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Review Article

Phytochemicals for Non-insulin Diabetes Mellitus: A Minireview on Plant-Derived Compounds Hypoglycemic Activity

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Abstract: Diabetes mellitus (DM), a group of chronic metabolic disorders characterized by hyperglycemia resulting from defects in insulin action and/or insulin secretion. It represents one of the main contributors to ill health and premature mortality worldwide and its prevalence has been rising during the last decades. Unfortunately, many antidiabetic agents for diabetes either have inadequate efficacy or significant mechanism-based side effects. A great deal of interest has been developed to the various natural bioactive compounds isolated and characterized from medicinal plants. This review focuses specifically on four nature phytochemicals such as polysaccharides, flavonoids, saponins and alkaloids whose properties are potencial to antidiabetic remedy.

Keywords: Diabetes Mellitus, Hypoglycemic, Phytochemicals

1. Introduction

Diabetes mellitus (DM) is a metabolic disorder which is characterized by the presence of persistent hyperglycemia due to defective insulin secretion, insulin action, or both [1]. Symptoms of high blood sugar include increased thirst, frequent urination and increased hunger [2]. Over time, diabetes can damage the heart, eyes, blood vessels, kidneys, and nerves. Furthermore, hyperglycemia can stimulate oxidative stress by the autoxidation of glucose in the presence of transition metals as well as the generation of reactive oxygen species (ROS) during the process of glycation, and also can induce vascular injury through complex overlapping pathways, formation of advanced glycation end products, activation of protein kinase C and generation of ROS [3]. The number of people with diabetes in the world has risen from 108 million in 1980 to 422 million in 2014 [4], with more than 80% of these deaths occurring in underdeveloped and developing countries [5]. The World Diabetes Foundation estimates that there will be 438 million people with diabetes by the year 2030. Type 2 diabetes mellitus is the most common form of diabetes comprising of 90% to 95% of all diabetes cases [6]. It is strongly influenced by the complex interplay of genetic determinants of individual susceptibility and environmental factors, including lifestyle, eating behaviour, and physical activity [7]. The global diabetes market featuring insulin products is worth $20.8 billion in the recent times, including administration and diagnostic devices. Monitoring devices and other related equipment are established with an investment of $13.5 billion. Global market for diabetes therapies and diagnostics is to be worth $51.2 billion in 2015.

The current synthetic agents for type 2 diabetes have their own characteristics and advantages on the hypoglycemic mechanism of controlling sugar, like sulfonylurea stimulating insulin release by pancreatic beta cells by inhibiting the ATP-sensitive potassium (channel [8], biguanides acting on the liver to reduce gluconeogenesis and causing a decrease in insulin resistance via increasing AMP-activated protein kinase (AMPK) signaling [9]. Alpha-glucosidase inhibitors reducing glucose absorbance by acting on small intestine to cause decrease in production of enzymes needed to digest carbohydrates, thiazolidinediones reducing insulin resistance by activating peroxisome proliferator-activated receptor-γ (PPAR-γ) in fat and muscle, etc. [10]. But these drugs are expensive, scarce especially in rural areas and can't improve other body's functions especially having certain side effects and even toxicity [11]. So, alternativing approaches to diabetes management such as isolation of phytochemicals with hypoglycemic activities from medicinal plants is therefore imperative. Current understanding is almostly based on the majority of data provided by *in vitro* and *in vivo* animal studies. However, these data cannot be extrapolated into the human setting without reliable human data which is warranted given the strong evidence of potential effects. Research had shown that some natural phytochemicals like polysaccharides, flavonoids, saponins and alkaloids have hypoglycemic effects.

2. Natural Hypoglycemic Substances

2.1. Polysaccharides

Polysaccharides are polymeric carbohydrate molecules composed of long chains of monosaccharide units bound together by glycosidic linkages. They are abundant in plants and the source of all biological energy [12]. Recently, polysaccharides have aroused great attention for their unique bioactivities and chemical structures. A variety of useful bioactivities, such as anti-aging, antioxidant, anti-tumor, anti-inflammatory, hypolipidemic and hypoglycemic properties have been reported [13]. Polysaccharides of plants, fungi, algae, animals and bacteria have shown anti-diabetic properties *in vivo* and *in vitro* experiments by alleviating β-cell dysfunction in addtion to eliciting other anti-diabetic activities [14]. Levan polysaccharide is effective in the protection of liver, kidney, pancreas and heart tissue from the damage of alloxan-induced diabetic rats [15]. Moreover, polysaccharide from *Acacia tortilis* is also devoid of adverse effect like constipation, reduced high-density lipoprotein cholesterol, increased serum glutamic pyruvate transaminase for which acarbose is criticized clinically [16].

