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Antioxidant and Blood Sugar-Stabilizing Activities of Extracts from Three Coloured Rice Varieties in Streptozotocin-Induced Diabetic Mice

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ABSTRACT

Purple brown rice (*Oryza sativa* L. indica), red rice (*Oryza sativa* L. Orysa), and black glutinous rice (*Oryza sativa* l. Glutinosa Tanaka) are three popular types of staple food, which are beneficial to human health. The present study was conducted to evaluate the antioxidant and hypoglycemic effects of three ethanol extracts from Vietnamese rice in streptozotocin-induced diabetic mice. Ethanol extracts were prepared from three varieties of rice, which included black glutinous rice (EOGT96), red rice (EOLO96), and purple-brown rice (EOLI96). Swiss albino male mice were divided into six groups: I (negative control), II (positive control), III (drug control group), IV (EOLT96), V (EOLI96), and VI (EOLO96). The antioxidant activity of the various extracts was evaluated using the DPPH (2,2-diphenyl-1-picrylhydrazyl) and nitric oxide methods. The total phenolic content and the α-amylase inhibitory activity were also determined. The DPPH results revealed that the EOLI96 produced the highest antioxidant activity (IC_{50} = 19.38 ± 0.64 μg/mL), and the EOGT96 was only 3.7 times less potent at scavenging free radicals than the quercetin standard. In comparison to the other two extracts from rice varieties, the extract from EOGT96 also had the highest total polyphenol content. Blood sugar levels were much lower in the group of mice given the EOGT96 than in the control group, and they were similarly comparable to those of the animals administered glibenclamide. The findings of this study revealed that ethanol extract from black glutinous rice can reduce diabetes by lowering high blood sugar levels when used at the appropriate dosage.

Keywords: Antioxidant, Blood sugar level, Diabetes, *Oryza sativa* l. Glutinosa Tanaka, *Oryza sativa* L. Orysa, *Oryza sativa* L. Indica.

Introduction

Diabetes is fast-growing and causes various complications.[1] In 2014, 420 million people worldwide were affected by the disease and the disease caused approximately 1.5 million deaths in 2019. Over the past few decades, there has been a steady increase in both the incidence and prevalence of the condition.[2] Oxidative stress has been identified as one of the major factors in the etiology of diabetes due to its production of free radicals, which can result in diabetic complications.[3] Current medications have several side effects such as fatigue, headache, a feeling of hunger, visual aura, excessive sweating, confusion, etc.[4] Therefore, there has been growing interest in the search for ingredients that can prevent the progression of diabetes by using natural antioxidants in herbs due to their ability to scavenge free radicals.[5] The influence of antioxidant-rich foods, such as fruits and vegetables, as well as currently prescribed medications with antioxidant efficacy, has recently been examined.[6,7] Mason *et al*. have summarized the impact of antioxidants that target the mitochondria on oxidative stress, cardiovascular health, and glycaemic management in humans.[8] Cereals are a rich source of energy for humans, especially the coloured varieties because they contain nutrients that have been linked to significant health benefits. Rice (*Oryza sativa* L.) has long been regarded as a rich source of carbohydrates for the daily meals of people in many Asian countries.

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The rice is often rubbed to remove its bran layer. Through this process, the health and nutritional benefits of whole grains are also lost. Whole grains such as brown rice contain health-promoting nutrients that help to prevent cardiovascular disorders, hyperglycemia, hyperlipidemia, and the pathogenesis of cancer cells.[9] Black glutinous rice, red rice, and purple-brown rice go well with various Asian cuisines and are the rice of choice in Vietnamese cuisines. This is because of their great benefits to health, such as preventing cardiovascular diseases, fighting some types of cancer, supporting the treatment of diabetes, and osteoarthritis, especially their positive effects on children's physical development.[10,11] However, little is known about the biological functions and activities of these rice varieties.

