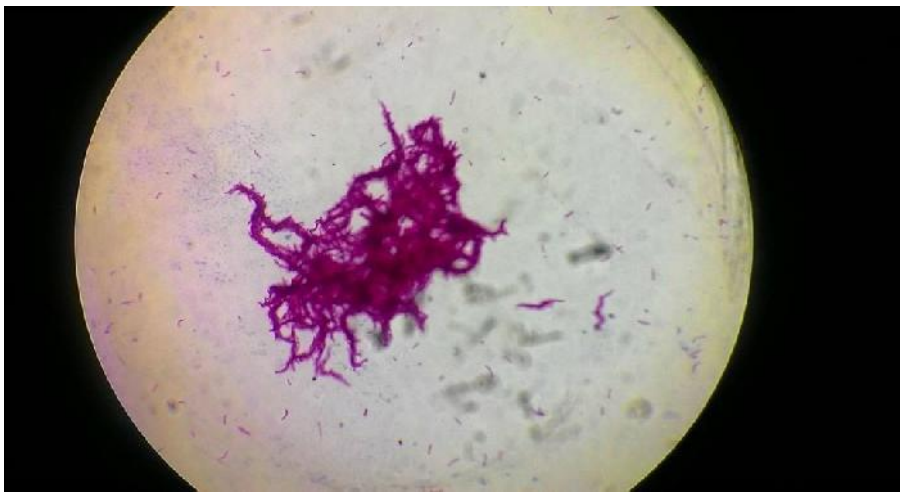

Fig showing: A serpentine cord formation of *M .tuberculosis* by Ziehl Neelsen staining (Middlebrook et. al., 1947)

4. Criteria for drug target selection

For selection of targets, there should be at least two criteria. First, the target should play essential role for the survival of the organism and second, similar targets should not be present in the human host (Emmerich et. al., 2021). It should be disease modifying and may have the noticeable function for the Patho-physiology of the disease (Chen et. al., 2019). The Bacterial Dna G pose the characteristic for becoming a drug target, it comprises of three main domains. N-terminal zinc binding domain (ZBD), RNA polymerase domain (RPD) and C-terminal helicase binding domain (HBD) (Ilic et. al., 2018).

5. Possible Inhibitors of DNA G

Extensive research in the field of bioinformatics and drug discovery has seen many possible molecules which have targeted Dna G in different organism such as *Aquifex aeolicus* and *Bacillus stearothermothilus* (Zumla et. al., 2013). But such molecules (ligands) have not been used in targeting the Dna G of *Mycobacterium tuberculosis.* So a random hit in such important replicating machinery could be a ray of hope in elucidation of novel therapeutics for Tb.

6. Some known Inhibitors of DNA G in other organism

Vidarabine- It is an antiviral medication which is effective against Herpes Simplex and Varicella zoster virus (Lehman, 1964).Doxorubicin- It is a type of chemotherapeutic drug alike Anthracycline. It slows or stops the growth of Cancer cells by blocking an enzyme called Topoisomerase-II (Argenziano et. al., 2020). Suramin- It is used for the treatment of human sleeping sickness caused by Trypanosomes (Khanra et. al., 2020). Carpaine- It is one of the major secondary metabolite of Papaya leaves which have been studied for its cardiovascular activity (Singh et. al., 2020). Fosmidomycin- is an antibiotic that was originally isolated from culture broths of bacteria of the genus *Streptomyces*. It specifically inhibits DXP reductoisomerase, a key enzyme in the non-mevalonate pathway of isoprenoid biosynthesis (Lell et. al., 2003). Thymoquinone – It is an active alkaloid of the seed Nigella sativa. It has shown many antibacterial, antispasmodic and analgesic properties in different studies (Surbhi and Prashant, 2018). Ellagic acid- It is a natural phenol antioxidant found in numerous fruits and vegetables. The anti-proliferative and antioxidant properties found in ellagic acid have prompted research into its potential health benefits (Priyadarsini et. al., 2002). Farnesene β-Farnesene β has one naturally occurring isomer. The *E* isomer is a constituent of various essential oils. It is also released by aphids as an alarm pheromone upon death to warn away other aphids. Several plants, including potato species, have been shown to synthesize this pheromone as a natural insect repellent (Bhatia et. al., 2015). Griselimycin – Cyclic peptide griselimycin was isolated in the 1960s from Streptomyces and its antibacterial and anti- mycobacterial activity was evaluated in the early 1970s (Aragaw et. al., 2022). Diospyrin- It is a plant product that has significant inhibitory effect on the growth of *Leishmania donovani* promastigotes. This compound inhibits the catalytic activity of DNA topoisomerase I of the parasite (Ray et. al., 1998).

7. References

Akbar N., Siddiqui R., Iqbal M. and Khan N.A. (2020): Antibacterial Activities of Selected Pure Compounds Isolated from Gut Bacteria of Animals Living in Polluted Environments. *Antibiotics (Basel)*, 9:190-193.

