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A comprehensive review on anti-diabetic property of rice bran

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ABSTRACT

Rice bran (RB) is one of the nutrient-rich agricultural byproducts. It is a composite of carbohydrates, lipids, proteins, fibers, minerals, and trace elements such as phosphorus, potassium, magnesium, calcium and manganese. The extraction and purification process influences the quality and quantity of rice bran oil, which is rich in tocopherols, tocotrienols, γ-oryzanol, and unsaturated fatty acids. The bioactive components of RB have been reported for exhibiting antioxidant, anti-inflammatory, hypocholesterolemic, anti-cancer, anti-colitis, and antidiabetic properties. *In vitro* and *in vivo* studies, and clinical trials in human volunteers revealed the anti-hyperglycemic activity of RB derived compounds. An updated comprehensive review on the antidiabetic property of RB and its derivative is required to appraise the current knowledge in the particular field. Thus, the present paper covered the composition and bioactivities of RB, and influence of extraction methods on the biological property of rice bran oil and rice bran extract. And the current review also focused on the reported anti-hyperglycemia activity of rice bran derivatives, and its probable mechanism.

1. Introduction

A multifaceted metabolic disorder characterized by the hyperglycemia (high blood sugar level) due to the flaws in insulin secretion or action or both is known as diabetes mellitus (DM). The damage in the β-cells of the pancreatic islets diminish the insulin secretion, and develop resistance to the action of insulin are the reasons for DM. Based on the defects, DM is classified as type 1 (impairment of the β-cells of the pancreatic islets) and type 2 (defects in insulin secretion) DM[1]. About 60% of diabetics in the world live in Asian countries[2]. China (109.6 million) and India (69.2 million) ranked top two, regarding the countries having the highest number of adults with DM. Globally, the prevalence of DM was 415 million in 2015 and predicted to reach up to 642 million by the year 2040[3]. The DM especially type 2 is caused due to overweight or obese, improper lifestyle like unhealthy diet, lack of physical activity, smoking, depression, and other genetic and age factors[4]. DM affects the health span of a human being, and also affects the socio-economic development[4,5]. In developed countries, about 10% of the total budget for health care is used for the management of diabetes and its hitches[4]. The trends of the DM prevalence among the Asian countries especially China and India are alarming the economic development and healthy lifestyle.

Rice is one of the universal cereal crops consumed by half of the world's population as their daily staple food for energy. Rice is cultivated in about 114 countries and the production is about 645 million tons of rice per year[6]. The projections of rice production based on the model established by the International Food Policy

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Research Institute propose that global rice cultivation will be influenced by the alteration in climate and in 2050 the production will be reduced by 12%-14% compared to that in 2000. Also, the projection suggested that the rice production in South Asian countries will be affected drastically with a decrease of about 65 million ton, which would result in lower consumption rate and higher price, and further lead to malnutrition in children[7]. Rice milling process will yield several by-products like rice husk, and rice bran (outer layer of the rice kernel comprised of pericarp, aleurone, sub-aleurone layer, and germ). The rice milling byproducts are used as an ingredient in the animal feed[6] and used for other purposes like bedding material. The rice bran (RB) is a good source of oryzanol, and tocols (tocopherols and tocotrienols)[8].

Rice bran has about 15%-20% of oil, known as rice bran oil (RBO). RBO is known for the health benefits[8]. The quantity and quality of the RBO varied based on the cultivars, extraction process, *etc*[9,10]. The non-conventional, eco-friendly, solvent free extraction methods are in use and also under development for the recovery of superior quality RBO from RB. Owing to the richness of good fatty acid profile with high nutraceutical value, RBO is used in food industries, as well as in pharmaceuticals. The Asian countries, especially Japan, Taiwan, China, Thailand, and South Korea have recognized RBO as one of the best edible oils[11].

RBO is reported for several health benefits. The current review summarizes the RB composition, its bioactivities, and influences of extraction method on the quality of RBO, and compiles the reported anti-diabetic property of RBO.

2. Composition and health benefits of rice bran

RB contains carbohydrates (34%-62%), lipids (15%-20%), proteins (11%-15%), fibers (7%-11%), other minerals, and trace elements such as phosphorus, potassium, magnesium, calcium, and manganese[12,13]. About 38.4% oleic acid, 34.4% linoleic acid, 21.5% palmitic acid, 2.9% stearic acid, 2.2% linolenic acid, and other saturated and unsaturated fatty acids are reported in RBO[14]. RBO is rich in tocopherols, tocotrienols, and γ-oryzanol, which stabilize the nutritional compounds from oxidative damages[14,15]. The defatted RB contains carbohydrates (58.41%), ash (14.59%), protein (14.27%), reducing sugars (12.44%), moisture (8.37%), and crude fiber (1.8%)[16].

