ABSTRACT
Internationally, wonderful resources are being devoted in prevention, diagnosis, and treatment of tuberculosis. Finding novel antitubercular agents are the key focus of several pharmaceutical companies as well as nonprofit government and non-government organizations. This review will highlight the unique antitubercular drug targets for upcoming solicitation of protein structure based drug discovery and development.

KEYWORDS: Tuberculosis, Antitubercular drug targets. Protein structure based drug discovery

INTRODUCTION
The lethal communicable disease tuberculosis is caused by several species of Mycobacteria including *Mycobacterium tuberculosis*, *M. bovis*, *M. africanum*, *M. microti*, *M. avium* and *M. leprae* that are intracellular, Gram-positive, non-motile, and rod-shaped obligate aerobic pathogens of higher vertebrates. The appearance of drug-resistant strains of *M. tuberculosis* has led to amplified pressure on present chemotherapy treatments. The features that contribute to MDR-TB are interrupted, erratic or insufficient rehabilitation, as well as an insufficient public health system. The degree at which new TB cases occur varies extensively, even in nearby countries, superficially because of changes in health care systems. There is a vital necessity to develop new TB drugs. The aim of this article is to
review some selected potential antitubercular protein drug targets involved in cell cycle of *mycobacterium tuberculosis*, gaining novel initiative to design new drug candidate to generate anti-TB drugs.

**LITERATURE REVIEW**

**SHIKIMATE KINASE (SK)**

Shikimate kinase (SK) and other enzymes in the shikimate pathway are potential targets for developing non-toxic antimicrobial agents, herbicides, and anti-parasite drugs, because the pathway is essential in the above species but is absent from mammals. The shikimate pathway is the biosynthetic route that converts erythrose-4-phosphate to chorismic acid in seven steps. Chorismic acid is an essential intermediate for the synthesis of aromatic compounds, such as aromatic amino acids, p-aminobenzoic acid, folate, and ubiquinone. The shikimate pathway is essential for algae, higher plants, bacteria, and fungi, whereas it is absent from mammals. This makes the enzymes in the pathway potential targets for the development of non-toxic antimicrobial agents, Shikimate kinase (EC 2.7.1.71), and the fifth enzyme in the shikimate biosynthetic pathway, from *Mycobacterium tuberculosis* is obviously an excellent target for developing novel anti *Mycobacterium tuberculosis* agents.\[1,2\]

**CHORISMATE SYNTHETASE (CS)**

The enzymes of shikimate pathway are good candidates for development of new therapies against TB. Enzymes from this metabolic pathway have been submitted to intensive structural studies. The last enzyme from this pathway is the chorismate synthase (CS), which catalyzes the conversion of the 5-enol-pyruvylshikimate-3-phosphate (EPSP) to chorismate. It is the only enzymatic reaction known of such transformation in biological systems, making the CS a unique enzyme in the nature. The CS requires reduced flavin mononucleotide (FMN), an essential cofactor typically found in many biological redox reactions. Surprisingly, the reaction catalyzed by CS does not involve an overall change in redox state. The reduced FMN donates an electron to EPSP to facilitate the loss of the phosphate and receive it back after the reaction. So, only flavin in its reduced form is functional and it is not consumed during the reaction.\[3\]

**ISOCITRATELYASE (ICL)**

The strategy for survival during chronic stages of infection entails a metabolic shift in the bacteria’s carbon source to C2 substrates generated by β-oxidation of fatty acids. Under these
conditions, glycolysis is decreased and the glyoxylate shunt is significantly up regulated to allow anaplerotic maintenance of the tricarboxylic acid (TCA) cycle and assimilation of carbon via gluconeogenesis. The glyoxylate shunt accomplishes this by converting isocitrate to succinate and glyoxylate by isocitrate lyase (EC 4.1.3.1), followed by addition of acetyl-CoA to glyoxylate to form malate by malate synthase. The carbon conserving glyoxylate pathway is present in most prokaryotes, lower eukaryotes and plants, but has not been observed in vertebrates.\[4-6\]

**PANTOTHENATE SYNTHETASE (PS)**
Pantothenate (vitamin B5) is a key precursor of the 4-phosphopantetheine moiety of coenzyme A (CoA) and the acyl carrier protein (ACP). Both CoA and ACP are necessary cofactors for cell growth and are involved in essential biosynthetic pathways. Pantothenate is biosynthesized in microorganisms, plants, and fungi, but not in animals, and the enzymes of the pantothenate pathway are considered to be potential herbicide and antimicrobial targets. The pathway to pantothenate is best understood in *Escherichia coli*, where it comprises four enzymatic reactions. The final transformation, to produce pantothenate, is catalyzed by pantothenate synthetase (EC 6.3.2.1), encoded by the *panC* gene. Pantothenate is biosynthesized by the condensation of D-pantoate and β-alanine.\[7-11\]

