Abstract

Currently, increasing prevalence of Non-Alcoholic Fatty Liver Disease (NAFLD) has become a worldwide health concern and it is one of the most common cause of chronic liver disease. It ranges from Non-Alcoholic Fatty Liver (NAFL, benign condition) to Non-Alcoholic SteatoHepatitis (NASH) which can result in fibrosis, cirrhosis, and ultimately, Hepatocellular Carcinoma (HCC). NASH is the more severe form of NAFLD and is characterized by the presence of hepatic steatosis, oxidative stress, inflammation and hepatocyte injury with or without fibrosis. The prevalence of NASH is seen more frequently in people with diabetes, obesity, insulin resistance, hyperlipidemia and hypertension. Therefore, NASH can be considered as hepatic manifestation of metabolic syndrome. At present, there is no approved drug for the treatment of NASH, although weight loss is recommended. Due to its high prevalence and lack of approved treatments, there remains a strong unmet medical need in NASH patients.

In this thesis, I am proposing G-protein coupled receptor 119 (GPR119) as a novel therapeutic target for the treatment of NASH. Since, GPR119 agonist increases plasma levels of the active forms of both Glucagon-Like Peptide-1 (GLP-1) and Gastric Inhibitory Peptide (GIP) in healthy and diabetic patients, the present study was undertaken to assess the effects of APD668, a GPR119 agonist, on postprandial lipemia and further explore the potential activity of GPR119 agonist alone or in combination with linagliptin, a Dipeptidyl Peptidase IV (DPPIV inhibitor) or fenofibrate, a Peroxisome Proliferator-Activated Receptors-α (PPAR-α) agonist in murine models of NASH.

**Keywords:** GPR119 agonist, GLP-1, diabetes, dyslipidemia, NASH, NAFLD