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REVIEW

Anthocyanins: Potent natural warriors in the battle against diabetes

Dicky Ardin Gurusinga, Muhamad Azhar , Tesia Aisyah Rahmania

Faculty of Military Pharmacy, The Republic of Indonesia Defence University, Bogor, Indonesia

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Correspondence

Tesia Aisyahh Rahmania
Faculty of Military Pharmacy
The Republic of Indonesia
Defense University
Indonesia
tesiaaisyah4@gmail.com

Abstract

Background: Over half of the world's population suffers from diabetes mellitus (DM), which affects insulin function. In 2021, Indonesia had 19.5 million DM patients, ranking fifth globally. There are two types: type 1 (DMT1) and type 2 (DMT2). Anthocyanins, flavonoid metabolites responsible for purple, blue, and red colours, are found in various Indonesian fruits, flowers, and plants, offering a natural source of these compounds. **Objective:** This review is to determine the potential of anthocyanins in treating DMT2 and identify plants rich in anthocyanins. **Method:** This study was conducted through an in-depth literature review of sources from PubMed, Google Scholar, the Ministry of Health, the International Diabetes Federation (IDF), and the World Health Organisation (WHO), focusing on anthocyanins and diabetes. The use of natural ingredients represents a promising therapeutic option for treating DMT2. **Results:** In-vivo research shows that anthocyanins in dark-coloured fruits and vegetables can increase insulin sensitivity, regulate carbohydrate metabolism, and reduce oxidative stress. Anthocyanins from extracts of rosella flowers, red spinach, and purple sweet potatoes can lower blood glucose levels and improve the function of pancreatic beta cells, making them a promising additional therapeutic alternative. While the findings are promising, further research is essential to fully understand the mechanisms and effectiveness of anthocyanins in diabetes therapy.

Introduction

Diabetes affects more than half of the world's population, according to the International Diabetes Federation (IDF). The percentage of diabetes sufferers in the 20-to-79-year age group will reach 10.5% or around 536.6 million people in 2021 and will increase to 12.2% or around 783.2 million people in 2045 (Sun *et al.*, 2022). According to the IDF, Indonesia is ranked 5th with the most diabetes sufferers, namely 19.5 million people in 2021 and 28.6 million people in 2024 (Kemenkes, 2014).

Diabetes mellitus (DM) is a complex metabolic disorder marked by chronic hyperglycaemia due to insufficient insulin production or action. Globally, diabetes affects 536.6 million adults aged 20–79, with projections suggesting an increase to 783.2 million by 2045. In Indonesia, diabetes is a pressing concern, with the prevalence rising from 19.5 million in 2021 to an

estimated 28.6 million by 2024, ranking the country fifth in the world for diabetes cases (Sun *et al.*, 2022; Kemenkes, 2024). The rising burden of diabetes necessitates innovative approaches to therapy that go beyond conventional pharmacological treatments. Anthocyanins, a subclass of flavonoids responsible for the red, blue, and purple pigmentation in plants, have emerged as promising natural compounds for diabetes management. These polyphenolic compounds are abundant in fruits such as blueberries, blackberries, and purple sweet potatoes, and in vegetables like red spinach and roselle flowers. Anthocyanins exhibit several biological activities relevant to diabetes therapy, including antioxidant, anti-inflammatory, and anti-hyperglycaemic effects (Martín *et al.*, 2017). Mechanically, anthocyanins improve insulin sensitivity by activating Peroxisome Proliferator-Activated Receptor Gamma (PPAR-γ), which regulates glucose metabolism. They enhance glucose uptake in

adipocytes and muscle cells by promoting the translocation of Glucose Transporter Type IV (GLUT4) to the cell membrane (Scazzocchio *et al.*, 2011). Additionally, anthocyanins inhibit α -glucosidase, reducing postprandial glucose absorption, and protect pancreatic beta cells from oxidative damage caused by Reactive Oxygen Species (ROS), thereby preserving insulin secretion (Jayaprakasam *et al.*, 2005; Wallace & Giusti, 2015). These multifaceted actions directly address the pathophysiology of type 2 diabetes, including insulin resistance and beta-cell dysfunction.

