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Original Article

Pharmacological studies of the genus rice (*Oryza L.*): a literature review

Estudos farmacológicos do gênero arroz (*Oryza L.*): uma revisão de literatura

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Abstract

Rice (*Oryza* L.) is an essential food for more than 50 percent of the world's population and is the world's second-largest grain crop. Pigmented rice comes in various colors, such as black, red, brown, and green. Anthocyanins, like cyanidin-3-O-glucoside and peonidin-3-O-glucoside, are the primary color pigments in colored rice, whereas proanthocyanidins and flavan-3-ol oligosaccharides, with catechins as the central synthesis unit, are found in brown rice. This review article's aim is to give information and a summary of rice activities, research methods, also mechanisms of action (*Oryza* L.). Intake of pigmented rice was already associated with a number of health benefits, including antioxidant activity, anticancer, antitumor, antidiabetic activity, and a reduced risk of cardiovascular disease. Rice contains several bioactive compounds, such as γ-oryzanol, phenolic acid, anthocyanins, proanthocyanidins, flavonoids, carotenoids, and phytosterols, which have been widely studied and shown to have several pharmacological activities. The use of current herbal compounds is rapidly increasing, including the practice of pharmacological disease prevention and treatment. Herbal remedies have entered the international market as a result of research into plant biopharmaceuticals and nutraceuticals. Through a variety of pharmacological activities, it is clear that *Oryza L.* is a popular herb. As a result, additional research on *Oryza L.* can be conducted to investigate more recent and comprehensive pharmacological effectiveness, to provide information and an overview of Rice (*Oryza* L.) activities, research methods, and mechanisms of action. Several natural substances are characterized by low water solubility, low stability, and sensitivity to light and oxygen, and the potential for poor absorption of the active substances requires modification of the formulation. To improve the effectiveness of pharmacologically active substances originating from natural ingredients, drug delivery systems that use lipid-based formulations can be considered innovations.

Keywords: rice, *Oryza* L., pigmented rice, non-pigmented rice, pharmacological activity, cyanidin-3-O-glucoside.

Resumo

O arroz (*Oryza L.*) é um alimento essencial para mais de 50% da população mundial e é a segunda maior safra de grãos do mundo. O arroz pigmentado possui cores variadas, como preto, vermelho, marrom e verde. As antocianinas, como a cianidina-3-O-glicosídeo e a peonidina-3-O-glicosídeo, são os pigmentos de cor primária no arroz colorido, enquanto as proantocianidinas e os oligossacarídeos flavan-3-ol, com catequinas como unidade central de síntese, são encontrados no arroz marrom. O objetivo deste estudo de revisão é fornecer informações e um resumo das atividades do arroz, métodos de pesquisa e mecanismos de ação. A ingestão de arroz pigmentado já foi associada a vários benefícios à saúde, incluindo atividade antioxidante, anticancerígena, antitumoral, antidiabética e redução do risco de doenças cardiovasculares. O arroz contém vários compostos bioativos, como γ-orizanol, ácido fenólico, antocianinas, proantocianidinas, flavonoides, carotenóides e fitoesteróis, que têm sido amplamente estudados e têm mostrado diversas atividades farmacológicas. O uso de compostos fitoterápicos atuais está aumentando rapidamente, incluindo a prática de prevenção e tratamento farmacológico de doenças. Os remédios fitoterápicos entraram no mercado internacional como resultado da pesquisa de biofármacos e nutracêuticos vegetais. Através de uma variedade de atividades farmacológicas, fica claro que *Oryza L.* é uma erva popular. Como resultado, pesquisas adicionais sobre *Oryza L.* podem ser conduzidas para investigar a eficácia farmacológica mais recente e abrangente, fornecer informações e uma visão geral das atividades, métodos de pesquisa e mecanismos de ação do arroz (Oryza L.). Várias substâncias naturais são caracterizadas por baixa solubilidade em água, baixa estabilidade e sensibilidade à luz e ao oxigênio, e o potencial de má absorção das substâncias ativas requer modificação da formulação. Nesse sentido, alguns aspectos como a melhorara na eficácia de substâncias farmacologicamente ativas provenientes de ingredientes naturais e nos sistemas de liberação de fármacos que utilizam formulações à base de lipídios podem ser considerados como inovações.

Palavras-chave: arroz, *Oryza L.*, arroz pigmentado, arroz não pigmentado, atividade farmacológica, cianidina-3-O-glicosídeo.