The RB extracts are rich in phenolic compounds, and anthocyanins. The richness and diversity in the composition of anthocyanins varied based on the cultivars. Particularly, colored rice varieties are rich in phytopigments. The phytochemical content such as total phenolic (36.14-305.30 mg gallic acid equivalent per gram of extract), total flavonoids (0.36-1.93 mg quercetin equivalent per gram of extract), and total anthocyanins content (0.00-487.25 mg cyanidin equivalent per gram of extract) were found to be varied based on the Thai rice cultivars (black, brown, and red rice varieties)[17]. Likewise, non-polar extraction of RBO yields different quality of RBO regarding total tocols and γ-oryzanol content, which was influenced by the cultivars[10].

The essential amino acids and proteins with hypoallergenic nature are enriched in RB, and hence RB function as an effective food ingredient[18,19]. RB is the best source of dietary fibers, which helps to improve the fecal production due to the laxative effect[20]. Intake of dietary fiber (10 gram per day increment) from the sources like fruit, cereal, vegetable and all three source (total dietary fiber) showed a reduction in the mortality risk of coronary heart diseases by 30%, 25%, 0%, and 27%, respectively[21]. Thus, fruits and cereals are good dietary sources of fiber to reduce the fatality risk of coronary heart disease. The rice unsaponifiables, mainly oryzanol is reported for many bioactivities like cholesterol-lowering property, and low-density lipoprotein-lowering property[22–24]. Some rice phytochemicals are known for their trypsin inhibition, pepsin inhibition, and anti-thiamine properties[25].

RB contains potent antioxidants[26,27] that help to treat and manage the oxidative stress associated diseases[28], cancer[29–31], and dextran sodium sulfate-mediated colitis *in vivo*[32]. Rice tocotrienols have been reported for the antioxidant[33], anti-cancer[34], and cholesterol-lowering properties[35]. The presence of the high amount of oryzanol attributed the RB as nutraceutical candidate by reducing the plasma cholesterol, declining the platelet aggregation, cholesterol absorption, treatment of hyperlipidemia and menopause-related consequences[36]. The rice anthocyanins are also known for the inhibition of cancer-cell invasion[37], inhibition of the growth of human breast cancer cells by inducing apoptosis[38], and inhibition of aldose reductase[39].

3. Influence of extraction methods

The extraction process affects the phytochemical content of RBO (contains oryzanol, and tocols) and RB extracts (contains phenolic compounds, flavonoids, and anthocyanins). The solvent (ethyl acetate, isopropanol, heptane, ethanol, methanol, and hexane) extraction, cold press, hot press extraction, supercritical fluid extraction (SFe), microwave, and ultrasonic-assisted extraction methods are used to recover the bioactive compounds from RB.

Imsanguan *et al*[40] investigated the effect of three different extraction methods such as soxhlet, solvent, and supercritical CO_2 extraction on yielding γ-oryzanol and α-tocopherol from RB. The study suggested that high yield of α-tocopherol was obtained using hexane based soxhlet extraction, but a higher rate of extraction (less extraction time) was observed using the supercritical CO_2 extraction. Also, high yield of γ-oryzanol from RB was obtained using the supercritical CO_2 extraction[40]. The yield and quality of the extract also vary based on the cultivars. Pengkumsri *et al*[10] reported the impact of extraction methods on the yield of γ-oryzanol and tocols containing RBO, and antioxidant properties of RBO from selective Thai rice bran. Hexane extraction exhibited high yield when compared to that of the hot press, cold press, and SFe methods. Moreover, the variation in the yield was observed among the cultivars. The results suggested that solvent extraction was found to be superior regarding the total tocols content, and free radical scavenging activities, followed by SFe and pressing methods[10]. Azrina *et al*[41] described the solvent based extraction of oryzanol and total lipid content from RB.

The use of solvents for the extraction of RB possibly leaves some traces of solvent in the product. The RBO and RB extract used in the food industries, and pharmacological preparations should be free from solvents. The hot/cold press[42] and SFe methods[43] are employed to recover the solvent-free RBO and are environmentally safe. The temperature and pressure affect the percentage of yield of RBO in SFe method[44]. The SFe method produced four times more oryzanol from RB than that of the mixed solvent extraction[45]. The temperature, pressure, and extraction time impacts the quality and quantity of the RBO in both solvent extraction and SFe methods.

Terigar *et al*[46] claimed that continuous microwave-assisted extraction yielded good quality RBO concerning some parameters such as fatty acid composition, acid value, wax, and iodine content when compared with the conventional solvent extraction procedures. Microwave pretreatment of RB prior to SFe produced superior quality extract regarding the increased recovery of total phenolic contents and enhanced antioxidant capacity[47]. The combination of ultrasonic pre-treatment and conventional extraction exhibited high yield of RBO with enhanced bioactivity[48,49]. The ultrasonic-assisted extraction has several advantages like high yield, reproducibility, less time and solvent, low temperature, and eco-friendly than that of the other extraction methods[50].