Numerous studies on the antioxidant and hypoglycemic properties of coloured rice, including one that examined the antioxidant activity of black glutinous rice bran, revealed that it is a source of many important minerals and phytochemicals.[12] Another study has investigated phenolic constituents of Thai rice extracts and their correlation with antioxidant potential using both chemical and cell assays.[13] Additionally, pre-germinated brown rice consumption was found to alter lipid and blood glucose levels in patients with type 2 diabetes or impaired fasting glucose, according to research.[14] An investigation of the blood-glucose-lowering effects of brown rice on healthy and diabetic individuals revealed that brown rice was superior to milled rice for the treatment of diabetes and hyperglycemia.[15]

A study on the acceptability, tolerability, and substitution of brown rice for white rice to lower blood glucose levels among adult Nigerians helped to clarify the acceptance of brown rice as a white rice substitute to stabilize diabetes levels in Nigerian patients.[16] Moreover, glutinous brown rice consumption improved glycemic control in Japanese patients with type 2 diabetes when compared to white rice with the same content.[17] As for antioxidant capacity, a study

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indicated that germinated brown rice had much greater levels of antioxidant capacity and bioactive constituents than ungerminated brown rice.[18] Another report on antioxidant compounds in rice showed that the rice kernels are a rich source of antioxidant compounds, with black rice having significantly more antioxidant activity than purple and red rice.[19] However, the antioxidant content of other grains appeared to be higher than that of rice for whole grains in general, except γ-oryzanol and anthocyanins. Although there has been little in-depth, comparative research on the various varieties of rice. This international literature provided an overall picture of the anti-diabetic and antioxidant properties of rice. A few studies have investigated the antioxidant and antidiabetic effects of Vietnamese coloured rice. Although, there have been no studies on how these coloured rice varieties affect the glycemic index of patients.
This study was, therefore, aimed at examining the antioxidant and blood sugar-stabilizing effects of purple-brown rice, red rice, and black glutinous rice in streptozotocin-induced diabetic mice.

Materials and Methods

Sources of chemical reagents
The chemicals used in the study included Folin-Ciocalteu reagent (Darmstadt, Germany), streptozotocin (Sigma Chemicals, St. Louis, MO, USA), DPPH (2,2-diphenyl-1-picrylhydrazyl), Griess and ascorbic acid (MP Biomedicals, Illkirch, France), gallic acid (Riedel-de-Haen, Seelze, Germany), aluminum chloride, sodium carbonate, sodium nitroprusside, dinitro salicylic acid (BDH Labs, Kuwait City, Kuwait).

Sources of rice samples
In October 2016, rice samples were collected from a variety of locations in Vietnam, including red rice from the Dong Thap Muoi region, black glutinous rice from Thanh Hoa province, and purple-brown rice from Thai Binh Seed Company. The samples were handled and stored after collection in a dry location out of the sun.

Source of mice
Swiss albino male mice weighing 20-25 g (6-8 weeks old) were obtained from the Pasteur Institute in Ho Chi Minh City. They were divided into groups and fed for 1 week under standard conditions (relative humidity of 70%-80% and lighting time of 12 hours) to acclimatize to experimental conditions.

Ethical clearance
All the requirements and conditions of the rice experiment were strictly followed based on the policy of the Pasteur Institute (Ho Chi Minh City) and the Decision of the Ministry of Health of Vietnam (Decision 6455/2003/QĐ-BYT: Appendix 5 Provisional Instructions, 2.2 Experimental animals).

Preparation of various ethanol rice extracts
Fifty grams (50 g) of each rice sample were macerated in 96% ethanol at a 1/10 w/v ratio. After 24 hours, the extracts were filtered to collect the solution. The extract was obtained by using a vacuum rotary evaporator at 40^{o}C to obtain 96% ethanol crude extracts of the 3 rice varieties as follows: black glutinous rice (EOGT96), red rice (EOLO96), and purple-brown rice (EOLI96). The samples were stored at 4°C.[20]

Determination of the antioxidant activity of various rice extracts by DPPH assay
The antioxidant activity of all varieties of black glutinous rice, red rice, and purple-brown rice was evaluated using the DPPH (2,2-diphenyl-1-picrylhydrazyl) standard method.[21] A sample of 50 µL was mixed with 2 mL of a 6.10^{-5} M DPPH solution in methanol. The reaction mixture was then left in the dark for 15 minutes. The experiment was designed with three replicates. A T70 UV-visible spectrometer was used to measure the decrease in absorbance at a 517 nm wavelength. The antioxidant capacity was determined based on the IC_{50}, the concentration at which it was able to inhibit 50% of free radicals. Free radical scavenging activity was calculated as follows:

$$\% \text{ scavenging activity} = (A_c - A_s) \times 100/A_c \quad \text{-----------} (1)$$

Where A_c is the absorbance of the ascorbic acid sample that was utilized as the positive control, and A_s is the absorbance of the control sample, which was DPPH in methanol.[22]

Evaluation of the antioxidant activity of the various rice extracts by the nitric oxide method
The nitric oxide method was also used to evaluate the antioxidant activities of the various extracts according to the previously described technique.[23] A volume (2 mL) of 10 mM sodium nitroprusside in phosphate-buffered saline was mixed with test solutions in different concentrations and then incubated at ambient temperature for 30 min. Afterward, 0.5 mL of the mixture was added with Griess reagent (1 mL) and the absorbance was spectrophotometrically determined at 546 nm. The nitric oxide radicals scavenging activity was calculated as follows:

$$\% \text{ inhibition} = (A_b - A_s) \times 100/A_b \quad \text{------------} (2)$$

Where A_b represents the absorbance of the control (blank, without extract), and A_s stands for the absorbance of the extract.

