Natural products targeting mitochondria: A promising strategy for metabolic syndrome

QIANG Gui-Fen*

State Key Laboratory of Bioactive Substance and Function of Natural Medicines, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College and Beijing Key Laboratory of Drug Target and Screening Research, Beijing 100050, China

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Metabolic syndrome (MetS) is a complex pathophysiological state characterized by obesity, insulin resistance, dysglycemia, dyslipidemia and hypertension, which consequently contributes to coronary heart disease, stroke and other disabilities. The International Diabetes Federation (IDF) estimated that approximately 25% of the world’s population has MetS, with the increased prevalence in the advanced ages [1]. Metabolic syndrome originates from the imbalance between calorie intake and energy expenditure, and it is also affected by genetic/epigenetic factors. Up to now, no single remedy can cure MetS [2]. For drug therapy, natural products or medicinal herbal extracts have been used and proven effective in preventing and alleviating MetS with few adverse effects. It is well known that metformin, a natural product of Galega officinalis (goat’s rue or French lilac, a traditional herbal medicine in Europe), has been in use since 1957 as the first-line hypoglycemic agent. Metformin achieves anti-MetS effects with anti-obesity, lipid-lowering and improvement of insulin resistance [3]. Even, metformin was found to treat cancer, Alzheimer disease and aging. Of note, berberine, an alkaloid extracted from Berberis herbs which has been used to treat diarrhea and gastroenteritis in Traditional Chinese Medicine (TCM) with long history, was found to be the active pharmaceutical compound with its antimicrobial, anti-motility and anti-secretory properties. Recent studies reported that berberine potentially displays antidiabetic and lipid-lowering properties with reduction of body weight and improvement of insulin sensitivity [4]. Based on the traditional herbs, TCM has been utilized in a wide spectrum of diseases, its pivotal role in the Chinese culture was won by time-honored prescriptions and therapies. For MetS treatment, Jinqi Jiangtang Tablet (JQJTT), originated from a TCM formula composed of three herbs (Coptis chinensis, Astragalus membranaceus and Lonicera japonica), has been proven an effective prescription for diabetes in clinic [5]. Inspired by the successful application of natural products in MetS treatment, more and more single or combination of small molecules derived from traditional herbs were under investigation for anti-MetS drug discovery.

Mitochondria, as the powerhouse of the cell, play pivotal roles in energy (ATP) production, metabolism, and homeostasis, as well as orchestrate the cell survival and cell death signaling, which makes mitochondria a potential drug target of therapeutic importance in many diseases like cancer, ischemia, metabolic diseases and neurodegenerative diseases [6-7]. The current promising approaches include oxidative phosphorylation (OXPHOS) uncoupling, mitochondrial Ca2+ modulation, electron transport chain (ETC) inhibition and control of oxidative stress. Given that MetS is an imbalance between energy intake and energy expenditure, enhancement of energy expenditure becomes an attractive approach [8]. Brown adipose tissue (BAT) is rich in mitochondria with mitochondrial membrane protein-uncoupling protein 1 (UCP1) specifically and highly expressed on the inner membrane, which is responsible for burning fat and producing heat [9]. Brown fat activation and white adipose tissue (WAT) browning can increase the energy expenditure and improve glucose and lipid metabolism, which suggests an appealing therapeutic strategy for metabolic disorders [10-12]. Alkaloid, flavonoids, terpenoids, phenolic acids, long-chain fatty acids and other kinds of derivatives from traditional herbs have been tested in treating the MetS by promoting thermogenesis. Among them, Hui et al demonstrated that the polyphenol compound resveratrol regulated bile acid metabolism via gut microbiota remodeling, thereby activated brown fat and white fat browning, and ultimately improved glucose homeostasis in db/db mice [13]. AMP-activated protein kinase (AMPK), which is
important in keeping the ATP level normal, functions as a central regulator in maintaining the energy homeostasis and has become an emerging drug target for metabolic syndrome. AMPK activation has substantial beneficial effects in reducing lipid storage, blood glucose, blood pressure and nonalcoholic fatty liver disease (NAFLD) through phosphorylation of multiple substrates across distinct pathways [10]. As mentioned above, resveratrol, metformin and berberine have been proved to target mitochondrion and AMPK, and therefore exhibit the remarkable activities in treating MetS. Nevertheless, mitochondrial toxicology also needs to be considered in the prediction of drug safety, as to avoid the adverse effects by investigating whatever the direct drug-induced mitochondrial dysfunction or alterations in mitochondrial-relevant genes [7].

In this issue, we are pleased to publish one review and two original articles on pharmacology of natural products in treating metabolic diseases, including anti-obesity and hypoglycemic effects achieved via mitochondrial regulation. The issue begins with a paper reviewing the recent developments in the use of natural products for white adipose tissue browning as a novel strategy against MetS [13]. Hou et al. reported the hypoglycemic activity of puerarin, a natural flavone from Chinese medicinal herb Gegen, involving modulation of oxidative stress and mitochondrial function via AMPK activation [10]. Liu et al. found that the Chinese patent medicine, Jinqi Jiangtang Tablet: A review on its chemical constituents, quality control, pharmacokinetics studies, pharmacological properties and clinical applications [J]. J Ethnopharmacol, 2019, 236: 1-8.


References