Aragaw W. W., Roubert C., Fontaine E., Lagrange S., Zimmerman M. D., Dartois V., Gengenbacher M. and Dick T. (2022): Cyclohexyl-griselimycin is active against *Mycobacterium abscessus* in Mice. *Antimicrobial agents and chemotherapy*, *66*: 1-8.

Argenziano M., Gigliotti C. L., Clemente N., Boggio E., Ferrara B., Trotta F., Pizzimenti S., Barrera G., Boldorini R., Bessone F., Dianzani U., Cavalli R. andDianzani C.(2020): Improvement in the Anti-Tumor Efficacy of Doxorubicin Nanosponges in In Vitro and in Mice Bearing Breast Tumor Models. *Cancers (Basel)*, 12:162.

Baykan A.H., Sayiner H.S., Aydin, E. et al. (2022): Extra pulmonary tuberculosıs: an old but resurgent problem. *Insights into Imaging*, 13: 39.

Berdis A. J. (2017): Inhibiting DNA Polymerases as a therapeutic intervention against cancer. *Frontiers in Molecular Biosciences*, 4; 78-82.

Bhatia V., Maisnam J., Jain A., Sharma K.K.and Bhattacharya R. (2015): Aphid- Repellent pheromone E-β-farnesene is generated in transgenic Arabidopsis thaliana over-expressing farnesyldiphosphate Synthase 2.*Annals of Botany*, 115:581-591.

Bowman G.D., O'Donnell M.E. and Kuriyan J. (2004): Structural analysis of a eukaryotic sliding DNA clamp–clamp loader complex. *Nature*, *429*:724-730.

Carranza C., Pedraza-sanchez S., Oyarzabal-Mendez E.D. and Torres M. (2020): Diagnosis for Latent Tuberculosis Infection: New Alternatives. *Frontiers in Immunology*, 11: 2006.

Chaieb K., Kouidhi B., Jrah H., Mahdouani K. and Bakhrouf A. (2011): Antibacterial activity of Thymoquinone an active principle of Nigella sativa and its potency to prevent

bacterial biofilm formation. *BMC complementary and alternative medicine*, *11*: 29.

Chen P., Shi M., Feng G.D., Liu J.Y., Wang B.J., Shi X.D., Ma L., Liu X.D., Yang Y.N., Dai W., Liu T.T., He Y., Li J.G., Hao X.K., Zhao G. A. (2012): Highly efficient Ziehl-Neelsen stain: identifying de novo intracellular *Mycobacterium tuberculosis* and improving detection of extracellular M. tuberculosis in cerebrospinal fluid. *Journal of Clinical Microbiology*, 50: 1166-1170.

Chen Y.A., Yogo E., Kurihara N., Ohno T., Higuchi C., Rokushima M. and Mizuguchi K. (2019): Assessing drug target suitability using Target Mine. *F1000 Research*, 8: 233.

Cobb M. (2017): 60 years ago Francis crick changed the logic of biology. *PLos Biology*, 15: 1-8.

Emmerich C.H., Gamboa L.M., Hofmann M.C.J. et al. (2021): Improving target assessment in biomedical research: the GOT-IT recommendations. *Nature reviews drug discovery*, 20: 64-81.

Frick D.N. and Richardson C.C. (2001).DNA Primases. *Annual review of Biochemistry*, 70: 39-80.

Goel S. and Mishra P. (2018): Thymoquinone inhibits biofilm formation and has selective antibacterial activity due to ROS generation. *Applied Microbiology and Biotechnology*, *102*: 1955–1967.

Gutierrez M.C., Brisse S., Brosch R., Fabre M., Omais B., Marmiesse M., Supply P. and Vincent V. (2005): Ancient origin and gene mosaicism of the progenitor of *Mycobacterium tuberculosis*. *PLos Pathogens*. 1:5-8.

Houben R.M. and Dodd P.J.(2016):The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. *PLoS Medicine*, 13: 1-5.

Ilic S., Cohen S., Singh M., Tam B., Dayan A. and Akabayov B. (2018): DnaG Primase-A Target for the Development of Novel Antibacterial Agents. *Antibiotics (Basel)*, 7:72.

Kelman Z. O. and Donnell M. (1995): DNA Polymerase III Holoenzyme: Structure and Function of a chromosomal replicating machine. *Annual review of Biochemistry*, 64: 171-200.

Khanra S., Juin S.K., Jawed J.J., Ghosh S., Dutta S., Nabi S.A., Dash J., Dasgupta D., Majumdar S. and Banerjee R. (2020): In vivo Experiments demonstrate the potent anti-leishmanial efficacy of Repurposed Suramin in visceral leishmaniasis.*PLoS Neglected Tropical diseases*, 14.

