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Review

Natural products for the treatment of type 2 diabetes mellitus: Pharmacology and mechanisms

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ABSTRACT

Epidemiological studies have implied that diabetes mellitus (DM) will become an epidemic accompany with metabolic and endocrine disorders worldwide. Most of DM patients are affected by type 2 diabetes mellitus (T2DM) with insulin resistance and insulin secretion defect. Generally, the strategies to treat T2DM are diet control, moderate exercise, hypoglycemic and lipid-lowing agents. Despite the therapeutic benefits for the treatment of T2DM, most of the drugs can produce some undesirable side effects. Considering the pathogenesis of T2DM, natural products (NPs) have become the important resources of bioactive agents for anti-T2DM drug discovery. Recently, more and more natural components have been elucidated to possess anti-T2DM properties, and many efforts have been carried out to elucidate the possible mechanisms. The aim of this paper was to overview the activities and underlying mechanisms of NPs against T2DM. Developments of anti-T2DM agents will be greatly promoted with the increasing comprehensions of NPs for their multiple regulating effects on various targets and signal pathways.

Contents

1. Introduction

Diabetes mellitus (DM) is a complex chronic systemic disease accompanied by metabolic disorders, including hyperglycemia, hyperinsulinemia and hypertriglycer- idemia. The incidence of DM has greatly increased, and the numbers of patients have risen to more than 422 million until now, which will reach to 592 million in 2035. Currently, the global prevalence has been accounted for 8.5% among adults, which is rising more rapidly in middle- and low-income countries [1].

DM is classified into type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), in which T2DM accounts for nearly 95% of individuals [2]. T1DM is characterized by absolute insulin deficiency associated with pancreatic β cells destruction [3], while T2DM is mainly due to insulin resistance (IR) and deficiency in insulin secretion [4]. T2DM can cause multiple organs injury and a number of complications [5]. As shown in Fig. 1, some acute complications are mostly related to high mortality in diabetics, and the chronic complications are the most devastating consequence

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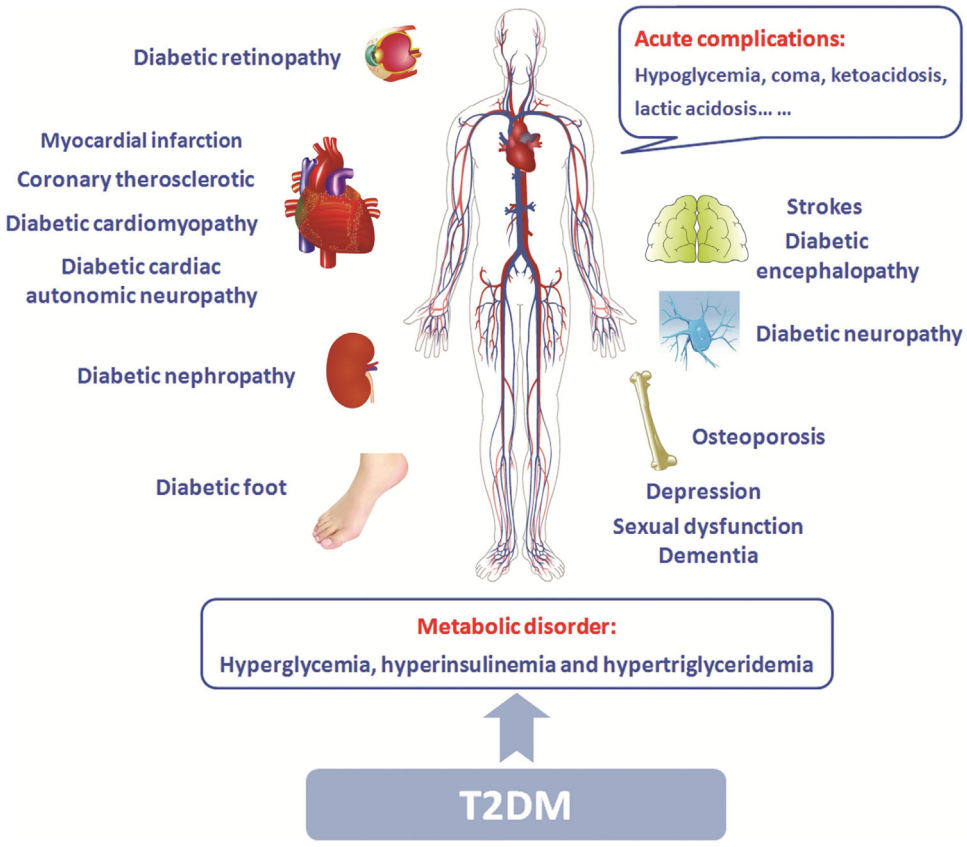

