Exploring the In-Vitro Antibacterial and Anti Tubercular Activity of Lamotrigine through Repurposing Approach

Niharika Pedamallu[1*], Manohar Babu Sitty[2], Raghunandhan B L[3], Ramya V[3], Tripura B[3], Bikash Ranjan Jena[4]

[1] Department of Pharmaceutical Sciences, Vignan's Foundation for Science, Technology and Research, Vadlamudi, Guntur, Andhra Pradesh, India
[2] Department of Pharmacology, Lidya College of Pharmacy, Eethakota, Ravulapalem, East Godavari, Andhra Pradesh, India
[3] Department of Pharmacy, SIMS College of Pharmacy, Mangaldasnagar, Guntur, Andhra Pradesh, India
[4] School of Pharmacy and Life Sciences, Centurion University of Technology and Management, Pitamahal, Odisha, India

***Correspondence Email: niharika.mpharm12@gmail.com**

Abstract:

Tuberculosis ranks as the second deadliest infection caused by a single causative agent worldwide. Resistance towards the existing anti tubercular agents is the result of under diagnosis, phenotypic and genetic variation among patients and non-adherence to the current therapy. Drug discovery towards tuberculosis is unsuccessful in the past decade and gap is being filled by a computational approach, drug repurposing, which reintroduces the existing drugs with new indications. Currently, this approach is being actively employed to address a range of prevalent conditions such as tuberculosis, cancer, AIDS and COVID-19. The present study focuses on repurposing Lamotrigine, an anti epileptic drug, for its antibacterial and antimycobacterial activities. In silico molecular docking studies of Lamotrigine were conducted using Molegro Virtual Docker 6.0 with drug targets (PDBs) of Escherichia and Mycobacterium. The antibacterial activity was assessed using various bacterial strains including Bacillus subtilis(NCIM 2698), Pseudomonas aeruginosa (NCIM2639),Klebsiella pneumoniae (NCIM 2957), Escherichia coli (NCIM 2344) through the agar disc diffusion method with Gentamycin as the standard. Additionally, in vitro antimycobaterial activity was analysed against M. tuberculosis H37Rv, H37Ra, M. bovis utilising the microtitre plate alamar blue assay (MABA) with the standards Rifampin, Ciprofloxacin, Streptomycin, Pyrazinamide. The presence of both antibacterial and antimycobaterial activity of Lamotrigine was indicated by 20 and 14 mm diameter of zone of inhibition observed with Escherichia coli and Pseudomonas aeruginosa on agar plate as well as the development of blue colour in the microtitre well at a concentration of 1.6 µg mL^{-1} during MABA.

Keywords: Drug repurposing, Lamotrigine, Molecular Docking, Antibacterial activity, Antimycobacterial activity.

1. Introduction:

Tuberculosis (TB) is a prevalent bacterial infection, impacting approximately 25% of the global population and causing more than one million deaths annually, with resistant TB accounting for 29% of antimicrobial - resistant (AMR) fatalities [1]. The

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surge in multi drug-resistant strains (MDR-) and extensive-drug resistant (XDR-) TB is because of factors such as drug inefficacy, impermeable cell walls, enzyme modifications, and drug expulsion through cell wall proteins [2]. TB treatment, ranging from 6 months to 2 years in duration, also frequently results in drug resistance, adverse effects in patients, and inadequate elimination of the pathogen [3]. Difficulties in creating new medications and treatment plans are made worse by patient non-compliance, coexisting medical conditions, variability in drug metabolism, and negative reactions to drugs [4]. In the past few decades, attempts to create new antitubercular medications have not been entirely effective[5,6]. The introduction of new drugs remains a major bottleneck in the process of drug discovery [7]. The traditional drug development process need substantial time and resources in order to create a new molecule and introduce it into the market. Alternatively, computational drug repurposing is now seen as a viable and productive option, allowing for the identification of new medical applications for existing medications. Drug repurposing has become increasingly popular as a modern alternative to traditional drug development because of its economic, effectiveness, and reduced risk in recent times. In May 2012, the NIH initiated a program called "Exploration of Novel Therapeutic Applications for Established Molecules" to encourage drug repurposing.

