Dietary Red Raspberry Consumption

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Type 2 diabetes mellitus (T2DM) is a chronic metabolic condition characterized by glucose clearance abnormalities and insufficient insulin response. Left uncontrolled, T2DM can result in serious complications and death.

Keywords: red raspberries ; western diet ; type 2 diabetes mellitus ; pre-diabetes

1. Introduction

Type 2 diabetes mellitus (T2DM), is a chronic metabolic pathology, characterized by abnormalities in glucose clearance with chronic hyperglycemia and insufficient response to insulin, i.e., insulin resistance [1][2]. Adults and youth worldwide are affected by T2DM with clinical manifestations and disease progression varying substantially across individuals [1]. The diminished capacity for plasma glucose clearance induces the pancreas to compensate by secreting more insulin, resulting in hyperinsulinemia and an overburdening of the pancreas that can eventually lead to a decrease in β-cell functioning [2]. Chronic, uncontrolled hyperglycemia can lead to damage of tissues and organs, through excessive glycation phenomena, resulting in microvascular and macrovascular perturbations, in turn affecting the nervous system, eye, kidney, and heart. Serious complications due to long-term, uncontrolled diabetes include kidney disease, cardiovascular disease (CVD), amputation, blindness, and even death [3], leading to an increased need for medical care and loss of productivity in the long term [2].

Both modifiable and non-modifiable factors that place individuals at high risk for developing T2DM have been identified, most notably pre-diabetes, a condition characterized by abnormally elevated blood glucose [4], and the metabolic syndrome (MetSy), a combination of metabolic abnormalities that increase the likelihood of developing diabetes and cardiovascular disease (CVD) [5]. While a cure for T2DM remains elusive, current treatments include pharmaceutical and insulin therapies along with diet and lifestyle modifications aiming at optimal management of the disease [6].

Non-modifiable risk factors for T2DM include but are not limited to: age (with risk increasing after 40 y and greatly increasing after 60 y), sex (males appear more susceptible), genetics/family history of diabetes, ethnicity/race (e.g., African American, Hispanic, Native American, Asian American, and Pacific Islander), and in case of women, diagnosis of gestational diabetes [1]. Modifiable risk factors include: conditions associated with the MetSy, severe or morbid obesity (BMI ≥ 40), non-alcoholic fatty liver disease (NAFLD), other conditions related to insulin resistance, poor diet, and lack of physical activity. It is important to note that certain prescription medications, such as thiazide diuretics, atypical antipsychotics, glucocorticoids, and statin-type drugs, prescribed for high cholesterol and dyslipidemia, may also increase blood glucose levels placing the patient at risk for T2DM [1][7][8].

Globally, the prevalence of diabetes has grown from 108 million people in 1980 to 422 million people in 2014 with a rapid increase in countries experiencing epidemiological transition, greater compared to developed countries [9]. In 2018, 34.2 million adults and children in the United States (US) were living with diabetes and an estimated 7.3 million adults remained undiagnosed (21.4% of diabetic adults), with 90–95% of cases classified as T2DM [10]. With the national and global prevalence of diabetes growing rapidly, there is an urgent need to address this crucial public health issue.

The negative economic impacts of diabetes result not only from direct costs, such as increased healthcare utilization and hospitalization, but from indirect costs such as diabetes-induced disability, premature death, and absenteeism from education and work [11]. In 2019, 9.3% of the world's adult population was living with diabetes, an estimated 463 million adults aged 20–79 y, while an additional 7.5% of the population, 374 million adults in the same age range, were living with pre-diabetes [2]. This translates to a global economic burden of USD 760 billion, an amount projected to rise to USD 825 billion by 2030. Investigating the efficacy of dietary interventions that could be utilized in lifestyle modifications for diabetics, such as including red raspberries (RR) in a balanced diet, may reveal potential benefits for public health as well as US agriculture [10].

Red raspberries (*Rubus idaeus* L.) constitute a low-glycemic index fruit containing a small amount of carbohydrates and relatively high amount of dietary fiber per weight unit [12]. Their phytonutrients and bioactive compounds may reduce the risk for chronic diseases and improve their management when consumed as part of a well-balanced diet. The major bioactive polyphenols found in RR are anthocyanins, which produce the brilliant red coloring of the berry, and ellagitannins/ellagic acid, found only in a few select foods [13]. The possible health-promoting benefits of RR consumption include improved insulin response, glucose, and lipid metabolism, as well as antioxidant and anti-inflammatory properties [12].

