The benefits of black rice bran and the potential of its bioactive compounds as antidiabetic agents
Manfaat bekatul beras hitam dan potensi senyawa bioaktif sebagai agen antidiabetik

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Abstract
Prevention strategies for diabetes have been found to minimize the risk of the disease through lifestyle treatments such as physical exercise and nutrition. Plants with strong antioxidant activity have previously been discovered to be effective therapy for Type 2 Diabetes Mellitus. A total of 12 English articles were reviewed. Black rice bran, in its raw extract form, modulate the activity of enzymes, hormones, and molecular signaling related to glucose homeostasis in the body. Black rice bran increases the defense of pancreatic β cells against apoptosis. Bioactive substances in black rice bran such as anthocyanins, proanthocyanidins, γ-oryzanol regulate diabetes-related molecular signaling which ultimately leads to improvement in glucose levels, insulin levels, restoration and protection of pancreatic β cells against apoptosis. These bioactive substances are also possible in suppressing oxidative stress, increasing antioxidant status and decreasing inflammation which is a common condition in diabetes. The conclusion of this literature review was black rice bran has the potential to have an antidiabetic effect through various mechanisms, in which this effect is possible due to the bioactive substances contained in it.
Keywords: Antidiabetic, bioactive compounds, black rice bran, diabetes

Abstrak
Bekatul beras hitam sebagai produk samping dari beras memiliki manfaat sebagai agen antidiabetes yaitu dengan menurunkan kadar glukosa darah karena adanya perbaikan produksi dan kerja insulin, penurunan inflamasi dan stres oksidatif. Studi ini bertujuan untuk membahas secara mendalam manfaat antidiabetik dari bekatul beras hitam. Penelitian menggunakan desain literature review, yaitu mengkaji artikel ilmiah yang relevan bersumber dari database PubMed, ScienceDirect dan Google Scholar. Artikel yang dirujuk yaitu 10 tahun terakhir (2012-2022). Terpilih 12 artikel ilmiah untuk dikaji. Pemilihan artikel dimulai dari tahap identifikasi, skrining, dan inklusi. Hasil kajian menunjukkan bahwa bekatul beras hitam, dalam bentuk mentah maupun ekstrak, dapat memodulasi aktivitas enzim, hormone, dan persinyalan molekuler yang berkaitan dengan glukosa dalam tubuh. Bekatul beras hitam juga meningkatkan pertahanan sel β pancreas terhadap apoptosis. Zat bioaktif dalam bekatul beras hitam seperti antosianin, proantosianidin, γ-oryzanol mengatur persinyalan molekuler terkait diabetes yang akhirnya menimbulkan perbaikan kadar glukosa darah, kadar insulin, restorasi dan perlindungan sel β pancreas terhadap apoptosis. Zat-zat bioaktif ini juga berpotensi dalam menekan stress oksidatif, meningkatkan status antioksidan dan menurunkan inflamasi yang merupakan kondisi umum yang terjadi pada diabetes. Kesimpulan dari literature review ini adalah ekatul beras hitam berpotensi memiliki efek antidiabetic melalui berbagai mekanisme, dimana efek ini dimungkinkan karena zat-zat bioaktif yang terkandung di dalamnya.
Kata Kunci: Antidiabetes, bekatul beras hitam, diabetes, zat bioaktif

Introduction

Diabetes mellitus (DM) is a serious public health problem worldwide. According to the International Diabetes Federation, the incidence of DM has increased among individuals aged 20–79 years, reaching 463 million in 2019, and is expected to reach 700 million by 2045 (IDF, 2019). Diabetes mellitus is a group of metabolic diseases characterized by chronic hyperglycemia resulting from impaired insulin secretion, insulin action, or both. There are several types of diabetes, including type 1, type 2, and gestational diabetes. Type 2 diabetes mellitus accounts for 90–95% of all diabetes cases, with the largest proportion occurring in low- and middle-income countries (Banday et al., 2020).