Given their accessibility, safety, and therapeutic potential, anthocyanins represent a promising natural alternative or adjunct to conventional diabetes treatments. This review examines the role of anthocyanins in diabetes therapy, emphasising their mechanisms of action, evidence from in vivo studies, and the potential for clinical application. By understanding and leveraging these bioactive compounds, anthocyanins could contribute significantly to the development of sustainable and effective strategies for diabetes management.

Methods

This literature review systematically analysed relevant scientific publications sourced from inclusive databases like PubMed and Google Scholar. Data from authoritative organisations such as the Ministry of Health (Kemenkes), International Diabetes Federation (IDF), and World Health Organisation (WHO) provided a global perspective. A rigorous keyword-based approach, utilising inclusive terms like "anthocyanin", "Diabetes Mellitus", and "line therapy", identified pertinent journals and articles. This interdisciplinary approach ensured a comprehensive exploration of the subject matter, drawing insights from both scientific research and global health organisations.

Results

Table I presents an overview of studies investigating the role of anthocyanins in the therapeutic management of diabetes mellitus.

Table I: Studies of anthocyanins in diabetes mellitus

Animal	Plant	Doses	Impact	Reference
Mouse	Rosella flower petals (<i>Hibiscus sabdariffa</i> L.)	Taken orally for 14 days, 250 mg/kgBW, 500 mg/kgBW, and 750 mg/kgBW	dose of 500 mg/kgBB and 750 mg/kgBB had an effect antidiabetic	Dianasari & Fajrin, n.d.
Male Wistar strain mouse	Red spinach (<i>Amaranthus dubius</i>)	Red spinach extract 687 and 1376 mg/200 g	In comparison to the control group and the group undergoing acarbose treatment, the dosage of 1376 mg/200g/BW/day was found to be the most effective in lowering GDP and MDA levels.	(Citra <i>et al.</i> , 2024)
Male Wistar rats induced by alloxan	Sweet potato leaves	1.4 g/kgBW, 2.8 g/kgBW, and 5.6 g/kgBW dosages of sweet potato leaf ethanol extract, and 63 mg/kgBW of metformin	At an effective dosage of 700 mg/200 g BW, sweet potato leaf extract significantly reduced blood glucose levels in rats given alloxan, surpassing the effects of metformin.	(Asriyanti <i>et al.</i> , 2014)

Discussion

Pathophysiology of diabetes mellitus

Diabetes mellitus includes metabolic disorders caused by glucose, including insulin resistance, lipid metabolism disorders, increased blood glucose, inflammation, and oxidative stress. This can trigger the development of DMT2 and the emergence of various complications, even at the stage of diabetes. This disorder can occur due to a reduction in the number of β islet cells or damage to the function of β islet cells which ultimately causes hyperglycaemia which can attack almost all body tissues and cause acute and chronic diabetes complications (Liu *et al.*, 2023) The central metabolic disorders in type II diabetes mellitus

(DMT2) involve impaired insulin secretion by pancreatic β cells and insulin resistance in body cells (Galicia-Garcia *et al.*, 2020). β -cell dysfunction leads to reduced insulin production, which impairs the body's ability to regulate glucose levels effectively. Factors causing cellular dysfunction in DMT2 include impaired synthesis of insulin or insulin precursors, as well as impaired insulin secretion mechanisms and decreased expression of the glucose transporter GLUT2 (Galicia-Garcia *et al.*, 2020). In addition, excess free fatty acids (FFA), hyperglycaemia, endoplasmic reticulum (ER) stress, lipotoxicity, glucose toxicity, and glucose lipotoxicity may also play a role in disrupting β -cell function (Galicia-Garcia *et al.*, 2020).