Estimation of the total phenolic content of the various rice extracts
Total phenolic content (TPC) was estimated using a spectrophotometric method with Folin–Ciocalteau reagent.[24] One milliliter of the reaction solution was added to 5 mL of Folin–Ciocalteu reagent (10%), which was then thoroughly agitated. After 5 minutes, 4 mL of the 7.5% Na_2CO_3 was added, and the solution was then incubated for 30 minutes at 40°C. The optical density of the samples was measured at 765 nm. The total polyphenolic contents were measured and determined from the standard gallic acid curve.

Evaluation of the α-amylase inhibitory activity of the various rice extracts
The α-amylase inhibitory activity test was conducted based on the method described by Kazeem *et al*.[25] The rice extracts (250 µL) were incubated with α-amylase enzyme (from malt) in phosphate buffer pH 6.9 (0.5 mg/mL) at 37°C for 10 min. After that, 250 L of 1% starch was added, and the solution was again incubated for 5 minutes. By adding 500 µL of dinitrosalicylic acid to boiling water for 5 minutes, the reaction tinted the solution. After adding the dinitrosalicylic acid colour reagent, the water was brought to a boil for five minutes. The solution was slowly cooled to ambient temperature, then 5 mL of distilled water was added, followed by spectrophotometric measurements at 540 nm. Similar steps were taken to create the control, except distilled water was used in place of the rice extract. The positive control was starch soluble. The percentage inhibition of the α-amylase was calculated using the formula:

$$\% \text{ inhibition of } \alpha\text{-amylase} = (A_{control} - A_{sample}) \times 100/A_{control} \quad \text{---} (3)$$

Where $A_{control}$ is the absorbance of the control (distilled water), and A_{sample} is the absorbance in the presence of the extract.

Experimental groupings and treatments
A mouse model of type 1 diabetes was created based on the method described by Furman in 2021.[26] After the successful creation of a mouse model of type 1 diabetes, large numbers of diabetic mice were selected to evaluate the antihyperglycemic activity of the rice extracts according to a previously reported method.[26,27] Male mice were divided into six groups of 6 mice. Group I (negative control group) were normal mice. Mice with diabetes occupied group II (positive control group). Diabetes-prone mice in group III (the drug control group) were administered glibenclamide (10 mg/kg). Diabetic mice were given alcohol extracts from each kind of rice in groups IV (EOLT96), V (EOLI96), and VI (EOLO96). Fasting blood samples were collected in the morning of days 1, 7, 14, and 21, and a glucose oxidase method was employed immediately to estimate the blood glucose levels.

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Statistical analysis
All data were analyzed and presented as mean ± standard deviation using Microsoft Excel 2016 and SAS (r) 9.4. The student t-test was used to compare the mean values of various parameters. To examine the statistically significant differences in all experimental data, the significance level of $p < 0.05$ was used.

Results and Discussion

The DPPH free radical scavenging capacity of various rice extracts
Free radicals are linked to the pathogenesis of diabetes complications, cardiovascular and neurodegenerative diseases, cancer, and inflammatory diseases.[28,29] The DPPH assay is commonly used in antioxidant studies because it provides a simple, rapid, and stable way to screen a huge number of antioxidant samples. As shown in Table 1, out of the 3 ethanol extracts, EOLI96 had the best antioxidant capacity (IC_{50} = 19.38 ± 0.64 µg/mL) but was still 3.6 times less than the control ascorbic acid. This was followed by EOLT96 (20.22 ± 0.61 µg/mL) and EOLO96 (21.45 ± 0.72 µg/mL). The results also show that the ethanol extract of purple-brown rice displayed greater antioxidant capacity than red rice and black glutinous rice at the same concentration. The reason is that the anthocyanin content in purple-brown rice is higher than that of black glutinous rice, which is a natural colorant with a strong antioxidant capacity.[30] In addition, ethanol solution can extract a variety of antioxidant molecules with bioactivity.[31]