The main characteristic that initiates the pathophysiology of type 2 diabetes mellitus (type 2 DM) is a decrease in insulin production due to pancreatic cell malfunction and insulin resistance (van der Schaft et al., 2019). Dysfunction of pancreatic β-cells occurs because of complex interactions between the environment and molecular pathways. Under conditions of overnutrition, obesity, hyperglycemia, and dyslipidemia often result in insulin resistance and chronic inflammation, which ultimately trigger a decrease in islet integrity. At the beginning of the disease development, the production of insulin and the increase in pancreatic cell mass to compensate for the condition of insulin resistance allow serum insulin levels to increase and maintain normoglycemia, both during fasting and when stimulated by food consumption. However, insulin secretion worsens over time, and pancreatic cells are reduced, eventually resulting in a decrease in insulin levels (Galicia-Garcia et al., 2020).

Prevention strategies for diabetes that are currently being implemented to minimize its risk include lifestyle modifications and good nutritional intake. Plants with strong antioxidant activity have previously been used as effective therapies for type 2 diabetes mellitus (Rajendiran et al., 2018). Polyphenols derived from food sources have been shown to have the potential to lower blood glucose levels, oxidative stress, protein glycation, inhibit the activity of enzymes related to carbohydrate metabolism, improve β-pancreatic cell function, insulin secretion, and alleviate insulin resistance through various molecular biochemical pathways. Owing to their powerful antioxidant activity, polyphenols are considered effective as nutraceuticals and alternative therapies for diabetes (de Paulo Farias et al., 2021). Black rice bran is one source of nutraceutical antioxidants that can be used in complementary DM therapy (Zheng et al., 2020).

Black rice bran (*Oryza sativa L. indica*) has a high phytochemical content and is currently an increasingly popular staple food. As a byproduct of black rice milling, black rice bran has been shown to have strong pharmaceutical activity; therefore, it has the potential to be used as a functional food (Ghasemzadeh et al., 2018). Cyanidin 3-glucoside, the main anthocyanin in black rice bran, may improve insulin resistance (Belwal et al., 2017). Black rice bran has been shown to improve hepatic insulin signaling in diabetic rats (Hlaing et al., 2019; Zheng et al., 2020).

Previous reviews have discussed the anti-diabetic properties of rice bran (Sivamaruthi et al., 2018). Sapwarobol et al. (2021) discussed the benefits of rice bran as an antidiabetic, anti-hyperlipidemia, hypotensive, antioxidant, and anti-inflammatory. The health benefits of black rice have previously been discussed by Prasad et al. (2020); however, in-depth studies on the role of black rice bran in diabetes are limited, although it is known that black rice bran contains various bioactive compounds that have antioxidant and anti-inflammatory effects that can help prevent and overcome diabetes. Therefore, this literature review aimed to examine in depth the role of antidiabetics and the mechanisms of black rice bran.

Methods

This research is a literature review using a narrative method that summarizes and discusses the potential of black rice bran as an antidiabetic agent based on previous experimental studies using literature sources collected from the PubMed and Science Direct databases, as well as manually from the Google Scholar database.

The PICO elements used in this literature review were experimental animal studies using albino rats or mice (patients); interventions in the form of black rice bran in the form of extracts, oils, or processed products

(intervention); comparisons of standard therapies such as glibenclamide and/or metformin (comparison); and research results that show improvements in parameters related to diabetes (outcomes).

The scientific articles collected had a publication time span of 2012–2022, using the keywords "black rice bran" or "purple rice bran" or "Oryza sativa L. indica", "antidiabetic" and "diabetes" diabetes'. Boolean operators such as "AND" and "OR" were used to obtain more relevant search results. Four articles were obtained from the PubMed database, 365 articles from the ScienceDirect database, and 6170 articles from the Google Scholar database.