2.2. Flavonoids

Flavonoids are a subdivision of polyphenols that are highly present in fruits, vegetables, nuts, seeds, stem, flowers, tea, and the most ubiquitous part of plant constituents [17]. Chemically, flavonoids have the general structure of a 15-carbon skeleton, which consists of two phenyl rings and heterocyclic ring. Flavonoids include chalcones, flavanones and their derivatives [18]. It is important antioxidants and promotes several health effects. In recent years various approaches have been made to utilize the flavonoids in animal model to by incorporating few novel methods to improve its antidiabetic propert. Flavonoids in diabetes usually alternate the diabetes treatment by reducing the aldose rudctase, regenerating the pancreatic cells, enhancing insulin release and incresing calcium ion uptake [19]. The role flavonoids are quite important in fighting with the complications of diabetes mellitus than any other method of treatment [20]. Also, flavonoid stimulated glycogen synthesis in rat soleus muscle through mechanisms well known to insulin signal transduction [21]. Almost all the flavonoids having potential for antidiabetic activity but they are limited in usage on account of deprived solubility and bioavailability.

2.3. Saponins

Saponins are bioactive compounds generally considered to be produced by plants and second metabolites which act as a chemical barrier or shield in the plant defense system to counter pathogens and herbivores [22]. They have long attracted scientific attention, due to their structural diversity and significant biological activities [23]. Saponins have been found having pharmaceutical properties of anti-inflammatory, antifungal or antiyeast, antibacterial, antiparasitic, antitumor, antiviral and antidiabetes [24]. In the aspect of antidiabetes, saponarin activates AMPK in a calcium-dependent manner, thus regulating gluconeogenesis and glucose uptake [25]. Saponins from *Polygonatum kingianum* could effectively alleviate hyperglycemia in diabetic rats by up-regulating the expression of glucose transporter type 4 (GLUT4) while down-regulated the expression of G6P in insulin signal pathway [26].

2.4. Alkaloids

Alkaloids are a group of naturally chemical compounds that mostly contain basic nitrogen atoms. Specifically, they are amphipathic glycosides grouped phenomenologically by the soap-like foaming they produce when shaken in aqueous solutions, and structurally by having one or more hydrophilic glycoside moieties combined with a lipophilic triterpene derivative. Alkaloids are one of the largest classes of secondary metabolites and many alkaloids are pharmacologically active [27]. Medical use of alkaloid-containing plants has a long history. Three norditerpenoid alkaloids from the seeds had anti-diabetic effect by activating the phosphatidylinositol 3-kinase (PI3K)/Akt insulin signaling pathway and suppressing the protein-tyrosine phosphatase-1B (PTP-1B) in cellular models [28]. Vindogentianine, an indole alkaloid, had hypoglycemic activity by enhancing the glucose uptake and PTP-1B inhibition, implying its therapeutic potential against type 2 diabetes [29].

3. Hypoglycemic Mechanisms

In conclusion, the hypoglycemic mechanisms of these nature phytochemicals are α-glucosidase and α-amylase inhibition as well as up-regulating the expression of GLUT4 which is the insulin-regulated glucose transporter found primarily in adipose tissues and striated muscle, activating

AMPK, PI3K/Akt signal pathways and suppressing PTP-1B (Figure. 1). The AMPK system is a key player in regulating energy balance at both the cellular and whole-body levels, placing it at centre stage in studies of obesity, diabetes and the metabolic syndrome [30]. In type 2 DM, the major insulin-resistant organs include liver, muscle, and adipose tissue [31, 32]. Liver AMPK controls glucose homeostasis mainly through the inhibition of gluconeogenic gene expression and hepatic glucose production. Chronic muscle AMPK activation, by exercise training and by AICAR treatment, can further enhance muscle lipid breakdown and the capacity for ATP generation by transcriptional activation of mitochondrial fatty acid β-oxidation enzymes via PGC-1α [33]. The PI3K/AKT are important in internalizing the effects of external growth factors and of membrane tyrosine kinases. Activation of membrane kinases including epidermal growth factor receptor (EGFR) by external growth factors initiates receptor dimerization and subsequent events to activate these intraCell ular pathways. AKT is activated downstream of PI3K and has multiple targets [34]. PTP-1B acts as a negative regulator of insulin signaling by dephosphorylating the phosphotyrosine residues of insulin receptor kinase. PTP-1B dephosphorylates epidermal growth factor kinase as well as Janus kinase 2 (JAK2) and tyrosine kinase (TYK2) in cell growth control and cell response to interferon stimulation [35].

