Abstract

As a chronic multifactorial metabolic disorder characterized by hyperglycemia, diabetes mellitus has become one of the top death-leading diseases in the 21st century, and type 2 diabetes (T2D) accounts for more than 90% of all diabetes cases. Over the past few decades, the expenses for treatment of T2D have caused a heavy burden on global health system. Medicinal plants have for centuries been regarded as one of the major therapies human beings could rely on for treatment of various diseases, including T2D. Natural products research based on medicinal plants have provided a large number of potential drug candidates. However, natural products research still faces challenges such as bioassay-guided fractionation being laborious and time-consuming, and complete structural elucidation of complex natural products often being reported without determination of absolute configuration.

The overall aim of the present PhD thesis is on one hand to address the laborious and time-consuming process for identification of potential antidiabetic constituents’ from complex plant extracts by using off-line microplate-based high-resolution inhibition profiling combined with advanced hyphenated analytical technologies like HPLC-PDA-HRMS-SPE-NMR or HPLC-PDA-HRMS and NMR, and on the other hand to demonstrate the feasibility of dealing with the challenges of determining absolute configuration of natural product by using computational chemistry.

The antidiabetic activity in all projects of this thesis was against one, two or all three of the following T2D therapeutic targets: α-glucosidase, α-amylase and PTP1B. The medicinal plants used in the first and second project was Myrtus communis Linn., an evergreen shrub native to the Mediterranean area, with traditional use for treatment of diabetes. In the first project, microplate-based dual high-resolution PTP1B and α-glucosidase inhibition profiling combined with HPLC-HRMS and NMR were used to investigate the antidiabetic potential of the chloroform extract of M. communis leaves, resulting in identification of 14 bioactive triterpenoids and three bioactive phloroglucinol derivatives as well as determination of their mode-of-inhibition. Additionally, three previously undescribed phloroglucinol derivatives were identified. The results demonstrate the potential of M. communis as a bifunctional food for management of T2D. The first aim of the second project was to assess the antidiabetic activity of the ethyl acetate extract of M. communis leaves. Combined use of high-resolution α-glucosidase inhibition profiling with HPLC-HRMS and NMR identified one inseparable mixture and two pure α-glucosidase
inhibitors. The second aim was to investigate unique phloroglucinol derivatives from *M. communis*, which led to identification of 13 previously undescribed and two known galloylated alkylphloroglucinol glucosides, together with two known phloroglucinols. The absolute configuration of galloylated alkylphloroglucinol glucosides was for the first time determined by electronic circular dichroism (ECD) calculation and GC-MS experiments. In the third project, 48 crude extracts from 16 traditional Chinese medicinal plants belonging to six families were screened for α-glucosidase, α-amylase and PTP1B inhibitory activity. The results showed that 24 and 23 extracts showed more than 80% α-glucosidase and PTP1B inhibition, respectively, at a concentration of 50 µg/mL, while none of the extracts showed more than 20% α-amylase inhibition at 50 µg/mL. One of the most active extract - ethyl acetate extract of *Rhododendron capitatum* Maxim. was selected for further in-depth investigation by dual high-resolution α-glucosidase and PTP1B inhibition profiling, solid-phase extraction (SPE), and HPLC-PDA-HRMS-SPE-NMR, allowing identification of 19 previously undescribed and one known chromene meroterpenoids, among which ten exhibited dual inhibitory activity. Their biosynthetic precursor, and five other active secondary metabolites, including two known C-methylated flavanones and two known triterpenoids were also identified.

In conclusion, the results described in this thesis demonstrate the advantages of combined use of off-line microplate-based high-resolution inhibition profiling with hyphenated analytical techniques for natural products-based drug discovery: fast and efficient identification of both major and minor bioactive constituents from complex plant extracts.