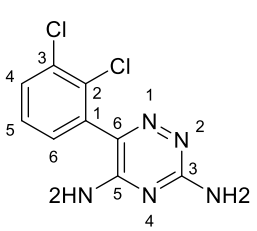
Drug repurposing is now being seen as an important tactic in addressing the difficulties of TB treatment by finding alternative uses for drugs already in existence [8]. This method has discovered multiple medications, like thioridazine for XDR-TB and chlorpromazine as a supplement in MDR-TB treatment along with Rifampicin and Streptomycin, and has displayed potential in utilizing FDA-approved ion channel blockers to decrease Mycobacterium infections in animal studies [9]. Furthermore, research has also pointed out the ability of antipsychotic medications to combat tuberculosis[10]. It is worth mentioning that repurposing has discovered many already sold drugs that have shown effectiveness against mycobacterial infections, such as fluoroquinolones, macrolides, linezolid, azole antifungals, antiretrovirals, antiparasitic drugs, statins, calcium channel blockers, NSAIDs, CNS agents, and disulfiram.

Strategies for drug repurposing involve identifying molecules that share similar gene expression profiles, molecular mechanisms, genetic risk loci, disease associations, or genes co-expressed with the candidate genes. The repurposing process typically involves two main steps: (i) in silico screening of existing drugs, followed by in vitro and in vivo screening, and (ii) clinical trials [11]. Drug repurposing not only shortens the drug development timeline but also addresses production and delivery challenges, thereby overcoming the limitations associated with traditional experimental drug development.

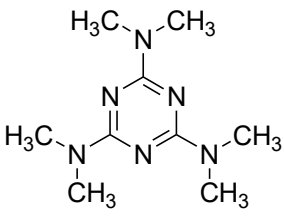
As a part of the above approach, a broad spectrum antiepileptic drug approved by USFDA for adjunct therapy in 1994, Lamotrigine or 3, 5-diamino-6-(2, 3-dichlorophenyl)-1, 2, 4-triazine was used to evaluate it's anti bacterial and antimycobacterial potentials. Lamotrigine is a phenyltriazine derivative used for the treatment of tonic clonic, partial and generalized seizures in patients with refractory and bipolar disorder [12]. Lamotrigine inhibits voltage sensitive sodium channel and high voltage activated calcium channel, thereby, reducing the neuronal release of glutamate. The drug also exhibits antidepressant properties by inhibiting the reuptake of serotonin [13].

N-heterocycles, including pyrimidines, pyrazoles, thiazoles, oxazoles and triazines are important scaffolds in medicinal chemistry known for their potent pharmacological activities [14]. Triazine derivatives containing imidazole substitution exhibit strong bacteriostatic effects against drug-resistant Staphylococcus aureus and non-tubercular Mycobacteria, with minimum inhibitory concentrations (MIC) as low as 1 μL, and are safe for mammalian cells. Triazine Schiff bases also demonstrate activity against Mycobacteria. In addition, triazines containing benzylamine interfere with the cell membrane and create DNA complexes to block replication,thereby show remarkable effectiveness against multi-drug-resistant Staphylococcus aureus outperforming chloromycin and amoxicillin [15,16]. Eventhough studies exhibit antimicrobial activities of triazine this activity is less appreciated. Among these, triazines are particularly noteworthy owing to their broad spectrum of biological activities, which include anti-inflammatory, analgesic, anti-protozoal, herbicidal, antiviral, antibacterial, antifungal and antitubercular properties. Several triazine-containing medications, including altretamine (antineoplastic agent), irsogladine(peptic ulcer and gastro-oesophageal reflux disease), almitrine(respiratory stimulant used for COPD), cycloguanil (active metabolite of Proguanil), bemotrizinol (organic UV filter), and atrazine (herbicide), are being marketed for their strong biological effects.

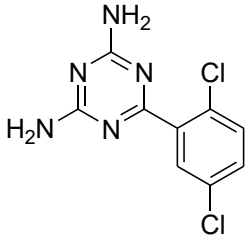
The present study focuses on assessing the in silico and in vitro anti bacterial and anti mycobacterial activity of lamotrigine.



