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Review

Anthocyanins as promising molecules and dietary bioactive components against diabetes – A review of recent advances

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ABSTRACT

Background: Diabetes is a metabolic disorder characterized by presence of chronic hyperglycaemia. Thus, strategies to maintain blood glucose levels are critical for the treatment of this devastating disease. Anthocyanins are naturally occurring compounds widely available in berries, and increasing evidence demonstrates a positive relationship between consumption of anthocyanins rich foods and lowers diabetes complications.

Scope and approach: This review highlights recent findings on the anti-diabetic effects of anthocyanins in various organs and particularly emphasizes on the studies that investigated the cellular and molecular mechanisms involved in the beneficial effects of this bioactive molecules.

Key findings and conclusions: Over the past two decades, numerous studies have demonstrated that anthocyanins can exert the beneficial effects in diabetes by acting on various molecular targets and regulate different signalling pathways in multiple organs and tissues such as liver, pancreas, kidney, adipose, skeletal muscle and brain. Anthocyanins can lower blood glucose levels by protecting β-cells, improving insulin resistance, increasing insulin secretion, improving liver function, and inhibiting carbohydrate hydrolyzing enzymes. The antidiabetic properties of anthocyanins may also attribute to their antioxidant capacity. Taken together, anthocyanins may be a novel small molecule for the prevention and treatment of diabetes.

1. Introduction

Diabetes mellitus (DM) is a noncommunicable and severe endocrine metabolic disorder which has the ability to induce serious complications in various organs (C. Zhang et al., 2012). The number of DM affected people are increasing day by day, and approximately the number would reach to around 300 million by the year 2025 (King, Aubert, & Herman, 1998). According to WHO studies, by 2030, DM would be the 7th leading cause of death worldwide (Mathers & Loncar, 2006). DM is characterised by an increase in blood glucose levels (Gowd & Nandini, 2015; Joladarashi, Salimath, & Chilkunda, 2011), which is due to either paucity of insulin secretion by pancreatic β-cells or inefficiency of cells to use insulin against glucose. However, both circumstances can affect the glucose uptake and its disposal by cells (Gowd, Gurukar, & Chilkunda, 2016). In the absence of proper medical care, DM can lead to severe secondary complications such as kidney failure, liver dysfunction (Manna, Das, Ghosh, & Sil, 2010; Ritz, 2006), blindness, heart attack, stroke, and nerve damage (Kam et al., 2016). Therefore, maintenance of normal blood glucose levels is mandatory for adequate body function. In human body glucose homeostasis is controlled by various organs including pancreas, liver, brain, intestine, adipose and muscle tissue with their sophisticated network of various hormones and neuropeptides. Among all organs pancreas play a critical role in glucose homeostasis by secreting glucose lowering hormone insulin and its opponent glucagon (Roder, Wu, Liu, & Han, 2016).

Reactive oxygen species (ROS) plays an important role in a variety of processes such as cell proliferation, inflammation and apoptosis (Covarrubias, Hernandez-Garcia, Schnabel, Salas-Vidal, & Castro-Obregon, 2008). At small doses, ROS plays a major role in the

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immune system and helps in maintenance of redox balance. However, over accumulation of ROS and free radicals can lead to oxidative stress (OS) and oxidative damage (T. Bao et al., 2016; Chen, Xu, Zhang, Li, & Zheng, 2016; Srinivasan, 2014) which further cause a deleterious effect to the antioxidant defence system. In the long run, OS causes mutations, and damage to various macromolecules such as DNA, protein, lipids, membranes and organelles such as mitochondria (Wei Chen, et al., 2016; Choi, Lee, Park, & Han, 2016; Rahman, Hosen, Islam, & Shekhar, 2012). Over accumulation of free radicals and ROS implicate in the development of age-related diseases and chronic disorders such as DM, cancer, atherosclerosis, neurodegenerative disorders (Chen et al., 2010; Chen, Su, Huang, Feng, & Nie, 2012; Chen et al., 2009; Rahman et al., 2012).

Oxidative stress plays an influential role in the implication of DM complications. Sustained hyperglycaemia can promote OS and thereby decrease the antioxidant defence mechanism through the formation of advanced glycation end products (AGEs) (Bonnefont-Rousselot et al., 2004). OS itself can play a critical role in genesis and progression of DM complications by causing perturbations to antioxidant defence system (Rains & Jain, 2011). It has a detrimental effect on protein, nucleic acids, and lipid moieties during DM and eventually leads to manifestation of micro and macro-complications (Giacco & Brownlee, 2010). Various feasible pathways were studied in investigating the possible routes of OS during hyperglycaemia including increase in polyol pathway flux, AGEs formation, overproduction of superoxides by the mitochondrial electron transport chain (METC) or activation of protein kinase-C (Rains & Jain, 2011). Hence, OS is an unfavourable process during DM, and DM can be managed by minimising the OS. Oxidative stress during DM can be decreased by inhibition of carbohydrate hydrolyzing enzymes such as α-amylase and α-glucosidase. The enzyme α-glucosidase is found in mucosal brush border which helps in digestion of oligosaccharides into monosaccharides (Hadrich, Bouallagui, Junkyu, Isoda, & Sayadi, 2015), whereas α-amylase is found mostly in saliva and helps in conversion of starch into absorbable molecules (Kim, Rioux, & Turgeon, 2014). Several drugs have been reported to treat DM, for example, acarbose is a glucosidase inhibitor, which is often prescribed to DM patients. However, the use of acarbose-like molecules often produces side effects like diarrhoea and other intestinal disturbances. Hence their usage is limited in DM treatment (Boue, Daigle, Chen, Cao, & Heiman, 2016). Life style and dietary habits are critical factors determining the onset and progression of DM. A proper diet including increase in proportion of fruits and vegetables can delay or prevent the manifestation of DM or improve the condition of individuals with an established DM complications (Sancho & Pastore, 2012). The benefits associated with a healthy diet can be attributed to higher concentrations of antioxidants found in fruits and vegetables such as flavonoid-polyphenolic compounds, tocopherols, and carotenoids (Ames, Shigenaga, & Hagen, 1993; Nöthlings et al., 2008; Xu et al., 2017). Among flavonoid-polyphenolic compounds, anthocyanins are coloured pigments which possess potent antioxidant properties. Numerous studies have reported the antioxidant activities of anthocyanins and their beneficial effects on health during inflammation, cancer, obesity and DM (Bowen-Forbes, Zhang, & Nair, 2010; Guo & Ling, 2015; Kähkönen & Heinonen, 2003).