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1. Introduction

Rice (*Oryza* L.) contains many sources of nutrients and essential components of functional foods, such as fiber, starch, minerals, and antioxidants (Fuller et al., 2016). Dietary fibers, such as polysaccharides, oligosaccharides, pectic substances, starch, gums, lignin, and many other related substances, have many health benefits for the body (Rebeira et al., 2022). The primary color pigments within colored rice are anthocyanins, such as cyanidin-3-O-glucoside then peonidin-3-O-glucoside, while brown rice contains proanthocyanidins and flavan-3-ol oligomers, with catechins as the central production unit (Ziegler et al., 2018). The utilization of pigmented rice is related to some health benefits, such as antioxidant activity, anticancer, antitumor, antidiabetic, and a reduced risk of cardiovascular disease (Kim et al., 2021). Rice contains nutritional compounds such as protein, fat, starch, vitamins (B1, B2, E), minerals (Zn, Mg, Mn, K, Ca), amino acids (glutamic acid, glycine, valine, arginine, aspartic acid, leucine, alanine, phenylalanine, proline, serine, tyrosine, and threonine) (Kusumawati et al., 2021; Yamuangmorn and Prom-U-Thai, 2021). Some of the pharmacological activities possessed by rice include antioxidant, anti-inflammatory, antiproliferative, anticancer, antidiabetic, antihyperlipidemic, antiaging, antiultraviolet, antiviral, antiobesity, antineurodegenerative, gastroprotective, nephroprotective, immunomodulatory, antiplatelet, hepatoprotective, and reducing the risk of coronary heart disease, as well as being tyrosinase enzyme inhibitors (Sui et al., 2016; Hou et al., 2013; Arjinajarn et al., 2017; Jiang et al., 2015; Chen et al., 2012; Pengkumsri et al., 2015; Sheikha et al., 2024; Phannasorn et al., 2021; Pannangrong et al., 2011; Ohnon et al., 2019; Candiracci et al., 2014; Kim and Lim, 2016; Pramai and Jiamyangyuen, 2016; Prom-U-Thai et al., 2016; Jung et al., 2021; Salee et al., 2022; Shao et al., 2014; Shalini et al., 2012; Min et al., 2010; Chen et al., 2006). The main components of rice are polyphenolic compounds, flavonoids, and anthocyanins (Tapas et al., 2008; Ghasemzadeh et al., 2018a), which have poor physicochemical stability in the digestive tract (Kesharwani et al., 2020). Flavonoids are included in the category of active compounds that have low solubility and bioavailability properties and low intestinal permeability; most flavonoids are included in the Biopharmaceutics Classification System (BCS) IV category (Li et al., 2019). The gastrointestinal tract degrade phenolics, and flavonoids are unstable in intestinal pH, which adversely affects their solubility, absorption, dissolution, bioavailability, and efficacy (Yao et al., 2010; Kesharwani et al., 2020). The results of pharmacological activity tests have shown poor efficacy in several studies compared to their comparison compounds despite the fact that rice contains a high level of secondary metabolites containing anthocyanins, flavonoids and phenols (Yamuangmorn and Prom-U-Thai, 2021; Arjinajarn et al., 2017; Chen and Inbaraj, 2019; Ghasemzadeh et al., 2018a; AlAli et al., 2021). It is therefore necessary to increase the pharmacological activity and physicochemical stability of rice extract (Chen and Inbaraj, 2019). One method involves a delivery system with lipid carriers through the oral route; however, the oral route shows low bioavailability and low solubility also membrane permeability (Arzani et al., 2015). Consequently, there is a great urgency to advance drug delivery systems in support of oral administration. The truth that the oral absorption of poorly water-soluble drugs can be enhanced by coadministration together with high-fat foods has led to the development of lipid-based formulations to increase drug solubility and absorption during oral administration (Subramanian, 2021). Lipid-based formulations are a promising approach to improving lipophilic drugs' water solubility and oral absorption. The primary purpose of this type of formulation is to maintain the solubility of the drug in the gastrointestinal tract (Cásedas et al., 2019; Mohammed and Khan, 2022). A lipid-based nanocarrier or lipid-based drug delivery system is one lipid-based formulation in nanotechnology preparations. The mechanism of action for the delivery of lipid-based drugs involves increasing the solubility of bioactive compounds in digestive tract fluids, increasing absorption by increasing wetting in the intestinal environment, directing the metabolic process of bioactive compounds through intestinal lymphatics, and changing the transport of enterocyte-based bioactive compounds. Lymphatics transport protect the bioactive compound from first-pass metabolism (Subramanian, 2021; Tan and Billa, 2021; Nakmode et al., 2022). Among the many lipid-based drug delivery systems, the Self Nanoemulsifying Drug Delivery System (SNEDDS) is one of the most studied oral drug delivery systems (Buya et al., 2020). Strategies for increasing the oral bioavailability of poorly water soluble flavonoids are summarized in Figure 1.

2. Methods

This review uses a comparative method, collecting various sources from research journals. This is a review article and not a systematic literature review. Original research and review/open review journals from the last 10 years, were included. This journal review was carried out using the PubMed, Scopus, and Science Direct databases. Exclusion criteria were: journals outside the last 10 years, journals that were not original research, and review or open review journals. Articles were retrieved using the search terms "*Oryza* L" OR "Rice" AND "pharmacological activities."

3. Results and Discussion

3.1. Phytochemical studies

Oryza L. contains several bioactive compounds, such as γ-oryzanol, phenolic acids, anthocyanins, proanthocyanidins, flavonoids, carotenoids, and phytosterols. These have been extensively studied and shown to have several pharmacological activities such as hepatoprotective (Sangkitikomol et al., 2010; Hou et al., 2010; Hou et al., 2013; Xiao et al., 2020), gastroprotective (Tonchaiyaphum et al., 2021), antibacterial (Martillanes et al., 2020; Sani et al., 2018), antivirus

