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PLASMODIUM FALCIPARUM LACTATE DEHYDROGENASE: AN IMPORTANT DRUG TARGET FOR THE DEVELOPMENT OF NEW ANTIMALARIALS

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ABSTRACT

Plasmodium falciparum lactate dehydrogenase (*Pf*LDH), a key enzyme in the glycolytic pathway of the malaria parasite, has emerged as a promising drug target due to its essential role in energy generation and its structural differences from human LDH. Several compounds, including natural products like TMDTP from *Alstonia boonei*, synthetic dihydroxynaphthoic acid analogues, and repurposed drugs such as posaconazole and atorvastatin, have demonstrated significant inhibitory activity against *Pf*LDH. These inhibitors exhibit diverse binding modes and selectivity over human LDH, underscoring the potential of *Pf*LDH as a target for developing new antimalarials with novel mechanisms of action. Continued research and optimization of *Pf*LDH inhibitors are crucial to address the challenge of drug-resistant malaria.

KEYWORDS: Plasmodium Falciparum, Lactate Dehydrogenase (PfLDG), Malaria Treatment, Enzyme Inhibition, Glycolysis, Parasite Metabolism,

INTRODUCTION

Recent researches proved the absence of Krebs (citric acid) cycle in the Plasmodium parasite, which is needed for energy generation, therefore, it depends on ATP generation via the anaerobic fermentation of glucose. Hence, glucose consumption in parasitized erythrocyte was found up to 100 times higher than in non- parasitized erythrocytes and the consumed glucose can be used for by production of lactate(1). The glycolytic pathway of the *Plasmodium* parasite is involved in the consumption of glucose and the LDH (2-hydroxy acid oxidoreductase), the last enzyme of this pathway which is essential for the anaerobic lifestyle of the parasite. It converts pyruvate to lactate and simultaneously the conversion of NADH to NAD+. The enzymatic conversion of pyruvate to lactate completed in six steps which include: (i) NADH binds the apoenzyme by starting the "loop open" conformation, (ii) pyruvate orientated in the active site to form the ternary complex by Arg171, (iii) Arg109 bind to the substrate by closing the substrate specificity loop over the active site and stabilize the transition state, (iv) pyruvate reduces into lactate with NADH by hydride transfer, (v) lactate release by opening substrate specificity loop, and (vi) NAD^+ released for regeneration of the apoenzyme. Catalytic His195 activated by Asp168 which allows a proton transfer during the reduction of pyruvate to lactate (2).

Glycolysis requires the constant supply of NADH and LDH works as the preliminary source for the regeneration of NADH from NAD in *Plasmodium*, this indicating that the inhibition of LDH leads to the stop of ATP production and resulting malarial parasite cell death. *Plasmodium falciparum* LDH amino acid sequence revealed a distinctive insertion of five amino acids in the active site loop (residues 103E-107), a highly conserved region in length which makes it differ from its mammalian counterparts and this is a characteristic for all *Plasmodium*

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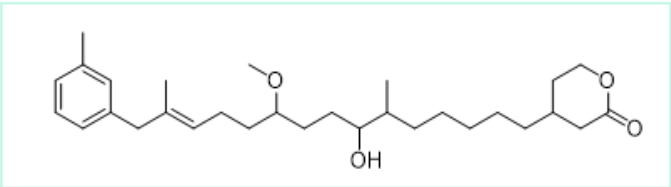
LDH.

Different studies show that *Pb*LDH was 97% identical to P*f*LDH, 99.4% like P*y*LDH and 90% similar to P*v*LDH. The structural differences between *Plasmodium* and human LDH make it a viable drug target. A drug like compound that can selectively inhibit the *Plasmodium* LDH over the human LDH isoforms may be a potent antimalarial with a different mode of action therefore, several researchers recognized the LDH as a potential drug target for antimalarial drug development.

RECENT INHIBITORS OF PFLDH AS ANTIMALARIALS

Olanlokun, et al.(3) isolated a novel compound Tetrahydro-4-((E)-7-hydroxy-10-methoxy-6, 14-dimethyl-15-m-tolylpentadec-13-enyl) pyran-2-one (TMDTP) from the stem bark of *Alstonia boonei*, and analysed the inhibitory effect on P*f*LDH and Plasmepsin II in-silico. They reported the binding energy of TMDTP with P*f*LDH was -7.6 Kcal/mol and structural stability study of the ligand shows, TMDTP induced an alteration in the C-α atoms which reduced the structural deviation and confirm the inhibitory activity of TMDTP. They also reported the electrostatic energy -11.8046, van der Waals energy -58.6698, solvation free energy 20.5334, gas phase free energy -70.4744, and calculated total binding free energy -49.9409.

TMDTP



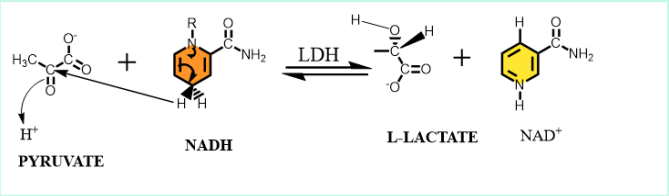
Another example of *in-silico* method for screening of *Pf*PDH inhibitors was screening of oxamic acid similar 3D structures through molecular docking by **Muttaqin and Maji** (4).

