Title: Effects and underlying mechanism of plant secondary metabolites on insulin secretion regulation

Type 2 diabetes mellitus (T2DM) is a disease that associates insulin resistance and pancreatic β-cell dysfunction. Based on the current understanding of the pathophysiology of this disease, multiple anti-diabetic therapies have been developed to improve glycemic control and slow disease progression. Nevertheless, they have limited effectiveness and numerous side effects. In this context, plant extracts and their active constituents are considered an important area of seeking new anti-diabetic treatments.

This thesis aimed to find a natural source of secondary plant metabolites potentially able to protect β-cell function, induce insulin secretion in a glucose-dependent manner, and elucidate their mechanism of action.

Twenty plant extracts were phytochemically profiled using LC-MS, leading to identification and isolation of 39 pure compounds. Flavonoids, lignans and coumarins were screened for their ability to modulate β-cell function on INS-1 cell model. Some of the flavonoids and coumarins increased glucose-induced insulin secretion, while no such effect was observed for lignans. The mechanism of action of active metabolites was then investigated, by assessing their effects on cell electrical activity, intracellular calcium levels, and trace currents of calcium and potassium channels. The activity was also confirmed for pharmacopeial extracts containing coumarins.

These findings may have implications on the traditional use of angelica roots in treating T2DM. Insulinotropic effects of three pharmacopeial angelica roots were found and their metabolite profiles were correlated with pharmacological activity, with key structures responsible for modulation of insulin secretion identified. Mechanism of action of chosen metabolites was studied. Active plant metabolites may also become lead structures in the search for new anti-diabetic treatments, which should be further evaluated.

Keywords: type 2 diabetes, pancreatic beta-cell function, mechanism of action, coumarins, flavonoids, lignans.