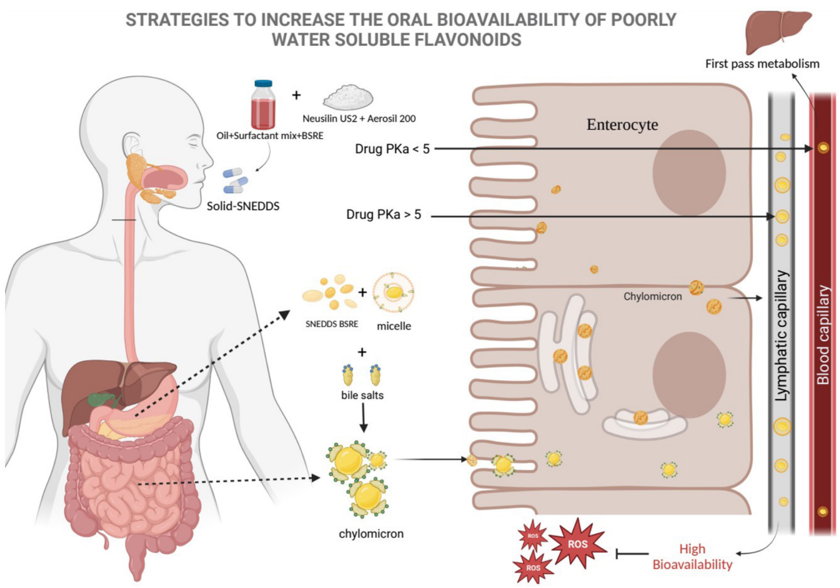

Figure 1. Strategies to increase the oral bioavailability of poorly water soluble flavonoids (created with BioRender.com).

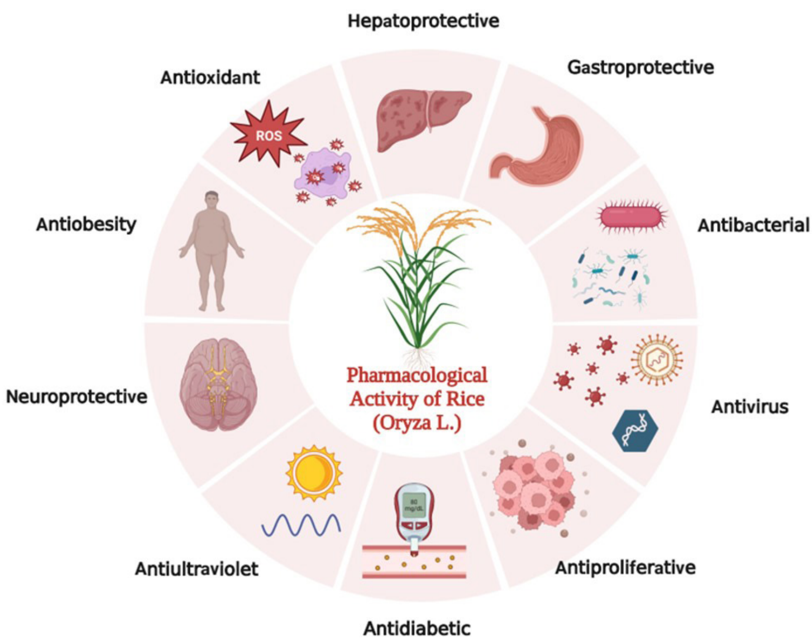

Figure 2. Several pharmacological activities of rice (created with BioRender.com).

(Yang et al., 2015), antiproliferative (Ghasemzadeh et al., 2018b), antidiabetic (Duansak et al., 2022; Liu et al., 2020), Antiultraviolet potential (Kusumawati et al., 2021), Neuroprotective (Pannangrong et al., 2011; Ohnon et al., 2019; Vargas et al., 2018), antiobesity (Duansak et al., 2022; Liu et al., 2020), antioxidant (Sui et al., 2016; Pramai and Jiamyangyuen, 2016). Some of the many pharmacological activities of rice are summarized in Figure 2.

3.2. Pharmacological studies

3.2.1. Antioxidant potential

Rice is the world's leading cereal crop and is consumed by more than half of the world's population. The bran layer that covers the rice grains is packed with nutrients and phytochemicals, including tocopherols, tocotrienols, γ-oryzanol, B vitamins, and phenolic compounds. Some of these substances are believed to play an important role in protecting against various degenerative diseases (Pramai and Jiamyangyuen, 2016). It has been commonly reported that anthocyanins play an essential function in reducing the risk of oxidative damage and are potential drug candidates for treating cancer and cardiovascular diseases (Hao et al., 2015). The study found that cyanidin-3-O-glucoside (Cy-3-G) has a strong antioxidant activity and can reduce the levels of free radicals, which is beneficial for the health of the cells. The ferric reducing antioxidant power and iron-reducing antioxidant strength of Cy-3-G were also found to be high (Del Rio et al., 2013; Cásedas et al., 2019; Andriani et al., 2022). Cyanidin-3-O-glucoside, commonly known as kuromanin, is one of nature's greatest quantities of anthocyanins. The possible therapeutic significance of this anthocyanin in the prevention or treatment of chronic disorders in which oxidative stress is possibly implicated via the regulation of some enzymes. Anthocyanins have been widely reported as antioxidant agents in a variety of in vitro, in vivo, and human investigations (Del Rio et al., 2013). Cyanidin-3-O-glucoside, also known as kuromanin throughout the text in Figure 3. Some of the research relating to rice varieties used to test antioxidant activity is summarized in Table 1.