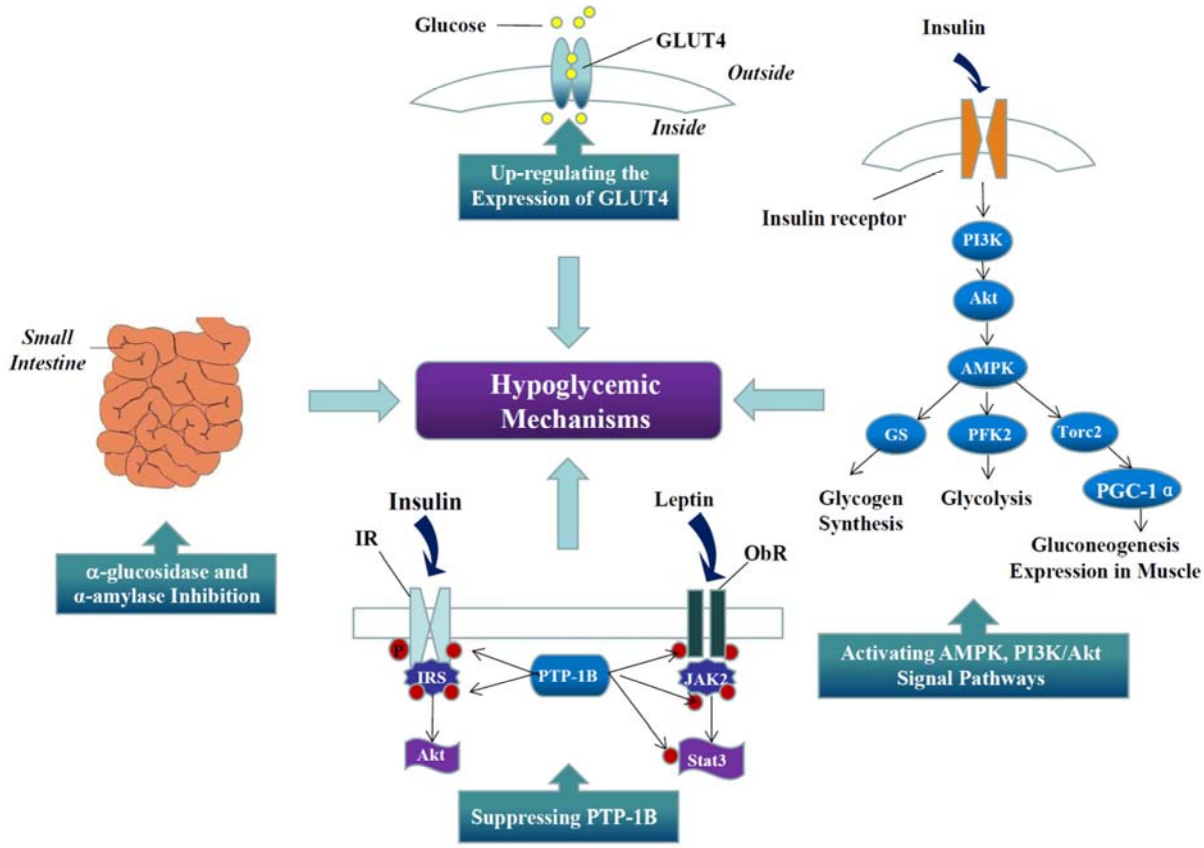

Figure 1. *Hypoglycemic mechanisms of nature phytochemicals.*

4. Discussion

Diabetes mellitus especially the type 2 diabetes is the most common chronic tetabolic disease in modern society. Those synthetic agents are associated with prominent adverse effects. With the development of modern molecular biology and pharmaceutical engineering, there is growing interest in the potential use of medicinal plants to treat various disorders due to the advantages of them being cheaper, less toxic and having fewer side effects. Diabetes is the wide spread pandemic disease resulting in increased morbidity and mortality, so it is of importance to develop a variety of hypoglycemic synthetic drugs with phytochemicals which are stable, less side effects of hypoglycemic activities and madicative for diabetes chronic complications. This review provides some feasible ideas to researchers in the hypoglycaemic field that it is significant of commercial and clinical value to deepening the research on further and clear pharmacology, toxicology and hypoglycemic mechanism of those natural phytochemicals which may have the potential to be used in the prevention or in the management of diabetes.