Mitochondria play an important role in the pathophysiology of T2DM through mitochondrial dysfunction, which causes the accumulation of Reactive Oxygen Species (ROS) and impaired electron transport, which can increase insulin resistance. Mitochondria are also involved in the production of ROS that damage protein structures and are associated with mtDNA variants DMT2 (Galicia-Garcia *et al.*, 2020). Insulin resistance, which is the primary indication of metabolic disorders in T2DM, is caused by several factors, including damage to β cells which are responsible for insulin production, damage to insulin signaling receptors by non-hormonal factors, and impaired insulin response to growth hormone and IGF-1 after eating (Galicia-Garcia *et al.*, 2020).

Skeletal muscle is a factor outside the pancreas which is important in the development of insulin resistance and DMT2. Insulin normally stimulates muscle glycogen synthesis and regulates glucose uptake from the blood. Impaired insulin action in skeletal muscle is often the initial stage in the development of systemic insulin resistance, which ultimately leads to DMT2 (Galicia-Garcia *et al.*, 2020). Even at high insulin levels, adipose tissue contributes to insulin resistance by impairing the inhibition of lipolysis, impairing glucose absorption, and increasing the release of free fatty acids (FFA) into the blood (Galicia-Garcia *et al.*, 2020). FFA accumulation in the liver can also affect insulin signalling, increase glucose production through gluconeogenesis, and interfere with the insulin response to glucose stimulation, which can ultimately lead to DMT2 (Galicia-Garcia *et al.*, 2020).

On the other hand, disturbances in the liver in regulating glycogen synthesis, suppression of glucose production, increased lipogenesis, and synthesis of pro-inflammatory proteins such as CRP can also cause insulin resistance. This disorder disrupts the normal regulation of hepatic glucose output, a function that depends on the combined action of insulin and glucagon (Galicia-Garcia *et al.*, 2020). Anthocyanin is a type of polyphenolic compound that has the potential to treat diabetes mellitus. In general, anthocyanins are found in almost all higher plants, around 30 families, but not in lower plants such as algae and mosses. Anthocyanins provide dark colours to plants in the form of red, blue, and purple dyes (Martín *et al.*, 2017).

In vivo research on the impact of anthocyanins

In research conducted by Dinasari and Fajrin (2015), water extract of Rosella flower petals (*Hibiscus sabdariffa L.*) was given to mice at doses of 250mg/kgBW, 500mg/kgBW, and 750mg/kgBW orally for 14 days. Blood glucose levels were measured on days seven and 15 using the Glucose test (Dianasari &

Fajrin, 2015). The results of the study showed that Rosella flower petal water extract at a dose of 500 mg/kgBW and 750 mg/kgBB had an antidiabetic effect, which is comparable to the use of positive control glibenclamide (Dianasari & Fajrin, 2015). In contrast, a dose of 250mg/kgBW did not show significant antidiabetic activity. Active compounds such as anthocyanins, flavonoids, vitamin C, and polysaccharides contained in Rosella flower extract have been proven to be able to reduce blood glucose levels, so that they have the potential to be anti-diabetic (Dianasari & Fajrin, 2015).

Research conducted by Apriliani and colleagues (2024) evaluated the effects of red spinach extract on diabetic mice. Research results show that red spinach extract, which contains anthocyanins and beta-carotene, has the potential to reduce blood glucose and malondialdehyde (MDA) levels (Citra *et al.*, 2024). Administration of red spinach extract at an optimal dose of 1376 mg per 200 grams of body weight per day showed a significant reduction in fasting blood glucose and MDA levels, exceeding the effect of standard acarbose therapy. The results of this study indicate that red spinach extract can be an alternative therapy for type II diabetes mellitus by reducing oxidative stress and increasing insulin sensitivity (Citra *et al.*, 2024).

Asriyanti and colleagues (2014) conducted a study to assess the impact of sweet potato leaf (*Ipomoea batatas*) ethanol extract on alloxan-induced blood glucose levels in male Wistar rats. 1.4 g/kgBW, 2.8 g/kgBW, and 5.6 g/kgBW doses of ethanol extract of sweet potato leaves were employed in this investigation, along with a negative control of 0.5% CMC and a positive control of 63 mg/kgBW of metformin (Asriyanti *et al.*, 2014). The findings demonstrated that ethanol extract of sweet potato leaves, at an effective dosage of 700 mg/200 g BW, was superior to metformin in reducing blood glucose levels in rats given alloxan (Asriyanti *et al.*, 2014). The extract's flavonoids, including anthocyanin, work to promote the release of adipocytokines like leptin and adiponectin, which raise insulin sensitivity without activating PPAR- γ , which triggers lipogenesis (Asriyanti *et al.*, 2014).