3.2.2. Neuroprotective potential

The riceberry is given once a day, with doses including 180, 360, and 720 mg/kg body weight (BW) for 2 weeks before and 1 week after induction of memory deficit and cholinergic lesions with specific cholinotoxin AF64A via bilateral intracerebroventricular administration. The results showed that rice berries could significantly prevent memory impairment and hippocampal neurodegeneration in the hippocampus. In addition, riceberry could also reduce hippocampal acetylcholinesterase activity and the formation of lipid peroxidation products (Pannangrong et al., 2011). The extract of black sticky rice and Anethum graveolens Linn improved memory in a study of post-stroke events. This was due to a decrease in oxidative stress, GFAP-positive cells, and neuroinflammatory cytokines such as TNF- and IL-6 (Ohnon et al., 2019). The brown and black rice bran extracts showed similar protective activity against neurons similar to human cells (SH-SY5Y). The content of phenolic

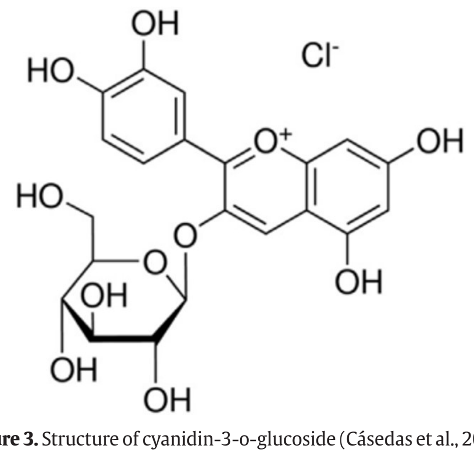

Figure 3. Structure of cyanidin-3-o-glucoside (Cásedas et al., 2019).

compounds in rice bran was separated into two types: the hydrophilic fraction and pellets. The primary phenolic compound in both samples was ferulic acid. Cyanidin-3-O-glucoside was the major anthocyanin in black rice bran. None of the extracts showed cytotoxicity in sulforhodamine B-induced metal assays. These results demonstrate the potential of brown and black rice bran extracts as sources of bioactive compounds with neuroprotective activity (Vargas et al., 2018).

3.2.3. Hepatoprotective potential

The liver is an important part of the body's detoxification process, as it helps to eliminate a wide range of drugs and substances that can cause damage. Exposure to harmful chemicals and toxins can cause the liver to function less effectively (Arjinajarn et al., 2017). A variety of plant extracts with strong antioxidant activity and potential hepatoprotective activity have been reported as functional foods. In addition to their use as food colorings, anthocyanins have attracted great interest from researchers because they have shown numerous biological activities, including protection from Alzheimer's and other diseases due to their powerful antioxidant activity. Furthermore, oxidative stress has been reported to be an important mechanism in the development and increase of liver diseases from various causes. Therefore, anthocyanins with antioxidant activity are believed to be beneficial to liver health, and several studies have reported hepatoprotective effects of anthocyanin extracts from foods and plants (Hou et al., 2013). Table 2 summarizes some of the hepatoprotective activities from several rice varieties. The Cyanidin-3-O-glucoside activates response element Nrf2-antioxidant as a hepatoprotective is summarized into Figure 4.

3.2.4. Antiultraviolet potential

Determining the sun protection factor (SPF) value of black sticky rice extract (Oryza sativa var. glutinosa) showed that increasing the extract's concentration will increase the SPF value. Black glutinous rice contains anthocyanins. Anthocyanins are derivatives of flavonoids through the phenylpropanoid pathway, which are derived from malonyl-CoA and p-coumaroyl-CoA precursors. Flavonoids have a protective effect from ultraviolet radiation due to their ability to transfer electrons to free radicals, activate antioxidant enzymes, and inhibit oxidation. In addition to providing a protective effect from ultraviolet radiation from the sun, anthocyanins can also provide a protective effect from ultraviolet radiation produced by reactive oxygen species (ROS). The most common type of anthocyanin found in nature is Cy-3-G; the photoprotective properties of cyanidin-3-glucoside help fight UV-A and UV-B radiation. Pre-treating cells with cyanidin-3-glucoside inhibited the deleterious effects of UV-B radiation, including the translocation of transcription factors NF-kB and AP-1, the overexpression of pro-inflammatory cytokine IL-8, and procaspase-3 cleavage (Kusumawati et al., 2021).

3.2.5. Antiproliferative potential

The antiproliferative activity of black, red, and brown rice bran was assessed on breast cancer cells (MCF-7 and

Table 1. Antioxidant activity of rice (*Oryza* L.).

