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Application of Dietary Anthocyanins in Type 2 Diabetes Mellitus Treatment

Jinyang Hu[1,*]

[1]College of Food Science and Nutritional Engineering, China Agricultural University, Beijing, 100083, China
*Corresponding author: jh2377@cornell.edu

Abstract:

Type 2 diabetes mellitus (T2DM) is a common metabolic disorder characterized by impaired glucose control around the world that causes huge health challenges globally with increased morbidity and mortality. Inadequate insulin secretion and decreased insulin sensitivity are considered as main contributors to T2DM. Anthocyanin, a type of flavonoid compound, is one potentially feasible dietary intervention for T2DM treatment in addition to clinical drug interference. Dietary anthocyanins can be found in various berries, vegetables, and beverages, which provide vibrant colors. Anthocyanins are also increasingly used as colorants in the food industry. It is also seen as a supplement because of its antioxidation properties. Meanwhile, several evidence demonstrate the potential relationship between dietary anthocyanin intake and T2DM management. In this work, recent epidemiologic studies on the potential effects of anthocyanins in controlling T2DM have been reviewed, especially focusing on the typical indexes such as glycemic levels, insulin levels, etc. Many studies illustrate that appropriate intake of dietary anthocyanins could control glycemic levels, adjust insulin levels, and reduce insulin resistance. Because of these functions, dietary anthocyanins may trigger positive effects on T2DM treatment. Dietary anthocyanins could be seen as a good dietary intervention in T2DM control that meets the requirement of long-term management for the specific chronic disease.

Keywords: dietary anthocyanins; type 2 diabetes mellitus; glycemic level; insulin level; insulin resistance.

1. Introduction

T2DM is a global health challenge characterized by impaired glucose regulation, contributing significantly to morbidity and mortality worldwide. The two main reasons contributing to T2DM are deficient insulin secretion and inadequate insulin response of insulin-sensitive tissues. According to IDF Diabetes Atlas, there were approximately 537 million adults diagnosed with diabetes in 2021 among which 90-95% were diagnosed with type 2 diabetes mellitus [1]. T2DM is a typical chronic metabolic disorder, which requires long-term management. Current therapeutic strategies primarily focus on pharmaceutical interventions and lifestyle modifications, yet persistent challenges such as medication side effects and patient adherence underscore the need for intervention from other aspects.

Anthocyanins, a class of flavonoid compounds responsible for the vibrant colors of fruits and vegetables, are usually used as a natural coloring agent in the food industry. Recently, it has garnered significant attention for its potential health benefits. The most popularized benefits are anti-inflammation and eye health. Meanwhile, recent investigations have identified anthocyanins as potential adjunctive therapies for T2DM. Several studies show the antioxidant properties of anthocyanins may retard some chronic diseases. Moreover, another function of slowing starch digestion has been proved. Starch is one of the primary sources of blood glucose. With the addition of anthocyanins, the binding of starch to starch digestive enzymes, because of structural change, would be interfered [2]. The interference induces decreased values of glycemic index, which is advantageous to glycemic control. The interfering impacts of anthocyanins on T2DM can be explained by various underlying mechanisms. Stability refers to the specific compound that can persist in different environmental conditions. Bioavailability refers to the rate at which a particular substance that successfully reaches its biological destination, which is similar to the utilization rate. Although the instability and low bioavailability of anthocyanins used to be seen as the potential limitation of the effectiveness of T2DM management, more and more studies have researched its solutions. These barriers hindered anthocyanins from playing a steady role in the intervention of T2DM, which is a burgeoning field of research.

The review aims to provide a comprehensive overview of current research progress on the implications of anthocyanins for T2DM management. By critically analyzing existing literature, elucidating mechanisms of action, and critically evaluating the existing clinical evidence, this review seeks to provide clarity on the therapeutic potential of anthocyanins. Ultimately, this review aims to contribute to a deeper understanding of anthocyanins' role in addressing the complexities of T2DM and inspire further exploration into therapeutic strategies.

2. Dietary Anthocyanins

2.1 Properties of Dietary Anthocyanins

Anthocyanin, which plays a role in coloring plants, is one of the members of phenolic substances. Dietary anthocyanins refer to these anthocyanins that people can obtain from food intake.

Dietary anthocyanins share some properties important for their work in the human body that cause positive effects. Firstly, dietary anthocyanin is used to being seen as a useful antioxidant. In vivo studies in humans show that intake of anthocyanins provides anti-atherosclerogenic effects, hepatoprotective benefits, and nephroprotection [3]. A crossover clinical trial involving 12 healthy participants consuming açaí juice and pulp (165.9 mg/L and 303.8 mg/kg of anthocyanins respectively) shows a rise in plasma antioxidant capacity up to 3- and 2.3-fold [4]. Secondly, anthocyanin is an effective anti-inflammatory agent. According to an animal experiment on mice, intake of mulberry fruit extracts with an anthocyanin concentration of 50 mg/mL can effectively reduce the IL-6, iNOS, and phosphop6 pro-inflammatory markers [5]. Besides, eye protection, anti-diabetic and anti-obesity effects are also important properties that anthocyanins offer to human bodies [6].