Purple sweet potato influences diabetes mellitus, and are rich in anthocyanins, antioxidants that can reduce the risk of diabetes. Pancreatic β cells can be prevented from oxidative damage brought on by glucose by eating a diet rich in antioxidants, such as anthocyanins. These cells can be shielded from the damaging effects of free radicals by using purple sweet potato extract (Anjani *et al.*, 2018). Purple sweet potatoes' anthocyanin content can therefore be considered a non-pharmacological dietary therapy alternative that aids in blood glucose

management and reduces insulin resistance in individuals with diabetes mellitus (Anjani *et al.*, 2018). Employing anthocyanins and other natural compounds to treat diabetes.

Mechanism of anthocyanins in reducing blood sugar

Anthocyanins have been found to increase insulin sensitivity in several *in vivo* studies. One mechanism is through the activation of peroxisome proliferator-activated receptor gamma (PPAR- γ) (Figure 1). Activation of PPAR- γ can improve insulin sensitivity and regulation of glucose metabolism, which in turn helps control blood glucose levels. Research by Jayaprakasam *et al.* (2005) showed that anthocyanins from some fruits can increase insulin secretion and increase the response of pancreatic beta cells to glucose, which is a potential indication for the benefits of the antibiotic (Jayaprakasam *et al.*, 2005).

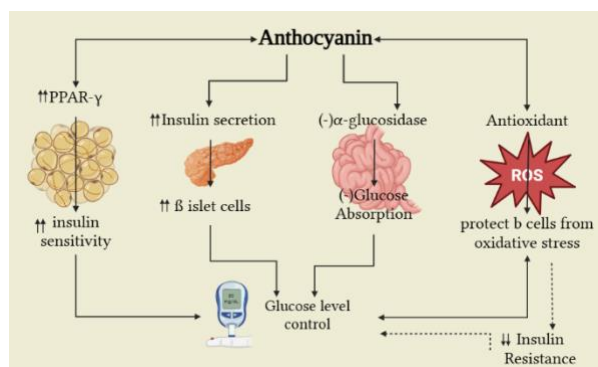


Figure 1: Anthocyanins mechanism in reducing blood sugar

Additionally, anthocyanins can change how enzymes involved in glucose metabolism function. The potential of anthocyanins as glucose-regulating agents is supported by their ability to inhibit α -glucosidase, an enzyme involved in the digestion of carbohydrates, which may reduce intestinal glucose absorption and regulate postprandial glycaemic elevation (Tsuda *et al.*, 2006). They can also lower α -glucosidase expression in human adipocyte cells. Anti-inflammatory and antioxidant substances, such as flavonoids, have potent antioxidant qualities, and anthocyanins, which serve to protect beta cells in the pancreas from oxidative stress, which can cause damage and dysfunction. Additionally, they can lessen the chronic inflammation that contributes to the pathophysiology of type 2 diabetes mellitus and the development of insulin resistance, respectively. Wallace and Giusti (2015) research found that anthocyanins' antioxidant properties help prevent

free radical damage and lessen the cell damage linked to diabetes mellitus (Wallace & Giusti, 2015).

Additionally, anthocyanins' interactions with molecular signalling pathways can alter a number of signalling pathways that are involved in the control of glucose metabolism. They can affect how genes involved in glucose transport, synthesis, and lipogenesis regulation are expressed in body cells. According to recent research, anthocyanins can lower serum levels of HDL and LDL cholesterol, which makes them helpful in managing cardiovascular risk factors in diabetics (Qin *et al.*, 2009).