**ENOYL-[ACYL-CARRIER PROTEIN] REDUCTASE (InhA)**
Two enzymes, InhA and KasA, have been proposed as targets for INH. Both are members of the type II dissociated fatty acid biosynthesis pathway (FASII) in *Mycobacterium tuberculosis*, consistent with the observation that INH interferes with the biosynthesis of mycolic acids, very long chain fatty acid components of the mycobacterial cell wall. InhA, an enoyl reductase that catalyzes the NADH-dependent reduction of long chain *trans*-2-enoyl-acyl carrier proteins (ACPs), was first identified as a target by Jacobs and coworkers. InhA is inhibited by INH, Barry and coworkers have also proposed that KasA, one of three ketoacyl synthases in the FASII pathway, is a target for INH *in vivo*.\[12, 13\]

**3-OXOACYL-[ACYL-CARRIER PROTEIN] REDUCTASE (MabA)**
The fatty acid elongation system FAS-II is involved in the biosynthesis of mycolic acids, which are major and specific long-chain fatty acids of the cell envelope of *Mycobacterium tuberculosis* and other mycobacteria, including *Mycobacterium smegmatis*. The protein Maba, also named FabG1, has been shown recently to be part of FAS-II and to catalyze the NADPH specific reduction of long chain β-ketoacyl derivatives. This activity corresponds to
the second step of an FAS-II elongation round. FAS-II is inhibited by the antituberculous drug isoniazid through the inhibition of the 2-trans-enoyl-acyl carrier protein reductase InhA. Thus, the other enzymes making up this enzymatic complex represent potential targets for designing new antitubercular drugs.[14]

**ORNITHINE ACETYLTRANSFERASE (OAT)**
*Mycobacterium tuberculosis* ornithine acetyltransferase (*Mtb* OAT; E.C. 2.3.1.35) is a key enzyme of the acetyl recycling pathway during arginine biosynthesis. It reversibly catalyzes the transfer of the acetyl group from N-acetylornithine (NAORN) to L-glutamate. *Mtb* OAT is a member of the N-terminal nucleophile fold family of enzymes. The three-dimensional structure of *Mtb* OAT will provide crucial information for elucidating the mechanism of OAT-catalyzed reaction and structure-based drug design.[15]

**LUMAZINE SYNTHETASE (LS)**
The enzymes involved in endogenous riboflavin biosynthesis pathways are not present in the human or animal host, they are promising candidates for the inhibition of bacterial growth. Two enzymes, lumazine synthase (EC 2.5.1.9; LS) and riboflavin synthase (RS), are catalyzing the penultimate and the last step of riboflavin biosynthesis. LS from *Mycobacterium tuberculosis*, which has shown the homopentameric state as well. The LS monomer shows some folding similarity to bacterial flavodoxins and is constructed from a central four-stranded β-sheet flanked on both sides by two and three α-helices, respectively. Lumazine synthase inhibitors can be considered as potential lead compounds for the design of therapeutically useful antibiotics.[16-17]

**QUINOLINATE PHOSPHORIBOSYL TRANSFERASE (QAPRT)**
Quinolinic acid phosphoribosyl transferase (EC 2.4.2.19), encoded by the *nadC* gene, is a key enzyme in *de novo* biosynthesis of NAD. The enzyme carries out the Mg2+ dependent transfer of the phosphoribosyl moiety from 5-phosphoribosyl-1-pyrophosphate (PRPP) to quinolinic acid (QA) yielding nicotinic acid mononucleotide (NAMN), pyrophosphate and CO2. In *Mycobacterium tuberculosis*, the three genes encoding the enzymes involved in the *de novo* biosynthesis of NAMN are part of a single operon (*nadABC*). In bacteria, the *nad* operon is transcriptionally regulated by a repressor encoded by the *nadR* gene in response to intracellular levels of nicotinamide mononucleotide (NMN). Alternatively, NAMN can be produced by a salvage pathway that proceeds via the phosphoribosylation of nicotinic acid (NA), generated by the degradation of NAD; this reaction is catalyzed by the enzyme
nicotinate phosphoribosyltransferase (NAPRT). Despite the similarity between their enzymatic reactions, QAPRT and NAPRT exhibit exclusive specificity for their respective substrates. In *Mycobacterium tuberculosis*, unlike most organisms, the salvage pathway appears to be disrupted. This is proposed to be a consequence of the lack of detectable NAPRT activity and results in secretion of NA produced by degradation of NAD. Relying entirely on the *de novo* pathway for its NAD requirements, *Mycobacterium tuberculosis* should be extremely vulnerable to drugs targeted against QAPRT.[18-23]

**GLUCOSAMINE-1-PHOSPHATE-N-ACETYL TRANSFERASE (GLmU)**

The glmU gene is essential in *Mycobacterium tuberculosis*, being required for optimal bacterial growth, and has been selected as a possible drug target for structural and functional investigation. GlmU is a bifunctional acetyltransferase/uridyltransferase that catalyses the formation of UDP-GlcNAc from GlcN-1-P. UDP-GlcNAc is a substrate for two biosynthetic pathways: lipopolysaccharide and peptidoglycan synthesis. The gene glmU has been identified as essential for optimal growth of *Mycobacterium tuberculosis* and is not present in humans; hence, it is of interest as a drug-design target.[24,25]

**REFERENCE**