The nitrite-free radical scavenging activity of the various rice extracts
NO is a potent oxidizing free radical that can damage cells, alter their structure and function, and cause organ failure, in addition to being the cause of numerous diseases. The black glutinous rice extract (EOLT96) e also strong antioxidant substances, which is very important in studiehad higher NO free radical scavenging activity than the other two types of rice extracts. However, the free radical scavenging activity of purple-brown rice extract (EOLI96) with an IC_{50} of 102.49 µg/mL was 4.16 times lower than that of the standard control, purified quercetin (IC_{50} = 24.64 µg/mL). The IC_{50} value of EOLT96 at 91.36 g/mL, was 3.7 times lower than quercetin. According to reports, whole grain red and black rice have more antioxidant activity than light brown rice. The removal during the polishing of a thin but antioxidant-rich bran layer of brown rice may result in lower antioxidant activity. This revealed that black rice is a better source of antioxidants in comparison with brown rice, which is commonly consumed in people's diets.[32, 33]

Total phenolic content of the various rice extracts
Polyphenols are one of the most important compounds and account for a significant proportion of plants. They have antioxidant activity.[34] In addition, phenolic antioxidants play a mediating role in amylase inhibition and are considered useful in the control of type 2 diabetes.[35] The total polyphenol content obtained depends on the rice variety and the type of solvent used in the extraction process. In alcohol extracts, EOLT96 (9.28 ± 0.14 mg GAE/g extract) contained a higher (32.7%) total polyphenol content than EOLO96 (6.99 ± 0.28 mg GAE/g extract) and 3% higher than that of EOLI96 (9.01 ± 0.08 mg GAE/g high extract). It can be inferred that black glutinous rice has more antioxidants than the other two rice varieties. The TPC content in the rice extract was much higher than that of the outer bran layer (2.5 ± 0.3 mg GAE/g), suggesting that this content can be used as an effective source of antioxidants for nutrition and functional foods.[36]

The α-amylase inhibitory activity of the different rice extracts
The pancreas secretes the enzyme α-amylase into the small intestine, where it hydrolyzes carbohydrates into oligosaccharides and then into blood glucose, which provides energy for all of the body's cells. Elevated carbohydrate intake, however, may result in high blood sugar, which worsens diabetes. Chronic hyperglycemia leads to diabetes mellitus. By delaying starch-hydrolyzing enzymes, α-amylase inhibitory action prevents the rise of diabetes. As shown in Figure 1, at concentrations of 15-37.5 mg/mL (corresponding to a final solution concentration of 288-1442 g/mL), EOLI96 and EOLG96 had nearly identical α-amylase inhibitory activity. At the maximum dose (45 mg/mL), the EOLO96 extract had the lowest α-amylase inhibition (67.3%) while black glutinous rice had the highest α-amylase inhibition (77.38%). As a result, it was discovered that EOLT96 and EOLI96 extracts are more potent than EOLO96 extracts in terms of inhibiting the α-amylase enzyme and reducing free radicals.

The hypoglycemic effects of the various rice extracts in streptozotocin-induced diabetic mice
Streptozotocin is a commonly used chemical for the induction of type I diabetes in laboratory animals. The cytotoxic effect of the STZ allergen is mediated by reactive oxygen species by attacking molecules in biological membranes and tissues, leading to the progression of diabetes-related complications. The hyperglycemic effect of the extracts in STZ-induced diabetic mice is shown in Figure 2. Administration of STZ (150 mg/kg) induced diabetes in mice with a blood glucose level higher than 18 mmol /L on the 7^{th} day after injection. There was a remarkable improvement in oral glucose tolerance in mice that were fed chronic rice extract till day 14. On day 21, mice from groups IV to VI displayed blood sugar stability with blood glucose concentration values of 7.0 ± 0.4, 7.6 ± 0.3, and 7.9 ± 0.6 mmol/l, respectively (equivalent to a reduction of 52.77, and 56.03%, respectively compared to the first-day blood glucose concentration). The same observation was made in the group of mice with black glutinous rice alcohol extract (group IV) compared to the drug control group (group III) at the same dose (blood glucose concentration 6.4 ± 0.5 mmol/l). Oxidative stress plays a major role in the onset of β cells damage and insulin resistance.[37] The mechanisms by which oxidative stress is increased in diabetes may be related to metabolic stress, autoxidative glycosylation, and non-enzymatic glycosylation.[38]

Table 1: Antioxidant capacity of different extracts from three coloured rice varieties.