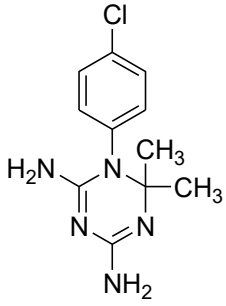
Lamotrigine



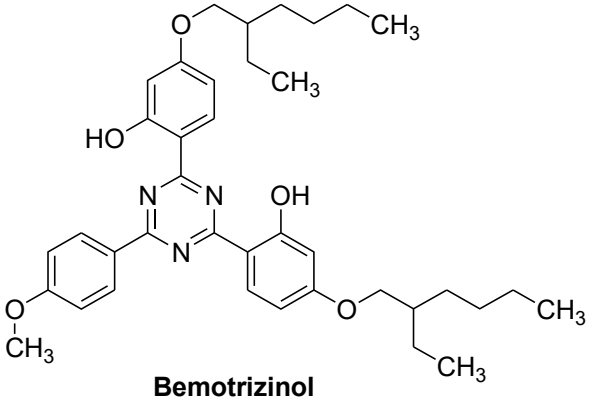
Altretamine



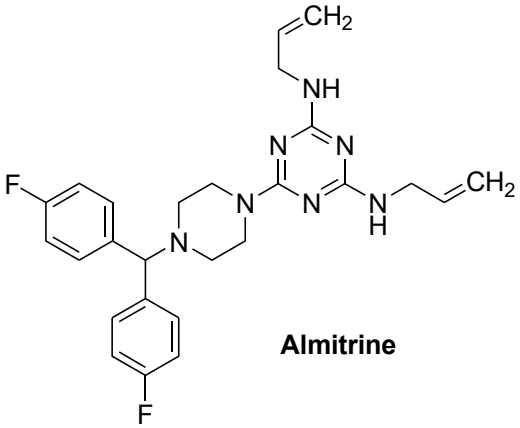
Irsogladine



Cycloguanil



Bemotrizinol



Almitrine

2. Materials and Methods:

Rankem has supported with the pure drug of lamotrigine and all the other chemicals used originated in Merck, India. In MABA assay, Middlebrook 7H9 broth Sauton's media, Alamar blue reagent and Resazurin were used. The Synergy Biotech plate reader was used to test surface fluorescence.

2.1. MolecularDocking Studies of Lamotrigine: Molecular docking studies of lamotrigine on bacteria and Mycobacterium drug targets was done in MolegroVirtual Docker 6.0 software. 3D structure of lamotrigine was obtained from the PubChem with code CID:3878 in .sdf format and was converted to .mol2 format in OpenBabel GUI interface and the geometry was optimized using Argus lab 2.0. The proteins of Mycobacterium tuberculosis (Pantothenate kinase(PDB:4BFZ) [17], Enoyl reductase (InhA) (PDB: 4TZK)[18], Decaprenyl phosphoryl-β-D-ribose-2'-oxidase(DprE1)(PDB: 6G83), Dihydrofolate Reductase (PDB: 4KM2)[19],and Escherichia coli dihydrofolate reductase(PDB: 6XG5) [20], were downladed in PDB format from RCSB: PDB (https://www.rcsb.org/) and were repaired in SPDBV 4.0. Cavities in the protein were detected and around the cavity of co-crystallised ligand a circular grid was generated in every PDB as mentioned in Table 1. Then the co-crystallised ligand was extracted and used along with Lamotrigine for docking with the protein in the grid generated in ten different poses. The pose with maximum Moldock score (in $KcalMol^{-1}$) was tabulated in table II.

2.2. Antibacterial activity of Lamotrigine:

2.2.1. Preparation of Lamotrigine Solution: 0.025g of Lamotrigine pure drug was mixed with 25mL of methanol, the solution was placed in the ultrasonic water bath for 15 minutes and then shaken for 15 minutes further. The solution (concentration 250 $\mu g\ mL^{-1}$) obtained was then filtered through 0.45µm membrane filter and was made to 100ml with methanol [21].