Conclusion

Anthocyanins, a class of flavonoids found in various fruits and vegetables, have shown promise as potential therapeutic agents for diabetes mellitus. These pigments enhance insulin sensitivity, stimulate insulin secretion, inhibit carbohydrate digestion, and possess potent antioxidant properties. *In vivo* studies have demonstrated their significant blood glucose-lowering effects. While further research is needed to fully elucidate their mechanisms of action and optimise their clinical application, incorporating anthocyanin-rich foods into a balanced diet offers a promising approach to prevent and manage diabetes.

Future research should prioritise well-designed clinical studies to evaluate the safety, efficacy, and optimal dosages of anthocyanins in diverse patient populations. These studies should explore their long-term impact on glycaemic control, insulin resistance, and diabetes-related complications. Additionally, investigations into standardised Preparation methods, pharmacokinetics, and potential interactions with existing diabetes medications are essential. Incorporating anthocyanins into evidence-based dietary or pharmacological interventions could potentially revolutionise diabetes management, offering a natural, effective, and accessible therapeutic option.

References

- Anjani, E. P., Zakiah Oktarlina, R., & Morfi, C. W. (2018). The substances anthocyanins in purple sweet potato against diabetes mellitus. *Majority*, 7(2), 257–262. <https://scispace.com/pdf/zat-antosianin-pada-ubi-jalar-ungu-terhadap-diabetes-melitus-54klhv7p83.pdf>
- Asriyanti, V., Pandu, Bangsawan, I., Didiek, & Hadi, P. (2014). Hypoglycaemic effect test of sweet potato (*Ipomoea batatas*) leaves ethanol extract against blood glucose level of Alloxan-induced white male wistar rat (*Rattus norvegicus*). *Jurnal Mahasiswa PSPD FK Universitas*

Tanjungpura, 1(1).

<https://jurnal.untan.ac.id/index.php/jfk/article/view/8033>

Citra, A., Nilasari, A., Wibowo Rini, B., & Listyawati, S. (2024). Effects of red spinach extract mira variety on fasting blood glucose and malondialdehyde of DMT2 model rats. *Jurnal Media Penelitian dan Pengembangan Kesehatan*, 34(2), 311–323.

<https://jurnal.polkesban.ac.id/index.php/jmp2k/article/download/2003/1110/11279>

Dianasari, D., & Fajrin, A. (2015). Antidiabetic activity test of flower petals roselle (*Hibiscus sabdariffa* L.) water extract in rats with alloxan induction method. *Jurnal Farmasi Sains dan Terapan*, 2(1), 54–58.

Direktorat Bina Farmasi Komunitas dan Klinik. (2005). *Pharmaceutical care for diabetes mellitus*. Direktorat Jenderal Bina Kefarmasian dan Alat Kesehatan Departemen Kesehatan RI.

<https://www.pustaka.akfarimambonjol.ac.id/index.php?p=stream-pdf&fid=39&bid=404>

Galicia-García, U., Benito-Vicente, A., Jebari, S., Larrea-Sebal, A., Siddiqi, H., Uribe, K. B., Ostolaza, H., & Martín, C. (2020). Pathophysiology of type 2 diabetes mellitus. In *International Journal of Molecular Sciences*, 21(17), 1–34. <https://doi.org/10.3390/ijms21176275>

Gupta, A., Sharma, M., & Sharma, J. (2015). A role of insulin in different types of diabetes. *International Journal of Current Microbiology and Applied Science*, 4(1), 58–77. <https://www.ijcmas.com/vol-4-1/Anuradha%20Gupta,%20et%20al.pdf>

Jayaprakasam, B., Vareed, S. K., Olson, L. K., & Nair, M. G. (2005). Insulin secretion by bioactive anthocyanins and anthocyanidins present in fruits. *Journal of Agricultural and Food Chemistry*, 53(1), 28–31. <https://doi.org/10.1021/jf049018>

Kemenkes. (2024, January 10). *Time to organize the sweet*. <https://sehatnegeriku.kemkes.go.id/baca/blog/20240110/5344736/saatnya-mengatur-si-manis/>