To continue the study, we selected 12 articles that were most relevant to the topic. Articles were selected for the assessment if they met the inclusion criteria for black rice bran research results and their effect on overcoming diabetes-related parameters. Searches for "anthocyanins", "proanthocyanidins", "phenolic acids", "flavonoids," and "-oryzanol" were also conducted to discuss bioactive substances that potentially play a role in the antidiabetic effects of black rice bran.
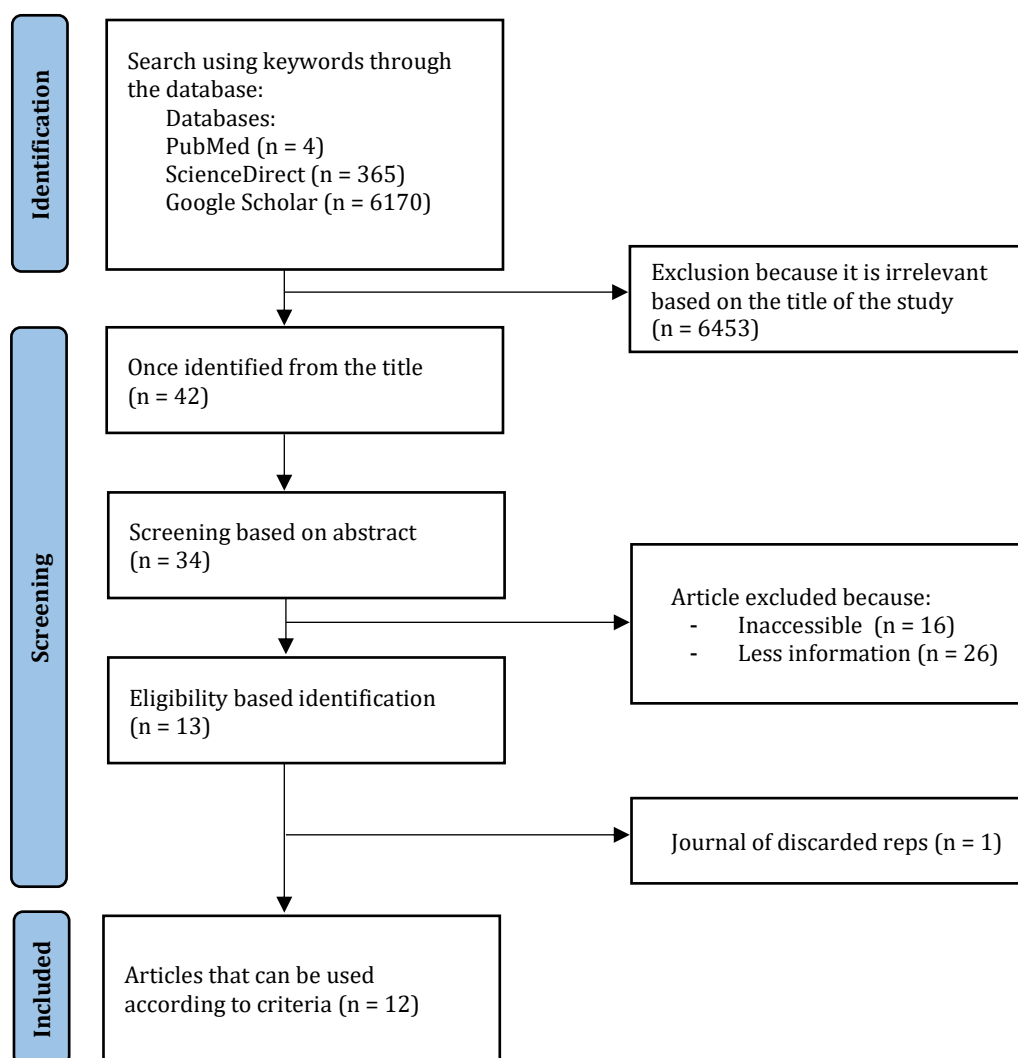
Figure 1. PRISMA diagram article selection scheme

The data obtained are then studied by summarizing and analyzing it through narrative elaboration and determining the conclusions of the literature review. Data analysis was carried out by describing and providing opinions regarding the antidiabetic potential of black rice bran in the 12 selected articles. Assessments related to bioactive substances in black rice bran that are potentially responsible for the antidiabetic effects were also performed.

