Abstract

The prevalence of type 2 diabetes (T2D) has been continuously increasing during the past few decades due to the global epidemic of physical inactivity, excessive sugar and fat consumption, causing heavy socioeconomic burdens both on individual and global economies. Medicinal plants have been used to treat a wide spectrum of diseases including diabetes for generations and are remaining important resource for modern drug discovery. Natural product research is, however, discouraging in modern pharmaceutical industry partly ascribed to the biochemical complexity of natural extracts and incompatibility with current high-throughput screening (HTS) campaigns. The presented doctoral study aimed at addressing this obstacle in classical natural product research. An approach by combined using of high-resolution bioactivity profiling and advanced HPLC-HRMS-(SPE)-NMR analysis platform for rapid identifying anti-diabetic constituents from crude natural extracts is introduced for this purpose.

Five validated targets for the management of T2D, namely SGLT-2, α-glucosidase, α-amylase, PTP1B and oxidant stress are involved in this doctoral study. In the first project, two different approaches by using either transient transfected cells or proteliposomes were implemented in order to establish a stable SGLT-2 inhibitory assay for the high-resolution inhibition profiling purpose. Even though neither of these two approaches were realized in this project, the proposing of using proteoliposomes can be still considered as an alternative in future SGLT-2 assays. In project 2 and 3, the crude extracts of 41 plants collected from China were screened for α-glucosidase, α-amylase, and PTP1B inhibitory activity. The active ones were investigated by microplate-based high-resolution α-glucosidase/α-amylase/PTP1B inhibition profiling, which allows direct correlation of HPLC peaks with one or more of the tested bioactivities, followed by structural elucidation of the active peaks.
through HPLC-HRMS and NMR. This lead to the identification 21 potential antidiabetic constituents from four different plants *Polygonum cuspidatum*, *Dioscorea bulbifera* L., *Boehmeria nivea* Gaudich and *Tinospora capillipes* Gagnep. In project 4, quadruple high-resolution $\alpha$-glucosidase/$\alpha$-amylase/PTP1B/radical scavenging profiling combined with state-of art HPLC-HRMS-SPE-NMR platform were used for studying the polypharmacological properties of *Morus alba* L., which is used as an anti-diabetic principle in many traditional treatment systems globally. The obtained results allowed a detailed polypharmacological profiling of individual constituents in crude extract of *M. alba*, providing the scientific rationale for developing *M. alba* into a polypharmacological herbal remedies.

Collectively, the current studies have shown the potential of this advanced bioanalytical platform in rapid identification of bioactive constituents from natural extracts. In addition to that, with our best wishes, the outcome of these studies can be regarded as substantiating example of current advanced bioanalysis technology accelerating drug discovery oriented natural product research.