Lehmann J. (1964): Twenty years afterward historical notes on the discovery of the Antituberculosis effect of Paraaminosalicylic acid (Pas) and the first clinical trials. *The American review of respiratory disease*, *90*: 953–956.

Lell B., Ruangweerayut R., Wiesner J., Missinou M.A., Schindler A., Baranek T., Hintz M., Hutchinson D., Jomaa H., Kremsner P.G. (2003): Fosmidomycin a novel chemotherapeutic agent for malaria. *Antimicrobial Agents Chemotherapy*, 47:735-738.

Lin P.L. and Flynn J.L. (2010): Understanding latent tuberculosis: a moving target. *Journal of Immunology*, 185: 15-22.

Lewis K. (2013): Platforms for antibiotic discovery. *Nature reviews. Drug Discovery*, 12: 371-387.

Mandalakas A.M., Kay A.W., Bacha J.M., Devezin T., Golin R., Simon K.R., Dhillon D., Dlamini S., DiNardo A., Matshaba M., Sanders J., Thahane L., Amuge P.M., Ahmed S., Sekadde M.P., Fida N.G., Lukhele B., Chidah N., Damba D., Mhango J., Chodota M., Matsoso M., Kayabu A., Wanless R.S. and Schutze G.E. (2020): Tuberculosis among Children and Adolescents at HIV Treatment Centers in Sub-Saharan Africa. *Emerging Infectious Diseases*, 26: 2933–2943.

Marrians K.J. (2008): Understanding how the replisome works. *Nature Structural and Molecular Biology*, 15: 125-127.

Middlebrook G., Dubos R. J. and Pierce C. (1947): Virulence and Morphological Characteristics of Mammalian Tubercle Bacilli. *The Journal of Experimental medicine*, *86*: 175–184.

Priyadarsini K. I., Khopde S. M., Kumar S. S. and Mohan H. (2002): Free radical studies of ellagic acid, a natural phenolic antioxidant. *Journal of agricultural and food chemistry*, *50*: 2200–2206.

Randall J.R., Nye T.M., Woznaik K.J. and Simmons L.A. (2019): RNase H III is important for Okazaki fragment processing in *Bacillus subtilis*. *Journal of Bacteriology*, 201: 1-13.

Ray S., Hazra, B., Mittra B., Das A. and Majumder H. K. (1998): Diospyrin abisnaphthoquinone: a novel inhibitor of type I DNA topoisomerase of Leishmania donovani. *Molecular pharmacology*, *5* :994–999.

Reiche M. A., Warner D.F. and Mizrahi V. (2017): Targeting DNA replication and repair for the development of novel therapeutics against tuberculosis. *Frontiers in Molecular Biosciences*, 4:75-78.

Riccardi N., Canetti D., Rodari P., Besozzi G., Saderi L., Dettori M., Codecasa L.R. and Sotgiu G. (2021): Tuberculosis and Pharmacological interactions: A narrative review *Current Research in Pharmacology and Drug discovery*, 2: 1-10.

Sia I.G. and Wieland M.L. (2011): Current concepts in the management of tuberculosis. *Mayo Clinic Proceedings*, 86: 348-361.

Singh S.P., Kumar S., Mathan S.V., Tomar M.S., Singh R.K.,Verma P.K., Kumar A., Kumar S., Singh R.P. and Acharya A. (2020): Therapeutic application of *Carica papaya* leaf extract in the

management of human diseases. Daru: *Journal of Faculty of Pharmacy, Tehran University of Medical Sciences*,28:735-744.

Smith I. (2003): Mycobacterium tuberculosis pathogenesis and molecular determinants of virulence. *Clinical Microbiology Review*, 16: 463- 496.

Sultana Z.Z., Hoque F.U., Beyene J. et al. (2021): HIV infection and multidrug resistant tuberculosis: a systematic review and meta-analysis. *BMC Infectious Diseases*, 51:1-13.

Wang B., Dong W., Li H., D'Onofrio C., Bai P., Chen R., Yang L., Wu J.,Wang X., Wang B., Ai D., Knoll W., Pelosi P. and Wang G. (2022): Molecular basis of (E)-β-farnesene-mediated aphid location in the predator *Eupeodescorollae*. *Current biology CB*, *32*:951–962.

Zumla A., Nahid P. and Cole S. T. (2013): Advances in the development of new tuberculosis drugs and treatment regimens. *Nature reviews drug discovery*, 12: 388–404.

Access this Article in Online

Website: www.ijarbs.com

Subject: Biotechnology

Quick Response Code

DOI:10.22192/ijarbs.2023.10.01.008

How to cite this article:
Asif Iqbal. (2023). DNA G Primase: A potent target for the development of anti-tuberculosis therapeutics: A review study. Int. J. Adv. Res. Biol. Sci. 10(1): 96-101.
DOI: http://dx.doi.org/10.22192/ijarbs.2023.10.01.008