Fig. 1. The acute and chronic complications of T2DM.

caused by long-term high level of blood glucose. The microvascular lesions can cause diabetic retinopathy, diabetic nephropathy and diabetic neuropathy [6]. Additionally, the macrovascular complications include cardiovascular and cerebrovascular diseases [7]. Besides, T2DM can also cause the morbidity of depression [8], sexual dysfunction [9] and dementia [10]. For the chronic nature, T2DM has become a costly disease for patients and their families as well as the health system [11].

Weight loss and lifestyle changes can partly suppress hyperglycemia to manage T2DM [12]. Nevertheless, some anti-diabetic drugs are required to control glycemic level. However, some undesirable adverse effects including hypoglycemia, fluid retention, osteoporosis and heart failure have occurred after application of oral anti-diabetic agents [13–15], which limit their clinical applications. Thus, it is necessary to develop new anti-diabetic candidates with few side-effects to control hyperglycemia, hyperinsulinemia and hypertriglyceridemia.

Natural products (NPs), including herbal formulas and its extracts, have been used to treat human diseases with the unique system of theories and therapies for thousands of years [16], which have also been increasingly applied to treat T2DM [17,18]. In recent years, the effects and mechanisms of NPs have attracted more and more attentions [19]. Therefore, the articles about NPs against T2DM were included in this review. The aim of this paper was to overview the main factors/pathways associated with T2DM, and comprehensively review the current understandings of NPs against T2DM.

2. Pathogenesis process of T2DM

IR and β cell dysfunction can lead to absolute insulin deficiency, which are the critical inducements of T2DM. Insulin sensitivity can be affected by glucose and lipids overloading, oxidative stress, inflammation, adipokines, autophagy, and disordered insulin secretion [20]. Obesity, a main predisposition, plays an important role in the pathogenesis of T2DM [21–23], which can lead to cellular oxidative stress and IR, cytokines release, lipid-induced impairment, and dysfunctional protein tyrosine phosphatase signaling [24,25]. During oxidative stress, the generation of reactive oxygen species (ROS) can cause DNA damage, organelle injury and cell dysfunction [26,27].

With the overloaded nutrient intake, excess calories are stored in adipose tissue. Nonetheless, the unlimited expansion ability of fat cells to store calories is finite, and thus the hypoxia appears in adipose tissue. Subsequently, hypoxia inducible factor-1 (HIF-1) [28] is activated to cause the increased expression of c-Jun N-terminal kinase (JNK) and inhibitor nuclear factor kappa-B kinase (IKK) to produce inflammation in adipose tissue [29]. In turn, with the aggravation of inflammation, a large number of inflammation cytokines are released to further exacerbate IR [30] and lipolysis [31]. In addition, inflammation cytokines can further reduce the activity of peroxisome proliferator-activated receptor γ (PPARγ), and accelerate the fat cell death and inflammation [32]. With IR development, the activity of insulin as an anti-lipolytic hormone decreases [33]. Hyperinsulinemia can activate the lipoprotein lipase and caused free fatty acid (FFA) released from lipoprotein triglycerides hydrolysis. Whilst, endoplasmic reticulum (ER) stress is involved and JNK pathway is activated (shown in Fig. 2) [34]. Accordingly, IR and increased flux of FFA in adipose tissue can form a vicious cycle. High level of FFA is released from fat cells into circulation, transported and accumulated in other organs to further induce the lipotoxicity and expedite the systemic IR [33].

Liver, as one target organ sensitive to insulin, plays the most important role in maintaining stable level of blood glucose through

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