Antibacterial activity of lamotrigine was ascertained by the agar disc diffusion method [22]. Bacteria used for this study were obtained from National Collection of Industrial Microorganisms (NCIM), Pune, India include Klebsiella pneumonia(NCIM 2957), Escherichia coli(NCIM 2344), Bacillus subtilis(NCIM 2698) and Pseudomonas aeruginosa (NCIM2639). The organisms maintained at 4^oC in the agar slants were subcultured by addition of the respective bacteria into the presterilised nutrient broth and incubated them for 24 hr at $37 + 1^0C$. Sterile nutrient agar medium

added to the presterilsed petri dish were inoculated with 24 hour old subcultures of the above bacteria. After resting the medium with inoculum, the Whatmann filter paper No.2 discs soaked and dried aseptically in methanol, the lamotrigine solution(250 μgmL^{-1}) along with the standard (Gentamycin) were placed on sterile innoculated media and left in the laminar air flow unit for one hour. After incubation for 24 hours at 37+ 1 ^0C, the zone of inhibition produced by the synthesised compounds was measured and compared against the zone produced by Getamycin. All the experiments were performed in triplicates [23].

2.3. Microtitre Alamar Blue Assay (MABA): Anti tubercular activity of Lamotrigine: The Lamotrigine's anti mycobacterial activity was tested in vitro using MABA assay [24]. A 96-well microtitre plate was prepared with 100 µL of Middlebrook 7H9 broth per well, followed by the addition of test compounds at various concentrations (0.8, 1.6, 3.125, 6.25, 12.5, 25, 50, 100 $\mu g\ mL^{-1}$) dissolved in DMSO. Each well, except the negative control(medium only) was then inoculated with 150 µL of the Mycobacterium tuberculosis H37Ra (106 $CFUmL^{-1}$), M. tuberculosis (ATCC 27294), M. bovis culture. Positive controls included were Rifampin (2 $\mu g\ mL^{-1}$), Streptomycin (6.25 $\mu g\ mL^{-1}$), Pyrazinamide (3.25 $\mu g\ mL^{-1}$) and Ciprofloxacin (3.125 $\mu g\ mL^{-1}$). Over 5 days, the plate was incubated at 37ºC. On the 6^{th} day, 25µL of resazurin (0.01% w/v) or 1:1 mixture of Alamar blue and Tween 80 (10%) was added to each well and incubated for an additional 24 hours [25].

3. Results and Discussion:

3.1. Docking Studes of Lamotrigine: An essential enzyme enoyl acyl carrier protein reductase (InhA), involved in the mycolic acids synthesis, which are components of the Mycobacterium cellwall, providing protection against hydrophobic drugs and dehydration [26]. Decaprenyl phosphoryl-β-D-ribose-2'-oxidase (DprE1), a flavoenzyme essential for the synthesis of both lipoarabinomannan and arabinogalactan layers which are critical for the survival of Mycobacterium. Together with DprE2, DprE1 catalyzes the epimerisation of the decaprenyl-phospho-ribose to decaprenyl-phospho-arabinose [27]. Pantothenate Kinase, a rate limiting enzyme in coenzyme A(CoA) biosynthesis, catalyses the phosphorylation of pantothenate. CoA serves as a cofactor that carriers acyl groups during respiration and lipid biosynthesis [28]. An enzyme in folate metabolism dihydrofolate reductase (DHFR) reduces dihydrofolate to tetrahydrofolate, plays a crucial role in the synthesis of aminoacids like methionine and glycine as well as nitrogenous bases such as purines and thymidine [29].

In silico docking of Lamotrigine on bacterial and Mycobacterium drug targets indicate the presence of specific activity. The MolDock score of lamotrigine on pdb 4BFZ, 4TZK, 6G83, 4KM2, 6XG5 was -86.0311; -93.3504; -93.2741, -85.7062,-93.2619 Kcal Mol^{-1} while the standard or co-crystallised ligands score were-136.328; -194.061; -211.361,-101.254, -113.791 Kcal Mol^{-1} respectively. The results of in silico docking, reveals the affinity of lamotrigine towards the protein from Table 2.