2.2 Main Sources of Dietary Anthocyanins

Anthocyanins widely exist in nature, ranging from fruits to vegetables. It takes the responsibility for red, blue, and purple colors in fruits and vegetables as the pigments. Different plants with various genotypes, environmental conditions, and maturity have anthocyanins of distinct composition and quantity [3]. Most dietary anthocyanins that people consume are from the intake of these plants with relatively high contents of anthocyanins.

Generally, the major sources of anthocyanins are berries, such as blueberries, elderberries, chokeberries, pomegranate, and Açaí. These berries are able to provide maximum anthocyanin amounts exceeding 282.5 mg cyanidin 3-glucoside per 100 g fresh weight of berries [6]. Meanwhile, there are lots of vegetables and beverages that provide rich contents of anthocyanins, including purple sweet potato and red wine.

Depending on different diet patterns, the daily consumption of dietary anthocyanin can be varied. The daily intake of Europeans with a Mediterranean diet is relatively higher than other regions because of regular red wine and extra-virgin olive oil consumption [7]. In the U.S., a cross-sectional study calculated the average anthocyanin intake of the working population (249 career firefighters as study sample) is 10.9-53 mg/d, which is mainly from blueberries (43%), then raisins and grapes (15%) [8]. In Australia and China, the average anthocyanin intake is 24.4 mg/d and 17 mg/d, respectively [9,10]. Moreover, according to the Chinese Dietary Reference Intakes (DRIs) Handbook published by the Chinese Nutrition Society in 2023, the specific proposed level of anthocyanin for adults is 50 mg/d, which may exert positive effects on human health [11].

3. The Functions of Dietary Anthocyanins in T2DM Management

3.1 Glycemic Levels

The unusual glycemic level is a symbol of the high risk of T2DM. There are several markers of human glycemic control, including fasting blood sugar (FBS), 2-h postprandial glucose (2-h PPG), and glycated hemoglobin (HbA1c). Among these, HbA1c is a good index to reflect the average glucose levels for several months, which can be used for evaluating the result of chronic T2DM management.

A meta-analysis that respectively analyzes 33 studies for FBS, 9 studies for 2-h PPG, and 14 studies for HbA1c demonstrates that the intake of anthocyanin leads to a significant reduction in FBS (-2.70 mg/dl, 95%CI: -4.07 to -1.31, $P < 0.001$), 2-h PPG (-11.1mg/dl, 95%CI: -18.7 to -3.48, $P = 0.004$), and HbA1c (-0.21%, 95%CI: -0.39 to -0.03, $P = 0.019$) [12]. Among the above studies, most of them adopted the treated natural anthocyanin-rich berries as the intervention. Another randomized double-blind placebo-controlled trial involving 160 Chinese participants aged 40–75 years with prediabetes or early untreated diabetes for 12 weeks randomly assigned participants to two groups, the study group consumed two capsules containing 80 mg anthocyanins twice per day, and the control group consumed placebo capsules, meanwhile, both of them were asked to maintain their daily diets without anthocyanin-rich foods to avoid dietary disturbance [13]. The results of this study illustrate a significant attenuation in HbA1c (-0.14%, $P_{t\text{-}test} = 0.005$, $P_{ANCOVA} = 0.024$) [13]. In addition, there is one randomized controlled crossover trial on 24 healthy participants showing that the intake of bread with black rice anthocyanin extract (4% BRAE/100g wheat flour) induced a non-statistically significant reduction in 2-h PPG compared to the control group but decreased 27% of the glycemic index (GI) of bread by anthocyanin fortification, which induces its potential in glycemic control [14].

3.2 Insulin Levels

Insulin, a polypeptide hormone secreted by β cells in the pancreas, is the main control factor of glycemic level. Therefore, controlling insulin production after food intake is critical for managing T2DM.

Several evidence show that the intake of anthocyanin can adjust insulin levels after meals. A crossover clinical study with 17 healthy male participants shows that by having anthocyanin-rich purple potatoes (approximately 152 mg anthocyanin/meal) with normal yellow potatoes the postprandial plasma insulin response is significantly lower after 20-60 min ($p < 0.005$) compared to consuming control meal with only yellow potatoes but higher than control meal treatment after 120 min [15]. This study proves that the supplement of anthocyanin can lower the peak value of insulin in blood plasma and delay the decline of insulin level thereafter, which makes the insulin level change gently and manageably. Thus, the anthocyanin supplement may be effective in regulating insulin production for T2DM management.