For their study, they used *Plasmodium falciparum* l-lactate dehydrogenase (PDB accession ID: 1LDG) complexed with NADH and oxamate as protein for docking by using some ligands and 2,2-diffluoro-2-hydroxyacetic acid which was similar to Oxamic acid in 3D was reported fas strong potential *Pf*LDH inhibitor in their study with -5.2 Kcal/mol binding free energy.

The reported inhibitors were found to be bind in three different patterns in the active site of *Pf*LDH. They bind either to the pyruvate site, the site of junction of the cofactor and pyruvate, or the adenine binding site (5). The natural phenol isolated from cotton plant was reported as selective inhibitor for *Pf*LDH over human LDH is presumed to bind at bridging site of cofactor NADH and the pyruvate in the active site of *Pf*LDH (6). Oxamic acid was reported as competitive inhibitor with pyruvate substrate for *Pf*LDH but some of its derivative failed to show selectivity over human LDH. Moreover, recent researches shows that some azole-based compounds show selectivity to inhibit *Pf*LDH over human analogue at submicromolar level (7).**Megnassan, *et al.***(8) identified forty one dihydroxynaphthoic acid analogues originated from hemigossypol-sesquiterpene found in cottonseed as an inhibitors for *Pf*LDH by using structure based-design approach at nanomolar concentration range and there 11 analogues shows ≤5 nm predicted IC50 value while standard natural inhibitor Gossypol shows 920nm IC50 value for *Pf*LDH. Their study revealed that, the predicted analogs displayed higher more than three orders IC50 value towards *Pf*LDH with favorable ADME-related properties such as NHNA12 shows 0.09 nM predicted IC50, but the actual inhibitory concentration of proposed analogs could be obtained after synthesizing and biological evaluations. Moreover, their study may be very useful to among researchers working in the synthetic medicinal chemistry field, which may lead to the discovery of hydroxynaphthoic acid-based inhibitors with potent inhibition against LDH of P. falciparum.

Another *in-silico* study was conducted to find antimalarial among 50 molecules similar to NADH as an inhibitor of *Pf*LDH (9). The researchers found three best molecules using docking studies *i.e.* Itraconazole (an anti-fungal agent), Atorvastatin (a medicine used for cardiovascular disease), and Posaconazole (a triazole based antifungal drug) with binding free energy of -218.5, -209.3, and -201.6 Kcal. mol^{-1} respectively found closest to NADH (-249.6 $Kcal.mol^{-1}$)(10).The active site residue Asn140, Gly29, Tyr85 were found in making interaction with Itraconazole while the residues Asp53, Thr97, Gly32,

Ile31, Gly99 shows interaction with Atorvastatin and Gly99, Gly29, Met30, Ile31, Asn140, Ser 245, Glu122 interacted with Posaconazole. (11) Further, *in-vitro* results for these compounds indicated that,(12) the Posaconazole was more active with IC50 value of 2.6±0.30 µm among Itraconazole and Atorvastatin with IC50 value of 9.3±0.80 and 13.1±4.50 µm respectively(13). They also investigated the active compounds against *P. berghei* infected mice as *in-vivo* and observed that all compounds inhibited parasite growth(14). The atorvastatin and posaconazole reduced parasitemia by 41% and 46%, respectively at 20 mg/kg test dose. (15,16)



CONCLUSION

Malaria remains a major global health challenge, with *Plasmodium falciparum* being the most lethal species responsible for severe cases and high mortality rates. The increasing prevalence of drug-resistant strains underscores the urgent need for novel antimalarial drugs with unique mechanisms of action. *Plasmodium falciparum* lactate dehydrogenase (*Pf*LDH) has emerged as a promising drug target due to its crucial role in the glycolytic pathway, which is essential for the parasite's energy production and survival. *Pf*LDH exhibits structural and functional differences from human LDH, making it a selective target for antimalarial drug development. Several studies have identified potent inhibitors that specifically target *Pf*LDH, disrupting the parasite's metabolic processes without affecting the host.

Advances in computational drug design, high-throughput screening, and structural biology have facilitated the discovery of novel compounds with high binding affinity and specificity for *Pf*LDH.Despite these promising developments, challenges remain in optimizing drug efficacy, pharmacokinetics, and safety profiles for clinical use. Further research is needed to explore combination therapies that target *Pf*LDH alongside other critical pathways to prevent resistance. Additionally, in vivo studies and clinical trials will be essential to validate the therapeutic potential of *Pf*LDH inhibitors. In conclusion, targeting *Plasmodium falciparum* lactate dehydrogenase represents a viable strategy for developing next-generation antimalarials. With continued research and innovation, *Pf*LDH inhibitors could play a pivotal role in combating drug-resistant malaria and reducing the global burden of this deadly disease.

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