3.2. Antibacterial Activity of Lamotrigine: Anti bacterial activity of Lamotrigine solution(250 $\mu g\ mL^{-1}$) with the organisms Klebsiella pneumonia, Escherichia coli, Bacillus subtilis and Pseudomonas aeruginosa was evaluated by agar disc diffusion method. Lamotrigine was inactive on Klebsiella pnuemonia and Escherichia coli but the zone of inhibition obtained with Pseudomonas aeruginosa and Escherichia coli were 14 and 20 mm respectively while Gentamycin produced zones of diameter 28,

25, 30, 28 mm with Bacillus subitils, Pseudomonas aeruginosa, Escherichia coli and Klebsiella pneumonia respectively as given in Table 3.

3.3. Anti tubercular activity of Lamotrigine: The antimycobacterial activity of drug was done in vitro on Mycobaterium tuberculosis H37Rv, H37Ra and Mycobaterium bovis by MABA. The Minimum Inhibitory Concentration (MIC) of lamotrigine was 1.6 μg mL^{-1} while MIC of Ciprofloxacin, Streptomycin and Pyrazinamide was 1.6, 3.125 and 1.6 μg mL^{-1} respectivelywith M. tuberculosis H37Rv were tabulated in Table IV. The drug was inactive on M. tuberculosis H37Ra and M. bovis when compared with Rifampin (2 μg mL^{-1}) and Streptomycin(3.125 μg mL^{-1}) from Table 4.

Table 1: Grid parameters of PDBs and aminoacids interactions with lamotrigine and co-crysatallised ligand

Compound	MOLDOCK Score (in Kcal/Mol)				
	4BFZ	**4TZK**	**6G83**	**4KM2**	**6XG5**
Grid parameters	Radius: 15, X: -17.81 Y:-13.40 Z: 11.98	Radius:13, X:5.51 Y:28.76 Z:58.39	Radius:15, X: 2.94 Y: -16.68 Z: 82.16	Radius:9, X: 21.37 Y: 30.96 Z: 19.68	Radius:7, X: -9.00 Y:28.68 Z: 17.36
Lamotrigine	Ala100, Lys103, Asp129,	Val 65	Ser59, Asn63, Cys129	Ile5, Ala7 Asp27, Ile94, Tyr100,	Ala7, Asp27, Ile94, Tyr100, Thr113,
Co-crystallised ligand	Asp129, Tyr153, Arg238, Tyr235	Val65, Asp64, Gly96, Tyr158, Lys165	Tyr 60, Arg 58, Ser 59, Gly 57, Gly 55	Leu 24, Trp 22, Arg 32, Arg 60	Ile5, Ile94, Asp27

Table 2: Results of in silico molecular docking studies of Lamotrigine with Bacterial and Mycobacterial drug targets

Compound	MOLDOCK Score (in Kcal/Mol)				
	4BFZ	**4TZK**	**6G83**	**4KM2**	**6XG5**
Lamotrigine	-86.0311	-93.3504	-93.2741	-85.7062	-93.2619
ZVZ_501 [A]	-136.328	-	-	-	-
NAD_500 [A]	-	-194.061	-	-	-
FAD_501 [A]	-	-	-211.361	-	-
EQ8_502 [A]	-	-	-165.106	-	-
ATR_201 [A]	-	-	-	-101.254	-
TOP_202 [A]	-	-	-	-	-113.791

Table 3: Results of Anti bacterial activity of Lamotrigine

Compound	Zone of inhibition in millimeters(mm)			
	Bacillus subtilis	**Pseudomonas aeruginosa**	**Escherichia coli**	**Klebsiella pneumonia**
LT Gentamycin	- 28 + 0.05	14 + 0.2 25 + 0.01	20 + 0.3 30 + 0.03	- 28 + 0.01

Table 4: Results of antitubercular activity of Lamotrigine with MABA Assay (M.tuberculosis H37Rv)

Compound	MIC (µg/ mL)
LT	1.6
Streptomycin	3.125
Pyrazinamide	1.6
Ciprofloxacin	1.6
Rifampin	2