Variety (source)	Method	Effect	Reference
Rice bran	Treated with various types of carbohydrase enzymes, such as Viscozyme, Termamyl, Celluclast, amyloglucosidase (AMG), Ultraflo, and Pentopan, to increase antioxidant activity.	All added carbohydrase enzymes were proven to increase the antioxidant activity of the rice bran extract by 1.5-3.3 times.	Kim and Lim, 2016
Brown, black, and white rice of various varieties available in Thailand	A total of 20 rice varieties were studied for their content of anthocyanins, phenols, flavonoids, α-tocopherol, DPPH activity, ferric reducing antioxidant power (FRAP), and Trolox equivalent antioxidant capacity (TEAC).	The highest content of total phenolic, flavonoid, and α-tocopherol was found in black rice, followed by brown rice, and pigmented rice varieties had the highest antioxidant activity.	Pramai and Jiamyangyuen, 2016
Thai rice (various varieties)	Treated using DPPH method.	There was a positive correlation between high levels of Zn and antioxidant activity; on the other hand, a negative correlation was found between levels of Fe and antioxidant activity.	Prom-U-Thai et al., 2016
Black rice	Treated with pulsed electric feld (PEF) in black rice using the specified treatment technique.	Optimizing the PEF treatment conditions to 5 kV/cm, 3000 beats, and 0.5 g/mL produced higher C3G, with levels of 92.59 ± 4.79 mg/g, and as much as 4.59 ± 0.27 mg/g P3G compared with the process involving no PEF, an increase of 60%.	Salee et al., 2022
Embryo, bran, endosperm flour, and black, red, and white rice grain flour	Treated using DPPH method.	The TPC (total phenolic content) was highest in bran, with an average of 7.35 mg GAE/g, and there was 60%, 86%, and 84% phenolic content in white, red, and black rice.	Shao et al., 2014
Black glutinous rice	Treated using DPPH method.	The results of the study showed that black glutinous rice extract has weak antioxidant activity, with an IC50 value of 318.883 ppm compared to the comparison compound, vitamin C, which had an IC50 of 3.688 ppm.	Kusumawati et al., 2021
Red and black glutinous rice bran.	Red and black glutinous rice bran were treated with DPPH method.	The antioxidant activity test results showed that the antioxidant activity of the red glutinous rice bran extract is more potent than the black glutinous rice bran extract.	Suhery et al., 2016
Black rice flour	This study aimed to identify and quantify the relationship of anthocyanins in several cultivars of black rice (Oryza sativa L.) to their antioxidant activities.	The antioxidant activity of black rice extract containing 41.69% anthocyanin was tested by a KBrO3-induced kidney injury model in rats.	Hao et al., 2015
A total of 15 rice varieties from Shangdong province, China.	This study was undertaken to determine whether or not there is a correlation between the color pigments in several varieties of rice (white, red, and black) and the total content of phenolic acids, proanthocyanidins, anthocyanins, antioxidant activity, and mineral content.	The correlation analysis results confirmed that the phenolic compound content significantly contributes to the antioxidant activity of the rice.	Shao et al., 2018
Cyanidin-3-O-β-glucoside synthesized from black rice.	Hepatotoxic testing was conducted using test animals in male mice strain C57BL/6 with an age of 8 weeks, induced with carbon tetrachloride compound (CCl4) and treated with black rice extract, which contains a high Cy-3-G compound (800 mg/kg BW).	The study found that Cy-3-G suppresses proinflammatory cytokine production by inhibiting the activation of hepatic stellate cells (HSC).	Jiang et al., 2015

BW - body weight, Cy-3-G - cyanidin-3-O-glucoside, DPPH - 2,2-diphenyl-1-picrylhydrazy radical scavenging activity, FRAP - ferric reducing antioxidant power iron-reducing antioxidant strength, HSC - hepatic stellate cells, IC50 - half maximal inhibitory concentrations, P3G - peonidin-3-glucoside, PEF - pulsed electric field, TEAC - trolox equivalent antioxidant capacity, TPC - total phenolic content.

Table 2. Hepatoprotective activities of several rice varieties.

Compound	Method	Results	Reference
Anthocyanin-rich extract black rice (AEBR)	*In vivo*	The administration of AEBR (500 mg/kg) together with alcohol significantly ($p<0.01$) reduced liver enzyme activity aspartate transferase (AST), alanine transferase (ALT), and gamma glutamyl transferase (GGT), malondialdehyde (MDA) levels, and liver TG and TC levels	Hou et al., 2010
Black rice bran extract, which is rich in anthocyanin compounds	*In vivo*	Similarly, preincubation of L-02 cells with Cy-3-G or P3G significantly reduced the injury rate to CCl4-induced hepatocyte cells, indicating higher cell viability, decreased aminotransferase activity, and improved cellular antioxidant status. Furthermore, Cy-3-G showed significantly more potent hepatoprotective activity than P3G at the same concentration.	Hou et al., 2013
Rice bran phenolic extract (RBPE)	*In vivo*	The administration of reduced-ethanol-equivalent diet (RBPE) reduced ethanol-induced mitochondrial dysfunction by altering membrane potential, mitochondrial DNA (mtDNA) content, and mitochondrial respiratory chain complex enzyme activity, resulting in increased adenosine triphosphate (ATP) production in the liver.	Xiao et al., 2020
Cyanidin-3-O-β-glucoside purified from black rice	*In vivo*	Additionally, Cy-3-G positively regulated liver oxidative stress and apoptosis	Jiang et al., 2015
Black rice anthocyanins nano-composite	*In vivo*	A highly significant protective effect was seen with anthocyanin nano-composite against methotrexate (MTX)-related hepatotoxicity, and reversing the effects of MTX on NC-like enzymatic and nonenzymatic indicators showed that anthocyanin nano-composite is a key mechanism in inhibiting the liver in opposition to MTX's chemotherapy-related adverse effects.	Sheikha et al., 2024
Black rice ethanolic extract (BREE)	*In vivo*	The rats treated with EA at a dose of 6 g/kg body weight daily showed an increase in total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), thiobarbituric acid (TBA), and F2-isoprostanes (p<0.05), and a decrease in high density lipoprotein cholesterol (HDL-C), superoxide dismutase (SOD), and glutathione (GSH).	Suhailah and Soheir, 2018
Black rice extract (BRE)	*In vivo*	The dietary supplementation of BRE improved the serum lipid profile.	Jang et al., 2012
White and colored rice bran oil (CRBO)	*In vivo*	Vitamin E, phytosterols, carotenoids, and chlorophyll are protective compounds in CRBO that reduce hepatotoxicity induced by APAP induction through impaired APAP metabolism and activation of antioxidant systems in both rats and humans.	Phannasorn et al., 2021
Riceberry (Thai purple black rice)	*In vivo*	The levels of liver marker enzymes, AST and ALT, were significantly increased in gentamicin-treated rats, and the total protein was significantly decreased. Gentamicin injection caused a significant increase in liver Malondialdehyde (MDA) levels and decreased SOD expression.	Arjinajarn et al., 2017