Result and Discussion

Black Rice Bran

Rice is the seed of the rice plant, which is one of the main sources of carbohydrates in the world, especially in Asia, and is one of the staple foods in Indonesia. Rice (*Oryza sativa L.*) is a plant belonging to the Gramineae (Poaceae) family. Black rice is becoming increasingly popular and widely consumed as a functional food because of its health benefits. This type of rice contains macronutrients, such as carbohydrates and proteins, as well as micronutrients, such as vitamins and minerals, which are higher than those in white rice. Black rice contains bioactive compounds such as anthocyanins (Kristamtini et al., 2012).

Rice bran is high in phenolic compounds, such as anthocyanins, proanthocyanidins, and γ-oryzanol, compared to other parts of rice. Black rice bran contains many phenolic acids such as ferulic acid, p-coumaric acid, vanillic acid, p-hydroxybenzoic acid, gallic acid, and strong protocatechins. Ferulic acid is the dominant phenolic acid in black rice bran (Jun et al., 2015).

Antidiabetic Potential of Black Rice Bran

Several studies have demonstrated the antidiabetic potential of black rice bran (Table 1). Based on in vitro models, Boue et al. (2016) showed inhibition of α-glucosidase activity and increased basal glucose uptake.

The study found that Black rice bran has insulin-like activity in regulating glucose uptake and the expression of Akt2, IRS1, INSR, and PI3K genes in mouse adipocytes, thereby increasing the expression of GLUT1 and GLUT4 genes. Wahyuni et al. (2016) also showed that the administration of black rice bran ethanol extract at a dose of 1 mL at stratified concentrations (6;125; 12,5; 25; 50 and 100 mg%) inhibited α-glucosidase activity in the intestinal tissue of diabetic rats.

In in vivo modeling, black rice bran ethanol extract at doses of 100 mg/kg lowered blood glucose levels to 151±38,8 mg/dL, and at stratified doses (50, 100, and 200 mg/kg), it increased insulin levels to 6,52±5,94; 11,5 Â ±3,5, and 15,20 ± 9,5 ng/mL and restored pancreatic Î²-cells in alloxane-induced mice (Wahyuni et al., 2016). Another study by Sari and Wahyuni (2017) showed a decrease in blood glucose levels of up to 131 mg/dL after treatment with black rice bran ethanol extract at a dose of 200 mg/kg for 10 days. Nakamura et al. (2017), using the intervention of black rice bran-enriched rice bread, also inhibited α-secretase activity up to 3.6 times, decreased amyloid 40 β-peptide, and lowered blood glucose levels in vivo models. Germinated black rice improved glucose, cholesterol, and triglyceride levels, decreased insulin resistance and glucose tolerance, and increased insulin secretion levels in mouse plasma (Chaiyasut et al., 2017).

Riceberry black rice bran oil (RBBO) also improves oxidative stress by decreasing malondialdehyde and increasing superoxide dismutase, catalase, glutathione peroxidase, coenzyme Q10, and antioxidant status in diabetic rats. RBBO also promotes regeneration of the pancreas, kidneys, heart, and liver (Posuwan et al., 2013). Black rice bran extract at a dose of 300 mg/kg/day prevents metabolic disorders, such as maintaining normal blood glucose, insulin, HOMA-IR, triglycerides, and cholesterol, and prevents kidney disorders by suppressing lipid peroxidation and increasing antioxidants (Wongmekiat et al., 2021). The antidiabetic effects that occur through improvement of metabolic parameters, reduction of oxidative stress, and restoration of damaged tissues have also been reported by Krisbianto et al. (2016) in diabetic rats treated with cereals enriched with anthocyanin extract from black rice bran.