In this review, we describe the DM and glucose homeostasis, role of OS in DM, modulation of DM by anthocyanins and anthocyanin rich sources in various organs and discussion of possible mechanisms involved. In addition, we also describe the antidiabetic effect of anthocyanins via inhibiting carbohydrate hydrolysing enzymes.

1.1. Anthocyanins

Anthocyanins are water-soluble polyphenolic pigments and secondary metabolites of plant products (Bunea et al., 2013), which are widely found in fruits and vegetables (Basu, Nguyen, Betts, & Lyons, 2014; Chen, Su, Xu, Bao, & Zheng, 2016; T. Wu, Tang, et al., 2013; T. Wu, Yu, et al., 2013). Anthocyanins are often referred to as flavonoids and are responsible for red-orange to blue-violet colours in various parts of plants especially in edible berries (Tao Bao et al., 2016; Chen, Xu, et al., 2016c; Liobikas, Skemiene, Trumbeckaite, & Borutaite, 2016; L. Zhang et al., 2017). To date, approximately 700 structurally different anthocyanins have been identified in nature, and the number is steadily increasing. Anthocyanins are found as aglycon derivatives called as anthocyanidins, and there are approximately 30 identified anthocyanidins till date. However, six of the anthocyanidins such as cyanidin, delphinidin, malvidin, peonidin, pelargonidin, and petunidin are predominantly found in nature among all identified anthocyanidins (Kamiloglu, Capanoglu, Grootaert, & Van Camp, 2015; Prior & Wu, 2006; X.; Wu et al., 2006). Among dietary consuming flavonoids, anthocyanins are most consuming flavonoids in the form of daily diet. Approximately 180–225 mg per day anthocyanins could be consumed according to US dietary consumption (Kamiloglu et al., 2015; McGhie & Walton, 2007).

2. Diabetes and regulation of glucose homeostasis

Diabetes and glucose homeostasis are related to assure normal body function, the maintenance and control of blood glucose levels is mandatory. The maintenance of relatively constant blood glucose levels is controlled by various organs of the body including pancreas, liver, brain, intestine, adipose and muscle tissue with their sophisticated network of various hormones and neuropeptides. As a major exocrine and endocrine organ, pancreas plays a key role in glucose homeostasis by secreting glucose lowering hormone insulin and its opponent glucagon (Roder et al., 2016) (Fig. 1). Regulation of hormone and peptide secretion by pancreas affects glucose homeostasis which contributes in onset of DM and its complications. Opposing and balancing action of insulin and glucagon, two hormones secreted by pancreas, preserve and maintain blood glucose levels within a range (4.4–6.1 mM) (Aronoff, Berkowitz, Shreiner, & Want, 2004). Increase in exogenous blood glucose levels followed by meals stimulates β-cells to secrete insulin to counteract elevated blood glucose levels (Komatsu, Takei, Ishii, & Sato, 2013). Insulin induces liver glycogenesis and inhibits gluconeogenesis, initiates the glucose uptake from various tissues such as muscle and adipose tissue thereby facilitating maintenance of normal blood glucose levels by removing exogenous glucose from blood stream. However, sustained elevated insulin levels may result in combined impotence of muscle and adipose tissue to facilitate glucose uptake and of the liver to supress glucose output which is referred to as insulin resistance, a hall mark of type 2 diabetes (Khan & Pessin, 2002). Whereas, glucagon secreted from α-cells plays exactly contrasting role to insulin. During sleep or fasting time α-cells secretes glucagon to promote hepatic glycogenolysis to maintain normal glucose levels in which glucose can be produced from stored glycogen in liver. In addition, glucagon also stimulates gluconeogenesis in liver and kidney during prolonged fasting to maintain blood glucose levels in a range (Freychet et al., 1988). Impaired insulin secretion by pancreatic β-cells or loss of cellular response to insulin such as insulin resistance can increase blood glucose levels. Sustained hyperglycaemia can lead to formation of AGEs followed by inducing OS and causing perturbations to protein moieties (Sancho & Pastore, 2012). Prolonged exposure to high blood glucose