AEBR - anthocyanin-rich extract black rice, ALT - alanine transaminase, APAP - acetaminophen, AST - aspartate transaminase, ATP - Adenosine triphosphate, BRE - black rice extract, BREE - black rice ethanolic extract, Cy-3-G - cyanidin-3-O-glucoside, CRBO - colored rice bran oil, EA - ethyl alcohol, GGT - gamma glutamyl transferase, GSH - glutathione, HDL-C - high-density lipoprotein-cholesterol, LDL-C - low-density lipoprotein-cholesterol, MDA - malondialdehyde, MTX - Methotrexate, P3G - peonidin-3-glucoside, RBPE - rice bran phenolic extract, SOD - superoxide dismutase, TBA - thiobarbituric acid, TC - total cholesterol, TG - triglyceride.

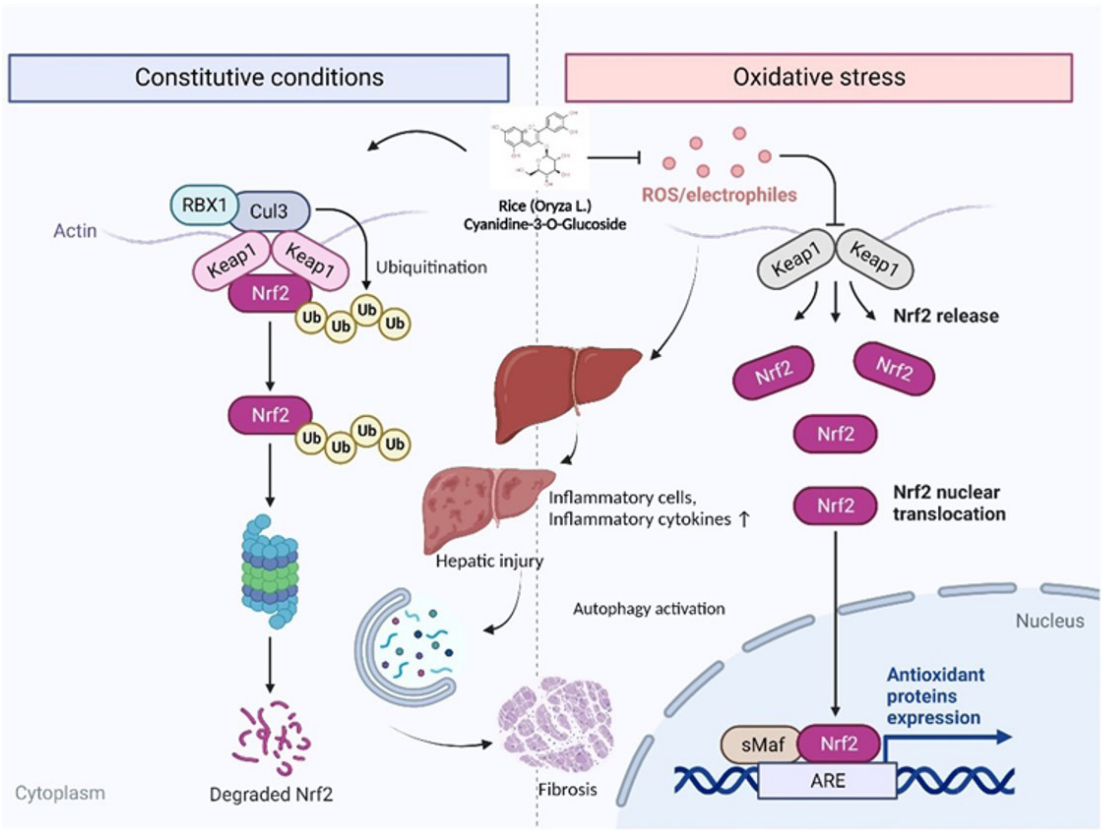

Figure 4. Cyanidin-3-O-glucoside activates response element Nrf2-antioxidant as a hepatoprotector (created with BioRender.com).

MDA-MB-231) using the MTT test. This revealed that the levels of flavonoid and phenolic compounds were significantly higher than those of ferulic acid and coumaric acid. The highest antioxidant activity was observed in black rice bran, brown rice bran extract, and brown rice. Black rice bran extract showed antiproliferative activity, with half maximal inhibitory concentrations (IC50) of 148.6 and 119.2 mg/mL against MCF-7 and MDA-MB-231 cells, respectively, compared to the activity of the bran extract (Ghasemzadeh et al., 2018b).

3.2.6. Gastroprotective potential

The effectiveness of 800 mg/kg black rice bran was almost comparable to that of omeprazole at 10 mg/kg, with rates of 78.9% and 85.2% for ulcer inhibition. Black rice bran cannot normalize the quantity of stomach mucus walls, downgrade gastric volume and total acidity, or increase gastric pH. However, it can enhance the nitric oxide levels in gastric tissue, with tissue MDA levels being normalized with DPPH radical scavenging activity. These results confirm the gastroprotective activity of black rice bran, with a potential mechanism of action through antioxidant activity. The major phytochemical components of black rice bran consist of carotenoid derivatives in the presence of phenolic compounds, and these components may be responsible for its gastroprotective activity. An oral dose of 2000 mg/kg black rice bran showed no acute toxicity in mice, confirming its safe use. Numerous noble chemical components can be found in black rice bran, with γ-oryzanol, α-tocopherol, phenolic acids, anthocyanins, and gallic acid being the most important substances. Because of their potent antioxidant activities, γ-oryzanol and tocopherol are thought to play the most vital roles in the advancement and acceleration of gastric ulcer rejuvenation (Tonchaiyaphum et al., 2021).