Table 1. Antidiabetic role of black rice bran

Writers	Forms Interventions	Study Types	Subjek	Doses	Findings	p-value
Boue et al. (2016)	Black Rice Bran	*In vitro*	Cell 3T3-L1 Adipocyte Culture of Mice	100, 500 µg/mL	– Inhibits α-glucosidase activity – Increase basal glucose uptake – It has insulin-like activity that regulates glucose uptake and gene expression in mouse adipocytes, thereby increasing the expression of GLUT1 and GLUT4 genes	
Wahyuni et al. (2016)	Ethanolic extract of black	*In vitro*	Mouse intestinal cell culture	1 mL extract at	Inhibits α-glucosidase activity Increase basal glucose uptake	< 0,05

Writers	Forms Interventions	Study Types	Subjek	Doses	Findings	p-value
	rice bran			consentration 6.125, 12.5, 25, 50, and 100 mg%	It has insulin-like activity that regulates glucose uptake and gene expression in mouse adipocytes, thereby increasing the expression of GLUT1 and GLUT4 genes.	
Wahyuni et al. (2016)	Ethanolic extract of black rice bran	*In vivo*	Aloxane-induced diabetic rats	50, 100, 200 mg/kg	– Lowers blood glucose levels – Improve insulin levels – Retains pancreatic β cells	< 0,05
Sari & Wahyuni, (2017)	Ethanolic extract of black rice bran	*In vivo*	Aloxane-induced diabetic rats	200 mg/kg	– Lowers blood glucose levels	< 0,05
Nakamura et al. (2017)	Black rice bran fortified bread	*In vivo*	mice C57BL/6	Feed mixed 5.4% black rice bran fortified bread	– Inhibition activity β-secretase – Lowers amyloid peptide β 40 – Lowers blood glucose levels	< 0,05
Posuwan et al. (2013)	Black rice bran oil Riceberry	*In vivo*	Hyperglycemic rats	Ad libitum feed enriched with 5%, 7.5%, and 15% bran oil	– Lowers oxidative stress – Improves the histological picture of the organ	< 0,05
Wongmekiat et al. (2021)	Black rice bran extract	*In vivo*	DM Type 2 Rats	300 mg/kg/day	– Prevents metabolic damage – Improves mitochondrial function – Maintain mitochondrial integrity and redox balance – Prevents oxidative damage to the kidneys	< 0,05
Lolok et al. (2020)	The combination of black rice bran and brown rice bran	*In vivo*	Rat	200mg/kg 460mg/kg	– Lowers blood glucose levels	< 0,05
Hlaing et al. (2019)	Black rice bran	*In vivo*	DM Type 2 Rats	50 mg/kg feed	– Improve hepatic insulin signaling via the PI3K/Akt pathway	< 0,05
Hlaing et al. (2018)	Black rice bran	*In vivo*	DM Type 2 Rats	50 mg/kg feed	– Prevents pancreatic damage – Improves insulin signaling – Improves glucose homeostasis	< 0,05
Hlaing et al. (2017)	Black rice bran	*In vivo*	DM Type 2 Rats	50 mg/kg feed	– Improves insulin sensitivity – Improves insulin signaling – Increases Superoxide Dismutation (SOD) – Maintains the viability of pancreatic β cells	< 0,05
Krisbianto et al. (2016)	Cereals enriched with black rice bran anthocyanin extract	*In vivo*	Hyperglycemic rats	40 and 80 ppm extract	– Lowers blood glucose levels, insulin resistance, and MDA – Relieve inflammation and steatosis in the pancreas, liver, and kidneys	< 0,05

Similar results were reported by Hlaing et al. (2017), who found that administration of black rice bran at a dose of 50 mg/kg feed improved insulin sensitivity, insulin signaling, SOD, and pancreatic β-cell defense against apoptosis in rats with type 2 Diabetes Mellitus induced by a high-fat diet and streptozotocin. GLUT2 normalizes after the administration of black rice bran, indicating that black rice bran increases glucose uptake and insulin secretion from the pancreas.