Two countries that may particularly benefit from foods that mediate the risks for and assist with management of T2DM are China and India. In 2019, China and India were estimated to have ≥20 million adults aged 20–79 y living with diabetes [2]. Along with the US, these countries have the highest rates of diabetes in the world, with numbers projected to grow substantially in the coming years. Due to potential health-promoting benefits of RR for T2DM and pre-diabetes, their production represents an immense opportunity for agriculture. Interestingly, in 2018, the US was the fifth largest producer of RR worldwide [14][15] which suggests significant potential for the US economy, including expanded export potential of this crop and an increase in its value, in promotion of RR as having evidence-based therapeutic uses in chronic diseases [13].

2. Red Raspberries: An Overview

The first records of the red raspberry (RR) date back to Troy in the first century A.D., with domestication and cultivation throughout Europe by the Romans in the fourth century, and utilization for art and medicinal purposes in medieval Europe. Today, these berries are cultivated worldwide by the metric ton with most of the production in the US from California, Washington, and Oregon [13]. While there are several varieties of raspberries, red raspberries constitute the most consumed variety and can be distinguished from other types of berries primarily by color and external texture [13].

Red raspberries can be consumed in raw or processed forms, such as frozen, dried, juiced, or powdered, as well as an extract of its bioactive constituents [12]. Main varieties of red raspberries include the following: Boyne, Heritage, Latham, Prelude, Bababerry, Candy, September, and Amity. Considered a low glycemic index food, RR contributes a minimal amount of carbohydrates and calories to the diet while providing an ample amount of dietary fiber and micronutrients, such as folic acid and vitamins C and K, magnesium, potassium, calcium, and iron. According to the United States Department of Agriculture (USDA) FoodData Central database, 1 cup (140 g) of frozen RR provides 70 kcal of energy and 17 g of total carbohydrates with 8.96 g of dietary fiber (6.4/100 g), thus constituting one of the highest sources of dietary fiber among whole foods [13][16].

2.1. Bioactive Compounds

Polyphenols with proposed biological activity contained in RR include anthocyanins, such as cyanidin and delphinidin, flavanols, flavonols, and phenolic acids, such as ellagitannins/ellagic acid [17]. Anthocyanins are plant pigments that give berries their red, blue, and purple coloring, with approximately 47 mg of anthocyanins per 100 g of RR [12][18]. Anthocyanins are of particular interest for mitigating chronic disease risk; however, their content appears to be greatly reduced during berry processing. For instance, anthocyanins are particularly sensitive to duration and temperature of storage and frozen berries tend to have an average of 42% less anthocyanins than their raw counterparts [12]. Another major polyphenol class found in RR are ellagitannins found in certain berries and nuts, muscadine grapes, and pomegranates. Like anthocyanins, ellagitannin content varies based on the storage and processing methods used. Ellagitannin bioavailability may be increased after conversion to urolithins by colonic bacteria, absorption by colonic enterocytes, and glucuronidation in the liver, a process with great inter-individual variability [19]. Although the bioavailability of both anthocyanins and ellagitannins is low and depends on several factors, such as the food matrix, dose and time of intake, interactions with gut microbiota as well as other polyphenols during digestion and absorption, there is increasing evidence that their biological activity may provide significant health benefits [13][20][21]. In addition to the bioactive compounds of RR there are post-ingestion metabolites such as short chain fatty acids that are shown to confer potential health benefits [22][23][24][25].

Dietary fibers are another important bioactive component of RR in that they promote growth of healthy gut microbiota [26], the composition of which has been shown to vary in individuals who are obese and/or have T2DM [21]. Dietary fibers including poly- and oligosaccharides remain undigested until reaching the large intestine where microbiota-derived metabolites such as short-chain fatty acids (SCFAs) are produced. Such metabolites can be utilized by the host for energy and decrease appetite through increased satiety and reduced production of the hunger hormone ghrelin, as well as other potential mechanisms under investigation [21][27].

2.2. Proposed Health Benefits

There is evidence that the benefits of dietary berries can be feasibly attained through daily consumption of 40–250 g of fresh, frozen, or dried berries, or their extracts [12]. Numerous health benefits have been documented from consuming RR and its bioactive constituents including improved glucose, insulin, and lipid metabolism, as well as antioxidant, anti-inflammatory and signaling properties which have the potential to reduce the risk for and modulate chronic metabolic diseases [12][23][24].

The proposed mechanism for the modulation of postprandial glycemia following consumption of dietary berries or their extracts is the inhibition of the enzymes α-amylase and α-glucosidase to prevent glucose absorption in the intestines [13]. RR extracts may be more effective at inhibiting α-amylase than other berry extracts, while anthocyanins, may enhance insulin secretion from pancreatic β-cells, thus improving insulin sensitivity [13].