Sample	DPPH (IC_{50}, µg/mL)	Nitric oxide (IC_{50}, µg/mL)	TPC (mgGAE/g extract)
EOLI96	19.38 ± 0.64	102.49 ± 0.57	9.01 ± 0.08
EOLO96	21.45 ± 0.72	128.57 ± 0.62	6.99 ± 0.28
EOLT96	20.22 ± 0.61	91.36 ± 0.81	9.28 ± 0.14
Standards	5.39 ± 0.44	24.64 ± 0.48	-

DPPH: 2,2-diphenyl-1-picrylhydrazyl; TPC: Total phenolic content; Ethanol extracts from: purple-brown rice (EOLI96); red rice (EOLO96); black glutinous rice (EOGT96).

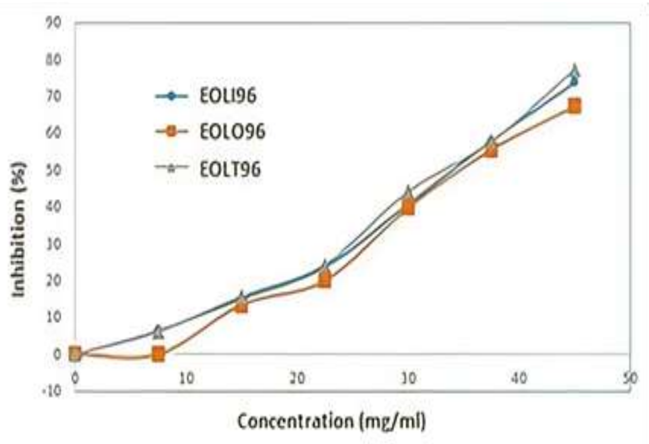

Figure 1: The α-amylase inhibitory activity of different extracts from three coloured rice varieties. Ethanol extracts from purple-brown rice (EOLI96), red rice (EOLO96), and black glutinous rice (EOLT96).

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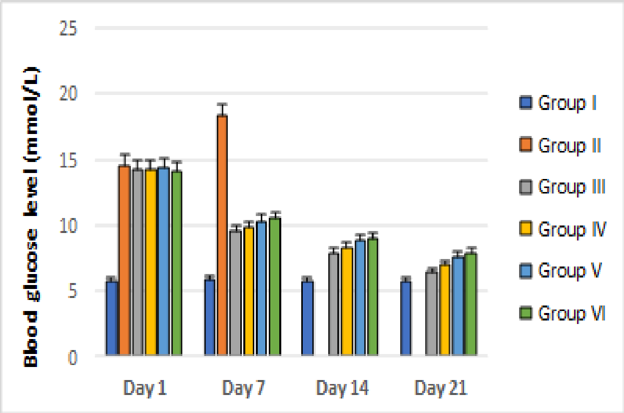

Figure 2: Glycemic index of type 1 diabetic mice model induced by STZ for 21 days. Group I: Normal control mice that received water; Group II: Streptozotocin-induced diabetic mice treated with water; Group III: Drug control group; Diabetic mice, which received ethanol extracts from Purple brown rice (Group IV), Red rice (Group V), and Black glutinous rice (Group VI).

Regular glutinous rice with the bran removed is not recommended for diabetes patients because it can increase blood sugar levels. However, glutinous brown rice or other brown rice can be useful for diabetes patients as they contain B-vitamins, chromium, γ-aminobutyric acid (GABA), and other colorant ingredients that help regulate insulin secretion. Oxidative stress plays an important role in the development of complex complications of type 2 diabetes.[39] Free radicals damage cell proteins, membrane lipids, and nucleic acids when they are overexpressed, which results in cell death.[40] Pancreatic α-amylase is an enzyme that aids in carbohydrate digestion and raises blood glucose levels after meals. A method to effectively reduce post-eating hyperglycemia with an inhibitory effect on α-amylase activity is crucial in preventing type 2 diabetes complications. Understanding antioxidants and the inhibition of natural α-amylase is critical for regulating post-meal hyperglycemia and preventing diabetes complications with minimal side effects.[41]

Conclusion

The findings of this study revealed that all the three ethanol extracts from the three coloured rice varieties (purple-brown rice, red rice, and black glutinous rice) have strong antioxidant activity. Meanwhile, the black glutinous rice extract had the highest antioxidant activity and great potential to prevent and reduce the incidence of diabetes. It is therefore recommended that utilizing black glutinous rice is crucial for the best diabetes management. Although purple-brown rice and red rice have not been shown to lower blood sugar, the study also recommends that they have extensive biological activity as antioxidants.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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