In addition, the proposed mechanism of increasing GLUT4 protein from black rice bran administration is through the expression of Myosin I (Myo1c) heavy chain and stimulation of pancreatic cell proliferation via the Ras/MEK pathway, along with Akt protein activation

(Hlaing et al., 2018). Hlaing et al. (2019) showed that black rice bran increases liver insulin signaling via the PI3K/Akt pathway in liver tissue models of in vivo diabetes by increasing Galnt5 and Igfbp4 expression. Black rice bran can suppress liver gluconeogenesis by suppressing G6Pase and PEPCK, which are important enzymes involved in this process.

Bioactive Compounds in Black Rice Bran Have Potential for Diabetes Management

Anthocyanins

Anthocyanins in food can increase insulin secretion through a variety of mechanisms that can potentially modulate diabetes. The modulating effect on type 2 diabetes mellitus is related to the insulin signal transduction pathways and antioxidant and anti-inflammatory defense mechanisms. Anthocyanin components, such as cyanidine, delphidin, and pelorgonidine glucoside, were found to be effective in increasing insulin secretion, improving insulin sensitivity, and reducing oxidative stress (Martín et al., 2017; Zhang et al., 2010).

Anthocyanin supplementation has been shown to reduce fasting glucose levels, increase Homeostatic Model Assessment-Insulin Resistance (HOMA-IR), and increase antioxidant capacity in patients with type 2 Diabetes Mellitus compared to placebo (Li et al., 2015).

Anthocyanins can decrease plasma glucose levels, insulin resistance, and glucose intolerance, and increased plasma insulin secretion has been reported in rats. Oxidative stress was also lower in the control group (Watanabe, 2016). An anthocyanin extract from mulberry fruit at a dose of 125 mg/kg reduced plasma insulin levels in Zucker diabetic fatty (ZDF) rats (Sarikaphuti et al., 2013). Improvements in serum insulin levels were also found in rats treated with black soybean skin extract containing anthocyanin extract (88.11 mg C3GE/g) and phenol extract (342.73 mg GAE/g) (Chayati et al., 2019).

Cyanidin-3-glucoside has cytoprotective properties in the form of suppression of ROS formation, lipid peroxidation, and inhibition of apoptosis in hyperglycemic MIN6N pancreatic cells (Lee et al., 2015). Similarly, bayberry extract containing anthocyanins of 300 gC3G/10g at a dose of 0.2 mL showed hypoglycemia effects, increased insulin secretion, and improved insulin signaling (C. De Sun et al., 2012). This suggests that the antidiabetic effects of anthocyanins are

related to decreased oxidative stress and improved antioxidant defence systems. AMPK activation is one of the antidiabetic effects of anthocyanins that triggers glucose uptake and insulin secretion by pancreatic cells. This activation of AMPK is usually accompanied by an increase in GLUT4 expression in the white adipose tissue and skeletal muscle (Rózańska & Regulska-Ilow, 2018).

Proantosianidin

Proanthocyanidin maintains normal insulin levels and decreases the apoptosis of pancreatic β-cells under diabetic conditions (Ding et al. 2013). In addition, proanthocyanidin intervention can relieve stress on the endoplasmic reticulum, which is active under diabetic conditions (Okudan et al., 2011; Selvaraj et al., 2007).

Proanthocyanins can relieve oxidative stress in rats with type 1 and type 2 diabetes mellitus through lipid peroxidation inhibition, ROS formation, and an increased GSH/GSSG ratio (Yokozawa et al., 2012). Boue et al. (2016) showed α-amylase inhibition activity, a 3,1-fold increase in glucose uptake, and increased expression of GLUT1 and GLUT4 mRNA, as well as genes encoding proteins in insulin signaling pathways, in the intervention of black rice bran extract rich in proanthocyanidin fractions.

In addition, proanthocyanidin increases the effect of incretin, improves insulin secretion, and prevents the apoptosis of pancreatic β-cells to achieve glucose homeostasis (Sulaiman, 2014; Ding et al., 2013).