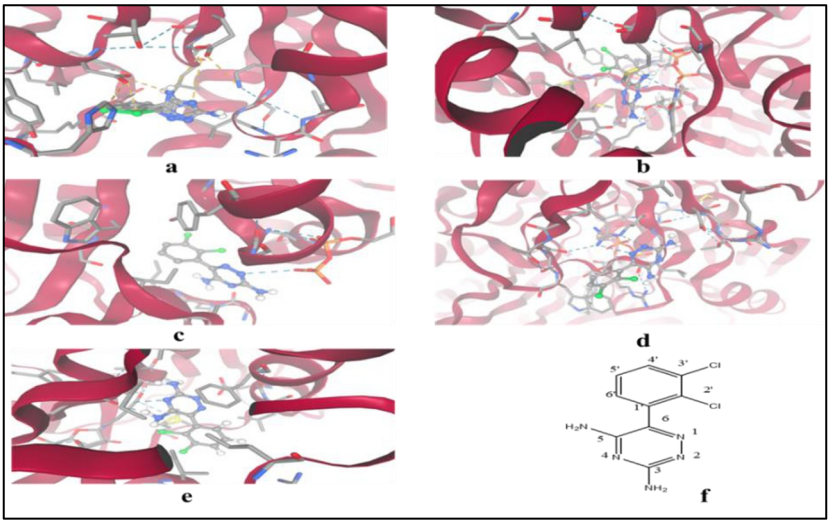


Figure 1: Lamotrigine in complex with protein PDB targets a) 4BFZ(PanK) b) 4TZK(INHA) c) 6G83(DprE1) d)4KM2 (DHFR) e) 6XG5 (E.coli DHFR) f) Chemical structure of Lamotrigine

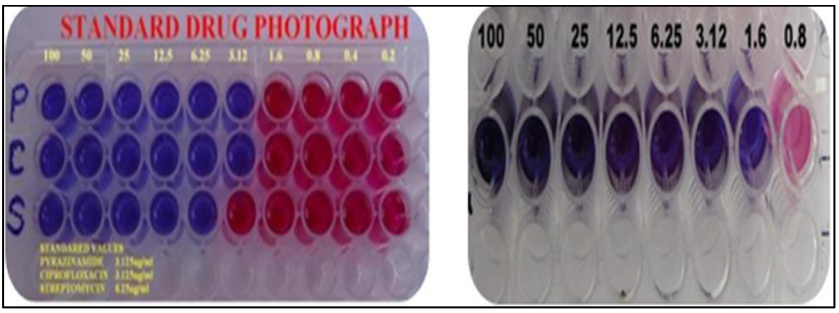


Figure 2: Result of MABA assay with standard drugs (Pyrazinamide, Ciprofloxacin and Streptomycin) on right side and lamotrigine solutions on M.tuberculosis H37Rv on left side. The colours produced with the addition of alamar blue and indicates the organism is sensitive(blue) and resistant (pink) to the dilution of standards and lamotrigine in the microtitre well

