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Review

Dietary triterpenes in the treatment of type 2 diabetes: To date

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ABSTRACT

At present, the importance of triterpenes in food and pharmaceutical industries is mainly based on their potential application in health food and medicine, particularly those commonly used in the treatment of diabetes and its complications. The purpose of this study is to review potential dietary triterpene in the treatment of diabetes and to identify the relationship of the structure and its activity of these compounds with their effective mechanisms. We summarized the latest developments of natural dietary triterpene and terpene-rich material, and discussed their underlying molecular mechanisms of anti-diabetic potential. We also suggested a better evaluation of the pharmacological profile of triterpenes and their derivate with a clear-cut choice of possible human pathologies.

1. Molecular and metabolic mechanisms of insulin resistance in type 2 diabetes mellitus

Diabetes mellitus (DM) is a metabolic disorder which results from intricate associations between multiple environmental and genetic or lifestyle elements. The disorder is distinguished with a chronic hyperglycemic status resulting from reduced sensitivity to insulin predominately presented in the liver, adipose tissues and skeletal muscles or due to insulin deficiency of non-autoimmune etiology and impaired insulin signaling (Manosroi, Moses, Manosroi, & Manosroi, 2011). Long term diabetes conspires with other comorbidities like ischemic heart disease, stroke, erectile dysfunction, blindness, delayed wound healing and micro or macro-vascular complications including retinopathy, neuropathy, and nephropathy (Long & Dagogo-Jack, 2011). (see Table 1)

The global pandemic of DM places an incalculable load on health care systems. This chronic metabolic disorder is influencing more than 336 million people worldwide, far beyond the 285 million as reported by the World Health Organization (WHO) for 2010 from global statistics collected in 2008. In another word, there might have been over 6.8% of global death rate (equal to 4 million) in 2010 that could be ascribed to diabetes directly or indirectly (Hussain & Marouf, 2013). Theoretically, this figure is expected to escalate by the year of 2030, explaining the reason for global diabetes cost in 2010 which was around 12% for total global health care (equal to $320 billion) (S. Sharma, Choudhary, Bhardwaj, Choudhary, & Rana, 2014). According to Marisa (Mendes & Bogle, 2015), a statistic report by International Diabetes Federation, China has the highest number of diabetic patients of 92.3 million, followed by 63 million in India and 24.1 million in USA, gaining enormous tolls at public health, individual, and economic levels.

There are two forms of primary syndrome, resulting from either lack of insulin secretion by beta cells of the pancreas (type 1 diabetes mellitus, T1DM or insulin dependent diabetes mellitus, IDDM), or induced by impaired sensitivity of insulin to target tissues (non-insulin dependent diabetes mellitus, NIDDM or type 2 diabetes mellitus, T2DM). Withal, T1DM stands for only 10% of all diabetes cases, influencing nearly 20 million of all age groups world-wide (Ozougwu, 2013). The main pathophysiological cause ascribing to the DM development is T2DM, accounting for at least 90%, among all diabetes mellitus cases (Ozougwu, 2013). This incidence of T2DM upsurges with age, and it was found that majority of cases are diagnosed after the age of 40 (Kaku, 2010).

A widely acknowledged concept for T2DM is a heterogeneous and polygenic disorder resulting from genetic susceptibility, characterized by damaged insulin signaling, or insulin resistance, and a relative insulin deficiency of non-autoimmune etiology, and environmental elements involving over eating, obesity, stress, lack of exercise, and aging

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Table 1
List of important terpenoids and their molecular targets used in the treatment of T2DM.

Plant Name	Phyto- constituents	Part used	Model	Target pathways/mediators	References
Ficus racemosa	α-amyrin acetate	Fruits	Streptozotocin induced diabetic rats (STZ)	NF-κB, IL-1β, COX-2, CREB, ERK, PKC, P38 MAPK	Falodun et al., 2009
Andrographis paniculata	Andrographolide	Leaves	Streptozotocin induced diabetic rats (STZ)	ERK, (AP)-1, I??B kinase ?? (IKK??)/ r (IRF)-3	Nugroho et al., 2012
Gymnema sylvestre	Gymnemic acid IV	Leaves	Streptozotocin induced diabetic rats (STZ)	MAPK, p38, GLUT4	Patel et al., 2012
Lagerstroemia speciosa	Colosolic acid, maslinic acid	Leaves	Streptozotocin induced diabetic rats (STZ)	MAPK, p38, GLUT4, PI3K, AMPK	Switi, Mohan, & Rani, 2014
Panax species	Ginsenosides	Rhizomes	Alloxan-induced hyperglycemic mice	NF-κB, Bax, caspase-3, caspase-8, Bcl-2, IAP, XIAP, cyclin B1, cyclin D, cdk2, cdk4, VEGF, MAPK, IL-1β, TNF-α, ICAM-1, JNK	Bu et al., 2012
Azadirachta indica	β-sitosterol	Whole parts	Streptozotocin induced diabetic rats (STZ)	COX, PGE2, NF-κB	Switi et al., 2014
Coleus forskohlii	Forskolin	Whole parts	Streptozotocin induced diabetic rats (STZ)	cAMP, PI3K, AMPK	Rozenberg, Smirin, Sampson, & Rosenzweig, 2011; Switi et al., 2014
Aralia elata	Elatosides E	Root cortex	Streptozotocin induced diabetic rats (STZ)	AMPK, IR/IRS-1/PI3K/Akt	
Aesculus hippocastanum	Escins	Seeds	Streptozotocin induced diabetic rats (STZ)	NF-κB, STAT3, JAK2, cyclin D1, Bcl-2, Bcl-xL, survivin, Mcl-1, VEGF, COX-2, MMP9	Switi et al., 2014
Bumelia sartorum	Bassic acid	Root bark	Streptozotocin induced diabetic rats (STZ)	JNK/IRS1/PI3K	Zarei et al., 2015
Momordica charantia	Charantin	Seeds, fruits	Streptozotocin induced diabetic rats (STZ)	MAPKs, SAPK/JNK, p38, and p44/42, of NF-κB	Desai and Tatke, 2015