3.2.7. Antiobesity potential

Rice bran has antioxidant and cardioprotective properties, which may help to improve things like blood pressure, hepatic steatosis, and inflammation. It is also possible that rice bran extract can help to organize adipose tissue growth and obesity. In addition to body weight, adipose tissue mass, and vessel density, real-time polymerase chain reaction was used to observe the mRNA expression of angiogenic variables such as matrix metalloproteinases, Mmp-2, Mmp-9, and the vascular endothelial growth factor (Vegf) in visceral and subcutaneous adipose tissues. The management of rice bran extract to high-fat diet-induced overweight mice reduced body weight and adipose tissue mass compared to untreated mice (Duansak et al., 2022). Supplementation of whole-grain black rice as a high-protein crop significantly reduced lipid accumulation in C57BL/6J mice, indicating that the bioactive compounds in this type of rice could be beneficial for preventing obesity-related dyslipidemia and steatosis of the liver. These findings support the idea that whole-grain black rice could help protect against obesity-related dyslipidemia and related health problems. Whole-grain black rice decreased body weight and the visceral weight gain caused by a high-fat diet, reduced serum total cholesterol (TC), triglyceride (TG), and non-high-density lipoprotein-cholesterol (non-HDL-C)/high-density lipoprotein-cholesterol (HDL-C) levels, and increased fecal sterols and fat excretion. In addition, whole-grain black rice reduced hepatic TG and TC levels via the adenosine 5′-monophosphate-activated protein kinase (AMPK) pathway (Liu et al., 2020).

3.2.8. Antimicrobial potential

Two extracts enriched with different bioactive compounds were obtained and characterized. Among them were phenolic compounds, particularly ferulic and ρ-coumaric acids, and γ-oryzanol, which were abundant in these extracts. The antimicrobial effect of rice bran has only been studied in a medical setting. According to the most recent estimates, at least 15 bioactive compounds in rice bran may contribute to its antimicrobial ability, which has been tested on a variety of bacteria. For example, rice bran extract inhibited *Salmonella typhimurium* entry and replication in mouse small intestinal epithelial cells in vitro. Furthermore, rice bran and its extracts inhibited Clostridium spp., *Salmonella enterica, Vibrio cholerae*, Shigella spp., and Escherichia coli replication and/or colonization. The results of this study revealed that the antimicrobial activity in these two extracts did not differ between gram-negative and gram-positive microorganisms (*E.coli* and *L.innocua* respectively), with a remarkable activity in the extract with a high γ-oryzanol concentration. (Martillanes et al., 2020). Rice bran is a rich source of prebiotic compounds and other bioactive components that are likely to protect against enteric pathogen infections and diseases. These properties are likely due to the various mechanisms by which rice bran protects against infection, including its antimicrobial activities, prebiotic effects, and the promotion of intestinal epithelial health and mucosal immune responses. Rice bran can also promote the growth of Lactobacillus rhamnosus GG (LGG) and/or Escherichia coli Nissle 1917 (EcN), improve gut health, reduce gut permeability, and provide effective protection against human rotavirus (HRV) diarrhea and shedding. When combined with LGG and EcN colonization, rice bran can also promote body weight gain, protect against damage to intestinal epithelium while maintaining intestinal homeostasis, and enhance innate IFN-α and IgA protective immunity during HRV infection (Yang et al., 2015). A study was conducted to compare the antioxidant, antibacterial, and color properties of four varieties of rice (*Oryza sativa* L.) and four varieties of glutinous rice (*Oryza sativa* var. glutinosa) from local cultivators and the Peninsular Malaysia market. Samples of both pigmented and non-pigmented rice were examined for their antioxidant, antibacterial, and color properties. Pigmented rice samples had the highest antioxidant properties, with total phenolic content, iron-reducing antioxidant strength (FRAP), and radical scavenging activity (DPPH) compared to non-pigmented rice samples. Pigmented rice samples also had the lowest minimum inhibitory concentrations (MICs) and minimum bacterial concentrations (MBCs), showing higher antibacterial properties to reduce the growth of Bacillus cereus (ATCC® 11778™). The darker the color of the rice, the higher its antioxidant and antibacterial activity (Sani et al., 2018).