3.3 Insulin Resistance

Insulin resistance (IR) refers to the impaired response of insulin-responsive cells to insulin or the decrease in the reaction of glycemic level to circulating insulin. One of the main factors contributing to T2DM is IR. The insulin resistance could be illustrated by the index of homeostasis model assessment of insulin resistance (HOMA-IR).

A meta-analysis that analyzed 14 studies with overall 951 study subjects for serum insulin and 11 studies with overall 811 study subjects for HOMA-IR demonstrates significantly reduced HOMA-IR index (-0.54, 95%CI: -0.94 to -0.14, P = 0.008) [12]. Also, a randomized controlled trial with 58 diabetic patients illustrates that the HOMA-IR index significantly decreased (-0.13, P = 0.035) in the group that was given 160 mg of purified anthocyanin twice per day compared to the placebo group [16].

Nevertheless, a 6-month double-blind randomized control trial involving 115 adults aged 50-75 with metabolic syndromes shows that the intake of blueberries (150 g/d) would not affect the insulin sensitivity of hepatic and adipose tissues [17]. This result may relate to the high-risk participants selection and the uncertain anthocyanin contents in blueberry intakes.

After the above studies, although the positive impact of dietary anthocyanin on IR is still controversial, most studies prove the intake of dietary anthocyanin is beneficial to insulin sensitivity, which is beneficial for the treatment of T2DM.

4. The Bioavailability of Dietary Anthocyanins May be the Limiting Factor

When anthocyanins are used as an intervention factor to T2DM treatment, except for function on metabolic adjustment, it is also important to consider its bioavailability to evaluate its effectiveness. Bioavailability refers to the contents of anthocyanins that can be truly available to the biological destination compared to the contents that are consumed by certain individuals. It is a crucial element that determines the nutritional value of anthocyanins. Anthocyanin has a very low bioavailability in the human body even compared to other phenolic substances, while the bioavailability also shows particular individual differentiation.

The absorption of anthocyanins mainly occurs in the digestive tract, starting from the oral cavity to the colon. The absorption of anthocyanins in the stomach is mainly transported by GLUT1 (glucose porter 1) and GLUT3. The rest of anthocyanins and its phenolic metabolites enter the intestine and colon for further absorption and metabolism. A vitro study demonstrated that anthocyanins are stable in the acidic gastric environment but tend to degrade substantially in the neutral upper intestines environment resulting from autooxidation [18]. The instability of digestion and absorption of anthocyanins in gastrointestinal tracts decreases the bioavailability of anthocyanins. Instead, the metabolites of anthocyanin are much more stable than anthocyanin in gastrointestinal tracts. Subsequently, remaining anthocyanins are absorbed by the liver or excreted with feces and urine.

To tackle the low bioavailability due to the instability of anthocyanin, there are several strategies have come up. Firstly, lipid-based anthocyanin complexes, including phospholipid-anthocyanin liposome, anthocyanin niosome, and NutraNanoSphere (NNS) micelle, are good strategies to solve the problem that anthocyanin, a polar molecule, cannot cross cell membrane in the gastrointestinal tract [19]. Secondly, polysaccharide-based anthocyanin complexes and protein-based anthocyanin complexes are able to play a role in enhancing the stability of anthocyanins and, therefore, improve their bioavailability [19]. In addition, nano-encapsulation, which is seen as an effective strategy for the transfer of bioactive compounds, is able to increase the bioavailability of anthocyanins in two major forms – nano-emulsion and nanoparticles [19]. It is a typical example of the encapsulation of anthocyanins to overcome the bioavailability limitation. Considering the above-mentioned strategies, the characteristic of low bioavailability is gradually not the limitation of anthocyanins as supplemental foods. Also, these effective strategies make better use of anthocyanins in the food industry.

5. Conclusion

Dietary anthocyanins, as a functional food ingredient, have become increasingly popular to be applied in various products in the food industry. Up to now, a lot of evidence has shown the potential function of dietary anthocyanins in the treatment of T2DM. Firstly, the intake of dietary anthocyanins may help control glycemic levels, exerting good control effects on FBS, 2-h PPG, and HbA1c. Secondly, dietary anthocyanin intake is beneficial for the adjustment of insulin levels in T2DM management. Thirdly, the intake of anthocyanin may reduce insulin resistance. Nevertheless, the application of dietary anthocyanins in T2DM treatment is limited so the intervention clinical drugs may still be essential if it is needed.

Moreover, these studies have some limitations. There are few studies on the determination of the effect of dietary anthocyanins on HbA1c, which is a good indicator of long-term glycemic levels. Most experiments do not last for six months or more for the monitoring of long-term glycemic change, which may be not convincing to evaluate the effect on chronic T2DM management. In order to understand the effects of anthocyanin on insulin levels, it may be a good choice for further studies to focus on the specific population – T2DM patients, which is lacking evidence now. Furthermore, the function of insulin resistance alleviation on high-risk participants may need more evidence. For further studies, the dose-dependent effect of anthocyanins on IR may be a good topic to dig deeper into.

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