Dietary berries may modulate lipid metabolism by increasing high-density lipoprotein cholesterol (HDL-c) through amplified synthesis of apolipoprotein-A1 in liver cells, decreasing triglycerides through down-regulation of transcription of genes involved in fatty acid synthesis, and through decreasing oxidative stress and inflammation in cells and tissues [25]. According to a meta-analysis of 32 randomized controlled trials, the attenuation of low-density lipoprotein cholesterol (LDL-c) was greater in participants with signs of dyslipidemia, with results being specific to anthocyanins purified from berry sources versus other food sources [26].

Most of the early research on RR focused on their antioxidant properties since oxidative stress and inflammation constitute important features of various chronic diseases, including T2DM and CVD [13]. An imbalance of reactive oxygen species (ROS) to antioxidants can lead to oxidative stress and damage to cells and tissues. Lipid peroxidation causes oxidized LDL-c accumulation, which can lead to plaque formation in arteries and stimulation of pro-inflammatory genes. This activation of the inflammatory response can lead to the inflammation observed in most chronic diseases [27]. Anthocyanins have been shown to act as antioxidants when ingested, causing increased synthesis of endogenous antioxidant enzymes such as glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD). However, anthocyanins like other antioxidant compounds may produce a pro-oxidant effect in very high doses. Those doses cannot practically be obtained via the diet, so the dietary intake of anthocyanins poses no concern. Such concerns might become more of an issue if high levels of supplementation are pursued. Anthocyanins have also been shown to reduce inflammatory cytokine gene expression in white adipose tissue (WAT) [28]. Ellagic acid has been shown to both reduce ROS production and inhibit the proliferation of oxidized LDL-c. Therefore, dietary berries and their bioactive compounds play a role in protecting cells and tissues during oxidative stress and assist in reducing inflammation [13][29].

References

1. American Diabetes Association Classification and Diagnosis of Diabetes. Diabetes Care 2016, 40 (Suppl. 1), S11–S24.
2. International Diabetes Federation. IDF Diabetes Atlas, 9th ed.; Karuranga, S., Malanda, B., Saeedi, P., Eds.; International Diabetes Federation: Brussels, Belgium, 2019.
3. Babey, S.H.; Wolstein, J.; Diamant, A.L.; Goldstein, H. Prediabetes in California: Nearly Half of California Adults on Path to Diabetes. Policy Brief (UCLA Cent. Health Policy Res.) 2016, PB20161, 1–8.
4. American Diabetes Association (ADA). The Burden of Diabetes in California. Available online: http://main.diabetes.org/dorg/docs/state-fact-sheets/ADV_2020_State_Fact_sheets_CA.pdf (accessed on 14 June 2020).
5. Harris, M.F. The Metabolic Syndrome Background. Aust. Fam. Physician 2013, 42, 524–527.
6. American Diabetes Association Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes. Diabetes Care 2019, 42 (Suppl. 1), S90–S102.
7. Chalasani, N.; Younossi, Z.; LaVine, J.E.; Diehl, A.M.; Brunt, E.M.; Cusi, K.; Charlton, M.; Sanyal, A.J. The diagnosis and management of non-alcoholic fatty liver disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Hepatology 2012, 55, 2005–2023.
8. Papatheodorou, K.; Banach, M.; Edmonds, M.; Papanas, N.; Papazoglou, D. Complications of Diabetes. J. Diabetes Res. 2015, 2015, 189525.
9. World Health Organization. Fact Sheet: Diabetes. Available online: https://www.who.int/news-room/fact-sheets/detail/diabetes (accessed on 9 November 2020).

10. United States Department of Health and Human Services (DHHS). National Diabetes Statistics Report, 2020; DHHS: Washington DC, USA, 2020.

11. Saeedi, P.; Salpea, P.; Karuranga, S.; Petersohn, I.; Malanda, B.; Gregg, E.W.; Unwin, N.; Wild, S.H.; Williams, R. Mort ality attributable to diabetes in 20–79 years old adults, 2019 estimates: Results from the International Diabetes Federati on Diabetes Atlas, 9th edition. Diabetes Res. Clin. Pr. 2020, 162, 108086.

12. Calvano, A.; Izuora, K.; Oh, E.C.; Ebersole, J.L.; Lyons, T.J.; Basu, A. Dietary berries, insulin resistance and type 2 diab etes: An overview of human feeding trials. Food Funct. 2019, 10, 6227–6243.