(Bahmani et al., 2014; Li, Ji, Zhong, Lin, & Lv, 2015). Diabetes is typically idiopathic, relating to environmental factors and multiple genes to varying extents. Under normal physiological circumstances, insulin controls blood glucose homeostasis within a narrow range via stimulation of glucose uptake into peripheral tissues mainly skeletal muscle as well as fat tissue through inhibiting the release of stored lipids from adipose tissue by liver. In T2DM, this mechanism is halted when insulin secretion is impaired via a dysfunction of the pancreatic β-cell, and compromised insulin action because of insulin resistance, therefore resulting in multiple metabolic abnormalities (Kaur, 2014).

It is well known that insulin resistance is the major contributor to the pathogenesis of T2DM. Clinically, insulin resistance is explained as a state when insulin in the body does not play a sufficient action proportional to its blood concentration to conserve a normo-glyceamia. On cellular level, it is defined as deficient insulin signaling strength from downstream receptor to the final substrates in multiple and mitogenic aspects of cellular functions (Fujioka, 2007). In insulin resistant plight, the lesion of insulin action in main target organs (liver and muscles) does not properly respond to insulin and by that inducing hyper-glycaemia and a reactive escalation of insulin excretion by β cells of pancreas. At this condition, the poor insulin responsiveness can only be reimbursed for limited time only, which further impairs insulin resistance. This depraved cycle finally points to brawl of fragile balance between insulin resistance and β cell functions, which leads to manifestation of T2DM (Matough, Budin, Hamid, Alwahaibi, & Mohamed, 2012).

Irrespective to the fundamental pathophysiological processes, the metabolic amendments that result from hyperglycemia ultimately lead to functional and/or structural changes in virtually all tissues. The most distinguished damage is to endothelium, which plays an imperative part in the pathogenesis of the macrovascular complications or due to injury of larger blood vessels (peripheral arterial disease, coronary artery disease, and stroke) and microvascular complications or due to injury to smaller blood vessels (diabetic nephropathy, neuropathy, and retinopathy). Though, other tissues are important as well as evinced, for instance by the contribution of structural changes in connective tissue, causing diabetic foot disorders in which severe infections could lead to amputation and impotence as well (Pivonello et al., 2010; Prabhakar, 2016).

Despite an enormous amount of research, the exact pathogenetic mechanisms leading to the complications of T2DM is still far from clear. Unifying theory where the root cause of T2DM is abnormalities in both insulin action and secretion (Chen & Kang, 2013a; Chen & Kang, 2013b). This was supposed to be the initiating step that led to direct result of obesity-associated exposure of tissues to elevated dietary nutrients, resulting in the accumulation of toxic metabolic by-products (Arora, 2010). Nonetheless, research has indicated that other factors may also be crucial, including inter-organ communication networks mediated by inflammatory molecules (cytokines) and peptide hormones, and activation of intracellular stress response pathways. Even though the detailed pathophysiological sequence leading to insulin resistance is still mostly indefinite, investigations have been ascribed to a deeper comprehension of the underlying molecular mechanisms (Soumaya, 2012, pp. 240–251). This review deals with the fundamental pathway related to basic pathophysiological mechanisms of insulin resistance in type 2 diabetes mellitus.

Insulin is a hormone, released by pancreatic beta cells in response to elevated levels of sugar in the blood. Insulin wields multiple effects upon target cells predominately muscle, liver, and adipose tissue. In general, insulin promotes storage of fuels (glucose, fatty acids and amino acids) as glycogen and triglyceridesplus that inhibits the breakdown of stored fuel during fed state (Steiner, Crowell, & Lang, 2015). The ratio constrains the glucose uptake of the whole body, which is the initial step of glucose transport into skeletal muscle cells, accounting for over 75% of glucose uptake; meanwhile, insulin has controlled functions on glucose output and breakdown of fats. During the fasting state,