Title: Optimized Lipid Nanoparticles for Pioglitazone Delivery: Molecular Docking Insights and In Vivo Efficacy in Nonalcoholic Steatohepatitis

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Abastact: Nonalcoholic steatohepatitis (NASH) is a progressive liver disease with limited therapeutic options, where pioglitazone (PGZ), a PPAR-γ agonist, has shown promise but suffers from poor solubility and systemic side effects. In this study, we developed and optimized lipid nanoparticles (LNP-PGZ) to enhance the targeted delivery and therapeutic efficacy of PGZ for the treatment of NASH. The formulation was designed to improve solubility and stability, and was characterized through detailed physicochemical analyses, including particle size distribution and *in vitro* dissolution studies. The optimized LNP-PGZ exhibited a particle size of 56.7 nm, a PDI of 0.113, an EE% of 85% and a DL% of 8.5%. Moreover, the optimized LNP-PGZ exhibited a controlled drug-release profile compared with free PGZ, suggesting improved therapeutic potential. Molecular docking studies further supported the formulation's effectiveness by demonstrating strong binding affinity of PGZ for key NASH-related targets, including PPAR-γ and STK25, highlighting its potential to modulate metabolic and inflammatory pathways. *In vivo* efficacy was evaluated in a rat model of NASH induced by a high-fat diet (HFD). Furthermore, LNP-PGZ significantly reduced liver damage in rats with HFD-induced hepatic injury, with 91.7% ($p < 0.001$) reduction in ALT and 86.8% ($p < 0.001$) in AST (Group IV) compared to the disease control (Group II). These findings collectively suggest that LNP-PGZ not only enhances its solubility and bioavailability but also amplifies its therapeutic benefits in NASH, potentially reducing off-target effects. This integrated approach, combining molecular modelling and *in vivo* validation, offers a promising platform for advancing safer, more effective treatments for liver diseases, such as NASH.

Keywords: Pioglitazone lipid nanoparticle solubility nonalcoholic steatohepatitis (NASH) molecular docking

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