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ANTI-LEISHMANIAL POTENTIAL OF STATINS: TARGETING 3-HYDROXY-3-METHYLGLUTARYL COENZYME A REDUCTASE (HGMR) IN LEISHMANIA DONOVANI

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Abstract:

Visceral leishmaniasis is a severe parasitic disease caused by Leishmania donovani, affecting millions worldwide. The sterol biosynthetic pathway, particularly ergosterol synthesis, plays a crucial role in parasite survival and represents a promising therapeutic target due its absence in human host.The role of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HGMR) as a potential drug target in leishmania donovani and evaluate the therapeutic potential of HGMR inhibitors. HGMR is a rate limiting enzyme in the mevalonate pathway responsible for ergosterol biosynthesis in Leishmania. Various studies demonstrate that inhibition of HMGR using statins such as atorvastatin and simvastatin significantly reduces parasite growth by disrupting membrane integrity and essential metabolic functions. Additionally, targeting this pathway shows minimal toxicity to host cells due to pathway differences.HGMR represents a promising and effective target for the development of novel antileishmanial therapies, with multiple inhibitors showing significant efficacy in experimental studies.

Key words: *Leishmania Donovani, HMGR, Atrovastatin, Antileashmanial activity, Statins*

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1.INTRODUCTION:

Visceral leishmaniasis (VL), caused by Leishmania donovani, is a severe and often fatal parasitic disease that continuous to pose a major global health challenge, particularly in tropical and subtropical regions such as the Indian subcontinent Sudan, and Brazil. It affects millions of individuals across nearly 100 countries and is recognised by global health authorities as a neglected tropical disease requiring urgent attention. The currently available chemotherapeutic options- including pentavalent antimonials, widely used for the treatment; however, their clinical utility is increasing limited by several drawbacks such as high toxicity, prolonged treatment regimens, high cost, and the emergence of drug resistant parasite strains. These amphotericin B, pentamidine, paromomycin, and miltefosine- have been limitations emphasize the pressing need to identify novel drug targets and develop safer, more effective therapeutic strategies, including drug repurposing and vaccine development.

In recent years, increasing attention has been directed toward the metabolic pathways essential for parasite survival, particularly the sterol biosynthesis pathway. This pathway plays a fundamental role in maintaining membrane structure, cellular integrity, and growth of *Leishmania* parasites. Unlike mammalian host cells, which primarily synthesize cholesterol, *Leishmania* and other trypanosomatids produce ergosterol and related 24-methyl sterols. These sterols are crucial for parasite viability and differ structurally from cholesterol by the presence of additional methyl groups and distinct double bonds. Importantly, although *Leishmania* can uptake cholesterol from the host, it cannot fully utilize it to replace its endogenous sterols, making the ergosterol biosynthesis pathway indispensable. This biochemical distinction between host and parasite provides a selective advantage for targeting sterol metabolism without causing significant harm to host cells.

The sterol biosynthesis pathway is initiated by the condensation of acetyl-CoA molecules to form HMG-CoA, which is subsequently reduced to mevalonate in an NADPH-dependent reaction catalyzed by HMG-CoA reductase (HMGR), the rate-limiting enzyme of the mevalonate pathway. This pathway leads to the production of essential isoprenoid intermediates involved in multiple cellular processes, including synthesis of sterols, protein prenylation, and regulation of cell growth and metabolism. In humans, HMGR is a membrane-bound enzyme localized to the endoplasmic reticulum, whereas in *Leishmania*, structural differences such as the absence of a transmembrane domain result in a soluble form of the enzyme. These structural and functional differences make parasite HMGR an attractive and selective drug target. In addition to HMGR, other enzymes such as squalene synthase and sterol methyltransferase have also been explored as potential targets, with several inhibitors demonstrating promising antileishmanial activity. Therefore, targeting the sterol biosynthesis pathway, particularly HMGR, represents a rational and promising approach for the development of novel therapeutic interventions against visceral leishmaniasis.

Ergosterol biosynthesis inhibitors have been widely reported to exhibit significant antiproliferative activity against fungi, yeast, and protozoan parasites. Among these, statins represent an important class of HMG-CoA reductase (HMGR) inhibitors that are primarily used as lipid-lowering agents in the management of hyperlipidemia and prevention of cardiovascular diseases. Based on their structural characteristics, statins are broadly classified into two categories. Class I statins, such as lovastatin, pravastatin, and simvastatin, are naturally derived compounds containing rigid hydrophobic ring structures linked to an HMG-like moiety. In contrast, Class II statins—including fluvastatin, cerivastatin, atorvastatin, and rosuvastatin—are fully synthetic molecules with larger and more complex side chains attached to the HMG-like structure, contributing to their enhanced pharmacological properties.