3.2.9. Antidiabetic potential

According to in vivo studies in mice, the antioxidant properties of γ-oryzanol are also mediated by the activation of antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase. Rice components, particularly macronutrients (starch, proteins) and bran compounds (γ-oryzanol, phytic acid, ferulic acid, γ-aminobutyric acid, tocopherols, and tocotrienols), have been identified as being potentially beneficial for diabetes prevention and control. The protective effects of rice bran constituents are mostly related to the reduction of the food glycemic index, which is partly due to the inhibition of α-amylase and α-glucosidase (vitamin E is an exception), with implications for blood glucose reduction. Ferulic acid has bioactive effects on several pathological processes of diabetes, including the potential inhibition of protein aggregation and amyloidogenesis (Pereira et al., 2021). There is little evidence to support the idea that consuming brown rice has any effects on blood sugar control or other metabolic indicators in people with prediabetes or Type 2 diabetes. However, there is some evidence that it may be helpful in reducing weight and improving HDL cholesterol levels in people who are trying to lose weight or lower their blood sugar levels. More research is needed to confirm these findings (Rahim et al., 2021). Red rice bran is a nutrient-rich natural food that contains flavonoids and anthocyanins, which have antioxidant properties. The antioxidant effects of EERRB demonstrate the mechanism of the repair effect in the diabetes mellitus rat group. The antioxidant effect functions similarly to the drug acarbose, which inhibits α-glucosidase and delays the breakdown of glucose in the digestive tract, preventing it from being channeled into the blood and causing increased glucose levels. Anthocyanins fight insulin resistance and increase insulin sensitivity by increasing glucose-4 transporter (GLUT4) translocation, activating activating AMP-activated protein kinase (AMPK), and decreasing insulin receptor substrate 1 (IRS-1) phosphorylation. Increased insulin levels, sensitivity, and an improvement in pancreatic β-cell function were demonstrated biochemically and computationally in Type 2 diabetes mellitus rats treated with EEBBM for 21 days in this study, but the microscopic histopathology results of the pancreatic tissue are unknown (Nurrohima et al., 2022). The Mechanism of Action of Cyanidin-3-O-glucoside Enhances Insulin Resistance: is summarized in Figure 5.

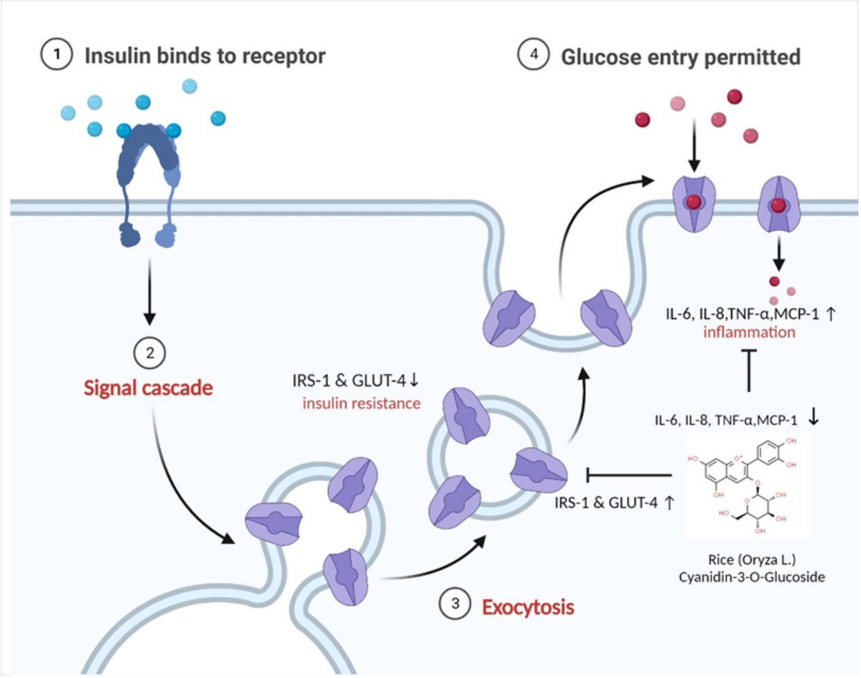

Figure 5. Cyanidin-3-O-glucoside ameliorates insulin resistance: mechanism of action (created with BioRender.com).

4. Conclusions

Pigmented rice comes in various colors, such as black, red, brown, and green. Anthocyanins, like cyanidin-3-O-glucoside and peonidin-3-O-glucoside, are the primary color pigments in colored rice, whereas proanthocyanidins and flavan-3-ol oligosaccharides, with catechins as the central synthesis unit, are found in brown rice. This review article's aim is to give information and a summary of rice activities, research methods, also mechanisms of action (*Oryza* L.). Intake of pigmented rice was already associated with a number of health benefits, including antioxidant activity, anticancer, antitumor, antidiabetic activity, and a reduced risk of cardiovascular disease. Rice contains several bioactive compounds, such as γ-oryzanol, phenolic acid, anthocyanins, proanthocyanidins, flavonoids, carotenoids, and phytosterols, which have been widely studied and shown to have several pharmacological activities. The use of current herbal compounds is rapidly increasing, including the practice of pharmacological disease prevention and treatment. Through a variety of pharmacological activities, it is clear that *Oryza* L. is a popular herb. As a result, additional research on *Oryza* L. can be conducted to investigate more recent and comprehensive pharmacological effectiveness, to provide information and an overview of Rice (*Oryza* L.) activities, research methods, and mechanisms of action. Several natural substances are characterized by low water solubility, low stability, and sensitivity to light and oxygen, and the potential for poor absorption of the active substances requires modification of the formulation. To improve the effectiveness of pharmacologically active substances originating from natural ingredients, drug delivery systems that use lipid-based formulations can be considered innovations. The primary color pigments within colored rice are anthocyanins, such as cyanidin-3-O-glucoside then peonidin-3-O-glucoside, while brown rice contains proanthocyanidins and flavan-3-ol oligomers, with catechins as the central production unit. The utilization of pigmented rice is related to some health benefits, such as antioxidant activity, anticancer, antitumor, antidiabetic, and a reduced risk of cardiovascular disease.

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