5. Conclusion

With the effects of globalization and industrialization, human environment, and human behavior and lifestyle have undergone significant changes, which have resulted in escalating rates of both obesity and diabetes. Currently available therapies for diabetes include insulin and various oral antidiabetic agents which are used as monotherapy or in combination to achieve better glycemic regulation. But many of those antidiabetic agents for diabetes either have inadequate efficacy or significant mechanism-based side effects. Therefore, the search for more effective and safer hypoglycemic agents has continued to be an important area of investigation. A lot of natural resources which contained phytochemicals such as polysaccharides, flavonoids, saponins, and alkaloids have hypoglycemic activities and some of their hypoglycemic mechanisms, which are α-glucosidase and α-amylase inhibition as well as up-regulating the expression of GLUT4, activating AMPK, PI3K/Akt signal pathways and suppressing PTP-1B have been clarified.

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References

[1] Mazzone T, Chait A, Plutzky J. Cardiovascular disease risk in type 2 diabetes mellitus: insights from mechanistic studies. [J]. Lancet, 2008, 371 (9626): 1800-1809.

[2] Kitabchi A E, Umpierrez G E, Miles J M, et al. Hyperglycemic crises in adult patients with diabetes [J]. Diabetes Care, 2009, 32 (12): e157.

[3] Jha P K, Sanyal S P. Hypoglycemic, antiperoxidative and antihyperlipidemic effects of saponins from *Solanum anguivi* Lam. fruits in alloxan-induced diabetic rats [J]. South African Journal of Botany, 2013, 88 (9): 56-61.

[4] Guariguata L, Whiting D R, Hambleton I, et al. Global estimates of diabetes prevalence for 2013 and projections for 2035 [J]. Diabetes Research and Clinical Practice, 2014, 103 (2): 137-149.

[5] Tahrani A A, Bailey C J, Del P S, et al. Management of type 2 diabetes: new and future developments in treatment [J]. American Journal of Medicine, 2012, 378 (9786): 182-97.

[6] Pigarova E A. Comments on: Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline From the American College of Physicians [J]. Obesity and Metabolism, 2012 (2): 66.

[7] Dey L, Attele A S, Yuan C S. Alternative therapies for type 2 diabetes. [J]. Alternative Medicine Review A Journal of Clinical Therapeutic, 2002, 7 (1): 45-58.

[8] Tsubouchi H, Inoguchi T, Inuo M, et al. Sulfonylurea as well as elevated glucose levels stimulate reactive oxygen species production in the pancreatic beta-cell line, MIN6-a role of NAD(P)H oxidase in beta-cells [J]. Biochemical and Biophysical Research Communications, 2004, 326 (1): 60-65.

[9] Meyler's Side Effects of Drugs (Sixteenth Edition), 2016, Pp 969-983.

[10] Yasmin S, Jayaprakash V. Thiazolidinediones and PPAR orchestra as antidiabetic agents: From past to present [J]. European Journal of Medicinal Chemistry, 2016, 126: 879.

[11] Zhao C, Wu Y J, Yang C F, Liu B, Huang Y F. Hypotensive, hypoglycemic and hypolipidemic effects of bioactive compounds from microalgae and marine microorganisms [J]. International Journal of Food Science and Technology. 2015, 50 (8): 1705-1717.

[12] Zhao C, Liao Z, Wu X, Liu Y, Liu X, Lin Z, Huang Y, Liu B. Isolation, purification, and structural features of a polysaccharide from Phellinus linteus and its hypoglycemic effect in alloxan-induced diabetic mice [J]. Journal of Food Science. 2014, 79 (5): H1002-1010.

[13] Tian C Y, Hai-Mei B O, Ji-An L I. Influence of mori fructus polysaccharide on blood glucose and serum lipoprotein in rats with experimental type 2 diabetes [J]. Chinese Journal of Experimental Traditional Medical Formulae, 2011.

[14] Wu J, Shi S, Wang H, et al. Mechanisms underlying the effect of polysaccharides in the treatment of type 2 diabetes: A review. [J]. Carbohydrate Polymers, 2016, 144: 474.

[15] Dahech I, Belghith K S, Hamden K, et al. Antidiabetic activity of levan polysaccharide in alloxan-induced diabetic rats. [J]. International Journal of Biological Macromolecules, 2011, 49 (4): 742-6.