13. Burton-Freeman, B.M.; Sandhu, A.K.; Edirisinghe, I. Red Raspberries and Their Bioactive Polyphenols: Cardiometaboli c and Neuronal Health Links. Adv. Nutr. 2016, 7, 44–65.

14. FAO. Food Land AgricUlturse Organization of the United Nations (FAO). FAOSTAT 2019. Available online: http://www.fa o.org/faostat/en/#data/RL (accessed on 10 March 2020).

15. Goodhue, R.E.; Martin, P.L. Chapter California Berries. In California Agriculture: Dimensions and Issues; The Regents of the University of California: Davis, CA, USA, 2018; pp. 1–16.

16. United States Department of Agriculture (USDA). Milk, FoodData Clentral. Available online: https://fdc.nal.usda.gov/fdc-app.html#/food-details/781084/nutrients (accessed on 5 May 2020).

17. Neveu, V.; Pérez-Jiménez, J.; Vos, F.; Crespy, V.; du Chaffaut, L.; Mennen, L.; Knox, C.; Eisner, R.; Cruz, J.; Wishart, D.; et al. Phenol-Explorer: An online comprehensive database on polyphenol contents in foods. Database 2010, 2010, bap024.

18. Khoo, H.E.; Azlan, A.; Tang, S.T.; Lim, S.M. Anthocyanidins and anthocyanins: Colored pigments as food, pharmaceutic al ingredients, and the potential health benefits. Food Nutr. Res. 2017, 61, 1361779.

19. González-Barrio, R.; Edwards, C.A.; Crozier, A. Colonic Catabolism of Ellagitannins, Ellagic Acid, and Raspberry Antho cyanins: In Vivo and In Vitro Studies. Drug Metab. Dispos. 2011, 39, 1680–1688.

20. Makki, K.; Deehan, E.C.; Walter, J.; Bäckhed, F. The Impact of Dietary Fiber on Gut Microbiota in Host Health and Dise ase. Cell Host Microbe 2018, 23, 705–715.

21. Hur, K.Y.; Lee, M.-S. Gut Microbiota and Metabolic Disorders. Diabetes Metab. J. 2015, 39, 198–203.

22. Torres-Fuentes, C.; Golubeva, A.V.; Zhdanov, A.V.; Wallace, S.; Arboleya, S.; Papkovsky, D.B.; El Aidy, S.; Ross, P.; Ro y, B.L.; Stanton, C.; et al. Short-chain fatty acids and microbiota metabolites attenuate ghrelin receptor signaling. FASE B J. 2019, 33, 13546–13559.

23. Seeram, N.P.; Burton-Freeman, B. The Seventh Biennial Berry Health Benefits Symposium. Food Funct. 2018, 9, 20–2 1.

24. Vara, A.L.; Pinela, J.; Dias, M.I.; Petrović, J.; Nogueira, A.; Soković, M.; Ferreira, I.C.F.R.; Barros, L. Compositional Fea tures of the “Kweli” Red Raspberry and Its Antioxidant and Antimicrobial Activities. Foods 2020, 9, 1522.

25. Basu, A. Role of Berry Bioactive Compounds on Lipids and Lipoproteins in Diabetes and Metabolic Syndrome. Nutrient s 2019, 11, 1983.

26. Yang, L.; Ling, W.; Du, Z.; Chen, Y.; Liping, Y.; Deng, S.; Liu, Z.; Yang, L. Effects of Anthocyanins on Cardiometabolic H ealth: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Adv. Nutr. 2017, 8, 684–693.

27. Weiskirchen, R.; Weiskirchen, S.; Tacke, F. Organ and tissue fibrosis: Molecular signals, cellular mechanisms and trans lational implications. Mol. Asp. Med. 2019, 65, 2–15.

28. Moruzzi, M.; Klöting, N.; Blüher, M.; Martinelli, I.; Tayebati, S.; Gabrielli, M.; Roy, P.; Di Bonaventura, M.M.; Cifani, C.; L upidi, G.; et al. Tart Cherry Juice and Seeds Affect Pro-Inflammatory Markers in Visceral Adipose Tissue of High-Fat Di et Obese Rats. Molecules 2021, 26, 1403.

29. Lee, W.-J.; Ou, H.-C.; Hsu, W.-C.; Chou, M.-M.; Tseng, J.-J.; Hsu, S.-L.; Tsai, K.-L.; Sheu, W.H.-H. Ellagic acid inhibits oxidized LDL-mediated LOX-1 expression, ROS generation, and inflammation in human endothelial cells. J. Vasc. Sur g. 2010, 52, 1290–1300.