The anti-diabetic effects of proanthocyanidins can be attributed to their antioxidant and anti-inflammatory properties. Rajasekhar et al. (2021) detected an increase in antioxidant status in the form of decreased lipid peroxidation activity and decreased inflammation characterized by a decrease in iNOS, TNF-α, IL-1β, and β-cell regeneration in the diabetic pancreas (Rajasekhar et al., 2021). Sun et al. (2016) also showed an increase in the number of antioxidant enzymes (SOD and GSH-Px) and a decrease in MDA, as well as a decrease in apoptosis, in diabetic retinopathy rats.

Phenolic Acids

The most abundant phenolic compounds found in black rice bran are protocatenate acid, ferulic acid, syringate, caffeic acid, and p-coumaric acid (Ghasemzadeh et al., 2018; Jun et al., 2015).

These phenolic components play an important role in modulating the expression of genes involved in pancreatic β-cell dysfunction and insulin secretion through several mechanisms, namely:1) synergistic action between polyphenols and phenolic acids in targeting signaling molecules, such as transcription factors; 2) reducing radical damage related to pancreatic β-cell dysfunction through antioxidant activity; and 3) triggering effectors and factors responsible for the continuity of insulin secretion (Saji et al., 2020).

Flavonoid
Flavonoids found in black rice bran include quercetin, apigenin, and catechins (Ghasemzadeh *et al*. 2018).

Flavonoids can modulate insulin secretion through changes in Ca2+ flux by L-type Ca2+ channels (L-VDCC), mechanisms, intracellular cAMP accumulation (PKA-mediated), activation of CaMK II, or gene transcription factors PDX-1, GLP-1, IRS-2, or Insig-1. Increased Ca2+ stimulates the processes that trigger these cellular pathways and enter pancreatic β-cells, as it is well known that calcium plays an important role in the mechanism of insulin secretion. Quercetin is involved in Ca2+ modulation either through influx or increased mobilization of Ca2+ from the endoplasmic reticulum via the L-type Ca2+ channel. Similarly, catechins, where the mechanism for increased insulin secretion is also related to the flux of Ca2+.151 Apigenin can prevent apoptosis through inhibition of NF-κB pathway activation, repair oxidative damage in pancreatic β-cells by decreasing DNA damage, ROS production, carboxylation of lipid peroxidation proteins, and restoration of cell apoptosis (Al-Ishaq et al., 2019; Soares et al., 2017).

γ-oryzanol
γ-Oryzanol is an ester that functions as a precursor of insulinotropic ferulic acid. γ-oryzanol reduces stress on the endoplasmic reticulum and protects β-cells against apoptosis under diabetic conditions (Kaup et al., 2013). Cheng et al. (2010) showed that γ-oryzanol improved insulin sensitivity in Type 2 diabetes mellitus rats. In in vitro models, tunicamycin-induced endoplasmic reticulum stress in MIN6 cells decreased ER stress-related gene expression, thereby triggering the restoration of glucose-stimulated insulin secretion and preventing apoptosis.

Similar results were found in in vivo models (Kozuka et al., 2015). Ghatak & Panchal (2012) showed that oral administration of GORZ at doses of 50 and 100 mg/kg decreased blood glucose levels and oxidative stress in diabetic rats.

Conclusion

Black rice bran contains various bioactive substances such as anthocyanins, pro-anthocyanidins, phenolic acids, flavonoids, and γ-oryzanol, which can act as antidiabetic agents through both anti-inflammatory and antioxidant pathways. This antidiabetic benefit is based on the ability of black rice bran to lower blood glucose levels, increase insulin levels, and regenerate and defend pancreatic tissue against apoptosis.

Research on the exploration of bioactive substances from black rice bran in the treatment of diabetes is still limited; therefore, further research is recommended to conduct phase 0 to IV clinical trials in order to develop efforts to use black rice bran as a complementary therapy for diabetes.

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