In addition to statins, several non-statin compounds lacking the characteristic HMG-like moiety have also been identified as HMGR inhibitors. These include agents such as cholestin, ketanserin tartrate, lanosterol analogs, and tunicamycin, which demonstrate inhibitory effects through alternative mechanisms. Interestingly, variations in enzyme sensitivity have been observed, with Class II HMGR enzymes showing significantly lower susceptibility to statin inhibition, typically requiring higher (millimolar) concentrations compared to the nanomolar inhibition observed in Class I enzymes. Furthermore, growing evidence suggests that statins possess antimicrobial properties beyond their lipid-lowering effects. They have been shown to significantly inhibit the growth and proliferation of protozoan parasites belonging to the Trypanosomatidae family, including *Trypanosoma cruzi* and multiple *Leishmania* species such as *L. major* and *L. mexicana*. These findings highlight the potential of statins and related HMGR inhibitors as promising candidates for repurposing in antiparasitic therapy.

1.1 Role of HMGR in parasite infectivity

The role of HMG-CoA reductase (HMGR) in parasite infectivity has been evaluated using transfected *Leishmania* promastigotes with enhanced HMGR expression. These genetically modified parasites, along with wild-type strains,

were used to infect differentiated THP-1 macrophage cells under controlled conditions. The infectivity of wild-type parasites was taken as the baseline (100%), and the relative infection rates of HMGR-overexpressing parasites were compared accordingly.

The findings demonstrated that parasites overexpressing HMGR showed approximately a two-fold increase in infectivity compared to wild-type organisms. This suggests that HMGR plays a significant role in enhancing the parasite's ability to infect host macrophages, likely due to its involvement in sterol biosynthesis and maintenance of membrane integrity. These results further support the importance of HMGR not only in parasite survival but also in its virulence, making it a promising target for antileishmanial drug development.

Studies in other organisms, particularly yeast, have demonstrated that the combined overexpression of sterol biosynthesis genes such as **ERG1** and **ERG11** results in a significant increase in total sterol content, reaching up to threefold compared to wild-type strains. These findings highlight the importance of coordinated regulation of enzymes within the sterol biosynthetic pathway.

HMG-CoA reductase (HMGR), being the rate-limiting enzyme of the mevalonate pathway, plays a crucial role in controlling the entry of substrates into the sterol biosynthesis pathway. By regulating this key step, HMGR influences the overall production of sterols, thereby affecting membrane composition, cellular growth, and organism viability. These observations further support the central role of HMGR in sterol metabolism and its potential as a strategic target for therapeutic intervention.

2.HMGR Inhibition Profiles

The antileishmanial activity of HMG-CoA reductase (HMGR) inhibitors has been evaluated using statins such as simvastatin (class I), atorvastatin (class II), and mevastatin. Among these, atorvastatin exhibited greater potency against *Leishmania donovani* promastigotes with an IC_{50} of approximately 19.4 µM, followed by mevastatin (≈23.8 µM), while simvastatin showed comparatively weaker activity (≈73.2 µM). At higher concentrations, simvastatin produced only partial inhibition. Importantly, all three statins demonstrated low cytotoxicity toward THP-1 differentiated macrophages, with IC_{50} values above 100 µM, indicating a favorable safety margin. The standard drug miltefosine showed stronger activity with a lower IC_{50} (~14.6 µM) against promastigotes.

In the intracellular amastigote stage, increased sensitivity to statins was observed. Atorvastatin showed an IC_{50} of approximately 6.75 µM, while mevastatin and simvastatin exhibited IC_{50} values of about 7.5 µM and 21.5 µM, respectively. This indicates that amastigotes are more susceptible to statin treatment compared to promastigotes. Miltefosine remained more potent with an IC_{50} of ~3.9 µM in this stage.

Enzymatic studies further confirmed that atorvastatin is a highly potent inhibitor of recombinant *Leishmania* HMGR, with inhibitory activity in the nanomolar range (~315 nM), whereas simvastatin and mevastatin required much higher (micromolar) concentrations (~43–42 µM) to achieve similar inhibition. Additionally, atorvastatin at low micromolar concentration produced strong suppression (~93%) of enzyme activity. Overall, these findings highlight atorvastatin as the most effective HMGR inhibitor among the tested statins, demonstrating superior antileishmanial activity with low host toxicity.

CONCLUSION:

Targeting HMG-CoA reductase (HMGR) represents a rational and promising strategy for the development of novel antileishmanial therapies, as the enzyme plays a central role in ergosterol biosynthesis and parasite survival. Evidence from multiple studies demonstrates that statins possess significant antiproliferative activity against *Leishmania donovani*, with atorvastatin consistently showing superior efficacy compared to other statins such as simvastatin and mevastatin. Atorvastatin exhibits stronger inhibition of both promastigote and amastigote stages and effectively suppresses HMGR activity at relatively low concentrations, while maintaining minimal cytotoxicity toward host macrophages.

Although these findings highlight atorvastatin as the most potent HMGR inhibitor among the evaluated statins, its antileishmanial activity has been demonstrated primarily at **low micromolar concentrations in vitro** and **nanomolar range at the enzyme level**, rather than as an established clinical dosage. Therefore, while atorvastatin emerges as a promising candidate for drug repurposing, further in vivo studies, pharmacokinetic evaluations, and clinical trials are essential to determine optimal dosing, safety, and therapeutic efficacy. Overall, continued research targeting HMGR may lead to the development of effective and selective treatments for visceral leishmaniasis.

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