4. Discussion:

Repurposing of drugs is essential because it is economial and quick way to discover new therapeutic applications for existing medications and can greatly decrease the risks by utilizing the established safety profiles of the drugs. Moreover, it can hasten the delivery of treatments for unaddressed medical conditions, thereby improving patient care. The present work employs a drug repurposing strategy to identify potential new uses for existing pharmaceuticals. Triazines are one such scaffolds possessing significant biological properties and are commercially available. In this study, we evaluated the antibacterial and antimycobacterial activities of the marketed triazine anticonvulsant drug, Lamotrigine. Molecular docking studies were conducted using Molegro Virtual Docker 6.0, with the protein targets of Escherichia coli and Mycobacterium tuberculosis. Structure of Lamotrigine was downloaded in .sdf format from PubChem and protein targets in .pdb format were retrived from RCSB: PDB (IDs 4BFZ, 4TZK, 6G83, 4KM2, and 6XG5). The results revealed a significant docking score of Lamotrigine compared to co-crystallized ligands in Figure 1. In vitro antibacterial activity was assessed using the agar disc diffusion method with Bacillus subtilis, Pseudomonas aeruginosa, Escherichia coli, and Klebsiella pneumoniae using Lamotrigine solution of concentration 250 μgmL^{-1}. In the present study, lamotrigine was inactive against Bacillus and Klebsiella. However, it produced zones of inhibition with diameters of 14 mm and 20 mm for Escherichia coli and Pseudomonas aeruginosa, respectively. The study done by Barath Srinivasan in 2015; reported that lamotrigine has good E.coli dihydrofolate reductase inhibitory activity in silico and IC_{50} and K_i were 348.9+ 6.7 μM and 15.24+2.78 μM respectively. Previous studies on Lamotrigine and its derivatives, specifically Lamotrigine ammonium salt metal complexes synthesised by Yong Qian in 2009 demonstrated good anti bacterial activity against gram +ve organisms while showing inactivity or mild activity against gram –ve bacteria when tested on Bacillus, Staphylococcus, Enterococcus, Escherichia and Enterobacter[30]. This was further supported by work done by Hina Siddiqui on Staphylococcus using quaternary ammonium salt of lamotrigine[31]. Research on N-heterocycle triazines revealed good antibacterial activity against Bacillus subtilis, Bacillus cereus, Staphylococcus aureus, and Pseudomonas aeruginosa. This study concluded that the antibacterial activity of triazines was enhanced by conjugation of heterocycles and further enhacement observed when

electron –withdrawing groups (EWG) such as –Cl, -Br, and –NO_2 were substituted on the heterocycles[32]. Unlike these findings, a study by Zehra revealed the toxic effect of Lamotrigine, along with other anticonvulsants, in presence of propylparaben on gut bacteria[33]. Study by Stokes in 2014, accumulation of immature 30S and 50S subunits in lamotrigine treated E.coli interferes with the ribosomal biogenesis in the bacteria under cold sensitive growth inhibition model[34]. In vitro antimycobacterial activity of lamotrigine was assessed with MABA assay using Mycobacterium tuberculosis H37Rv, H37Ra and M. bovis.The MIC of lamotrigine on M. tuberculi H37Rv was 1.6 µg/mL and was found to be inactive against M.tuberculi H37Ra and M. bovis. The MIC of the standard drugs Ciprofloxacin, from Figure 2, Streptomycin, Pyrazinamide and Rifampin was 1.6µg/mL, 6.25µg/mL, 1.6µg/mL and 2µg/mL respectively. The results of antimycobacterial activity of lamotrigine was supported with the study on a triazine, JSF-2019 possessing nitro group synthesised by Xing Wang et al., which demonstrated better in vitro antitubercular activity with release of nitric oxide radical and by inhibiting InhA in Mycobacterium[35]. Lamotrigine's in vitro antitubercular activity correlates well with study of antitubercular activity of thiazolo-1,2,4-triazine by Cai et al., on M. smegmatis where MIC was 50 µg/mL[36]. Lamotrigine demonstrated an MIC similar to that of the standard drugs Ciprofloxacin and Pyrazinamide indicating comparable effectiveness on M.tuberculi H37Rv. The inactivity of lamotrigine on M.tuberculi H37Ra and M. bovis highlights its limited spectrum of antimycobacterial activity.

5. Conclusion:

Lamotrigine, an adjuvant therapy for epilepsy also possesses substantial antibacterial and antimicrobial activity as revealed from the previous and present study. Further in vivo studies might introduce a better candidate for the treatment of tuberculosis and other bacterial infections. Additionally, molecular docking studies performed with electron withdrawing and electron releasing group substituted Lamotrigine particularly substitution of fluorine on 3rd and trifluoromethyl or thiol or heterocyclic ring on 5th position on the phenyl ring revealed the enhancement in the inherited antimicrobial and antitubercular activity.

6. Acknowledgement:

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7. Author Contributions:

Niharika Pedamallu has conceptualised the work, performed molecular docking studies, drafted the manuscript, Ramya V, Tripura B, Raghunandhan B L: implemented the work, and reviewed the literature and Manoha babu Sitty contributed discussion and finalized the manuscript.

8. Disclosure of Interest: The authors declare no conflict of interest.

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