[16] Bisht S, Kant R, Kumar V. α-D-Glucosidase inhibitory activity of polysaccharide isolated from Acacia tortilis gum exudate. [J]. International Journal of Biological Macromolecules, 2013, 59: 214-220.

[17] Seleem D, Pardi V, Murata R M. Review of flavonoids: A diverse group of natural compounds with anti-Candida albicans activity in *vitro* [J]. Archives of Oral Biology, 2016.

[18] Guan L, Liu B. ChemInform Abstract: Antidepressant-like effects and mechanisms of flavonoids and related analogues [J]. European Journal of Medicinal Chemistry, 2016, 121 (41): 47-57.

[19] Mohan S, Nandhakumar L. Role of various flavonoids: Hypotheses on novel approach to treat diabetes [J]. Iranian Journal of Medical Hypotheses and Ideas, 2014, 8(1): 1-6.

[20] Hussain S A, Marouf B H. Flavonoids as alternatives in treatment of type 2 diabetes mellitus [J]. 2013, 1: 31-36.

[21] Cazarolli L H, Folador P, Moresco H H, et al. Stimulatory effect of apigenin-6-C-beta-L-fucopyranoside on insulin secretion and glycogen synthesis. [J]. European Journal of Medicinal Chemistry, 2009, 44 (11): 4668-4673.

[22] Augustin J M, Kuzina V, Andersen S B, et al. ChemInform abstract: molecular activities, biosynthesis and evolution of triterpenoid saponins [J]. Cheminform, 2011, 72 (6): 435.

[23] Hua L, Wen H, Wen Y Q, et al. Anti-thrombotic activity and chemical characterization of steroidal saponins from *Dioscorea zingiberensis* C. H. Wright. [J]. Fitoterapia, 2010, 81(8): 1147.

[24] Sparg S G, Light M E, Van S J. Biological activities and distribution of plant saponins [J]. Journal of Ethnopharmacology, 2004, 94 (2-3): 219-243.

[25] Seo W D, Ji H L, Jia Y, et al. Saponarin activates AMPK in a calcium-dependent manner and suppresses gluconeogenesis and increases glucose uptake via phosphorylation of CRTC2 and HDAC5 [J]. Bioorganic and Medicinal Chemistry Letters, 2015, 25 (22): 5237.

[26] Lu J M, Wang Y F, Yan H L, et al. Antidiabetic effect of total saponins from *Polygonatum kingianum* in streptozotocin-induced daibetic rats. [J]. Journal of Ethnopharmacology, 2015, 179: 291-300.

[27] Iwasa K, Moriyasu M, Tachibana Y, et al. Simple isoquinoline and benzylisoquinoline alkaloids as potential antimicrobial, antimalarial, cytotoxic, and anti-HIV agents. [J]. Bioorg Med Chem, 2001, 9 (11): 2871-2884.

[28] Tang D, Chen Q B, Xin X L, et al. Anti-diabetic effect of three new norditerpenoid alkaloids in *vitro* and potential mechanism via PI3K/Akt signaling pathway [J]. Biomedicine and Pharmacotherapy, 2017, 87: 145-152.

[29] Tiong S H, Looi C Y, Arya A, et al. Vindogentianine, a hypoglycemic alkaloid from Catharanthus roseus (L.) G. Don (Apocynaceae) [J]. Fitoterapia, 2015, 102: 182-188.

[30] Hardie D G. AMPK: a key regulator of energy balance in the single cell and the whole organism. [J]. International Journal of Obesity, 2008, 32 Suppl 4: S7.

[31] Kelley D E, Goodpaster B, Wing R R, et al. Skeletal muscle fatty acid metabolism in association with insulin resistance, obesity, and weight loss [J]. American Journal of Physiology, 1999, 277 (277): E1130-41.

[32] Hashem R M, Rashed L A, Hassanin K M, et al. Effect of 6-gingerol on AMPK- NF- B axis in high fat diet fed rats [J]. Biomedicine and Pharmacotherapy, 2017, 88: 293.

[33] Zhang B B, Zhou G, Li C. AMPK: an emerging drug target for diabetes and the metabolic syndrome.[J]. Cell Metabolism, 2009, 9 (5): 407-416.

[34] Zhang J, Zhi X, Shi S, et al. SPOCK1 is up-regulated and promotes tumor growth via the PI3K/AKT signaling pathway in colorectal cancer. [J]. 2016.

[35] Tonks N K. PTP1B: from the sidelines to the front lines [J]. Febs Letters, 2003, 546 (1): 140-148.