Liu, Y., Wang, Q., Wu, K., Sun, Z., Tang, Z., Li, X., & Zhang, B. (2023). Anthocyanins' effects on diabetes mellitus and islet transplantation. *Critical Reviews in Food Science and Nutrition*, 63(33), 12102–12125. <https://doi.org/10.1080/10408398.2022.2098464>

Marín-Peñalver, J. J., Martín-Timón, I., Sevillano-Collantes, C., & Cañizo-Gómez, F. J. del. (2016). Update on the treatment of type 2 diabetes mellitus. *World Journal of Diabetes*, 7(17), 354. <https://doi.org/10.4239/wjd.v7.i17.354>

Martín, J., Navas, M. J., Jiménez-Moreno, A. M., & Asuero, A. G. (2017). Anthocyanin Pigments: Importance, Sample Preparation and Extraction. In *Phenolic compounds - Natural sources, importance and applications*. InTech. <https://doi.org/10.5772/66892>

Meidikayanti, W., & Wahyuni, C. U. (2017). Relationship between family support and quality of life in Type II diabetes mellitus at Pademawu community Health centre. *Jurnal Berkala Epidemiologi*, 5(2), 240–252. <https://doi.org/10.20473/jibe.V5I22017.253-264>

Mukhtar, Y., Galalain, A., & Yunusa, U. (2020). A modern overview on diabetes mellitus: A chronic endocrine disorder. *European Journal of Biology*, 5(2), 1–14. <https://doi.org/10.47672/ejb.409>

Qin, Y., Xia, M., Ma, J., Hao, Y. T., Liu, J., Mou, H. Y., Cao, L., & Ling, W. H. (2009). Anthocyanin supplementation improves serum LDL- and HDL-cholesterol concentrations associated with the inhibition of cholesteryl ester transfer protein in dyslipidemic subjects. *American Journal of Clinical Nutrition*, 90(3), 485–492. <https://doi.org/10.3945/ajcn.2009.27814>

Rózańska, D., & Regulska-Ilow, B. (2018). The significance of anthocyanins in the prevention and treatment of type 2 diabetes. *Advances in Clinical and Experimental Medicine*, 27(1), 135–142. <https://doi.org/10.17219/acem/64983>

Scazzocchio, B., Vari, R., Filesì, C., D'Archivio, M., Santangelo, C., Giovannini, C., Iacovelli, A., Silecchia, G., Volti, G. L., Galvano, F., & Masella, R. (2011). Cyanidin-3-O- β -glucoside and protocatechuic acid exert insulin-like effects by upregulating PPAR γ activity in human omental adipocytes. *Diabetes*, 60(9), 2234–2244. <https://doi.org/10.2337/db10-1461>

Solverson, P. (2020). Anthocyanin bioactivity in obesity and diabetes: The essential role of glucose transporters in the gut and periphery. *Cells*, 9(11), 2515. <https://doi.org/10.3390/cells9112515>

Sun, H., Saeedi, P., Karuranga, S., Pinkepank, M., Ogurtsova, K., Duncan, B. B., Stein, C., Basit, A., Chan, J. C. N., Mbanya, J. C., Pavkov, M. E., Ramachandaran, A., Wild, S. H., James, S., Herman, W. H., Zhang, P., Bommer, C., Kuo, S., Boyko, E. J., & Magliano, D. J. (2022). IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Research and Clinical Practice*, 183, 109119. <https://doi.org/10.1016/j.diabres.2021.109119>

Tsuda, T., Ueno, Y., Yoshikawa, T., Kojo, H., & Osawa, T. (2006). Microarray profiling of gene expression in human adipocytes in response to anthocyanins. *Biochemical Pharmacology*, 8, 1184–1197. <https://doi.org/10.1016/j.bcp.2005.12.042>

Wallace, T. C., & Giusti, M. M. (2015). Anthocyanins. *Advances in nutrition (Bethesda, Md.)*, 6(5), 620–622. <https://doi.org/10.3945/an.115.009233>

WHO. (2024, November 14). *Diabetes*. World Health Organisation. <https://www.who.int/news-room/factsheets/detail/diabetes>