Even though heat and microwaves affect the anthocyanins (one of the major bioactive compounds in RB extract) of RB[51], the precious conditions like temperature, duration of treatments aids to attain the high-quality RBO, and RB extracts for many applications in food and pharmacological industries.

4. Anti–diabetic property of rice bran

4.1. Clinical trials

The stabilized RB, RB water solubles and RB fiber concentrates are reported as an effective nutraceutical supplements to suppress diabetes-related consequences in human. Upon administration of these RB fractions [6 groups were administrated with stabilized RB, RB water solubles, and RB fiber concentrates in 6 different sequences; Each product was administered for 8 weeks with a washout period (4 weeks) between the administration of each product; Dosage: 20 g per day], both type 1 diabetic, and type 2 diabetic patients showed a significant reduction in their glycosylated hemoglobin, fasting glucose, and improvements in serum insulin level. Moreover, triglycerides, apolipoprotein B, LDL-cholesterol, and total serum cholesterol levels were reduced in both type 1 diabetic and type 2 diabetic patients by the intervention of RB fiber concentrates[52]. Supplementation of low fiber food for a week, followed by the supplementation of fiber-rich diet (40 g of rice bran fiber per day) for the next one week reduced the fasting and postprandial serum glucose levels in type 1 and type 2 diabetic patients. Moreover, the fecal weight was found to be increased due to the intake of high fiber diet, and also lactose was detected in the stool samples[53]. The intervention of stabilized RB (20 g per day for about 12 weeks) reduced serum total cholesterol, LDL-cholesterol, HbA1c and postprandial glucose levels, and increased the levels of adiponectin in type 2 diabetic patients[54]. The consumption of RBO-modified milk (18 g RBO per day for five weeks) showed no significant impact on insulin resistance but decreased the LDL-cholesterol and total serum cholesterol levels in type 2 diabetic patients[55]. Shakib *et al*[56] reported that the use of RBO (30 g per day) in salad dressing and cooking for six months reduced HbA1C, fasting and postprandial blood glucose, liver transaminases, serum uric acid, blood urea, erythrocyte sedimentation rate, and lipids levels in type 2 diabetic patients. The author also suggested that the use of RBO with healthy diet cuts off the risk of cardiovascular diseases.

The intervention of oil blend (20% sesame oil and 80% RBO) to type 2 diabetic patients for eight weeks showed a reduction in the HbA1c, fasting and postprandial blood glucose, low-density lipoprotein cholesterol, total cholesterol and triglycerides levels, and improvement in the high-density cholesterol level[57]. A comparative study on the therapeutic effect of RBO, canola oil, and sunflower oil in type 2 diabetic patients (postmenopausal women) suggested that the RBO and canola oil are beneficial to the diabetic patients. Both RBO and canola oil significantly reduced the total serum cholesterol, LDL-cholesterol, and triglyceride levels. The study suggested that the replacement of sunflower oil with RBO or canola oil (30 g per day) could reduce the risk of lipid disorders[58].

4.2. In vivo studies

The RB extract (0.1% Ricetrienol®) exhibited a protective effect in the obese diabetic KKAy mice by reducing the plasma MDA and increasing the plasma -tocopherol and the transcription of glutathione peroxidase 1. Ricetrienol® (0.1%) was found to be effective against the oxidative stress damages and was not effective against hyperglycemia and hyperlipidemia[59]. The oxidative damages in streptozotocin-induced DM rats were effectively reduced by the intervention of RBO[60]. Hsieh *et al*[60] reported the protective nature of RBO and revealed that RBO intervention for four weeks significantly reduced the level of 8-hydroxy-2′-deoxyguanosine (in mitochondrial DNA), which is a known compound to measure the oxidative DNA damages. Chen and Cheng[61] suggested that the high contents of γ-tocotrienol and γ-oryzanol present in the RBO were responsible for the antidiabetic property of RBO. Supplementation of RBO (10 g or 15 g of RBO per 100 g of diet for four weeks) containing high contents of γ-tocotrienol and γ-oryzanol reduced plasma triglyceride, hepatic triglyceride, and plasma LDL cholesterol level in streptozotocin/Nicotinamide-induced type 2 DM rats. Moreover, RBO treatment increased the excretion level of fecal bile acid and neutral sterol, and also improved the mRNA levels of hepatic cholesterol 7α-hydroxylase, LDL-receptor and 3-hydroxy-3-methylglutaryl coenzyme A reductase[61].

Siddiqui *et al*[62] investigated the anti-hyperglycemic property of tocotrienol-rich fraction (extracted from palm oil and RBO) using streptozotocin (55 mg/kg body weight) mediated type 1 DM-induced male Wistar rats. Intervention (eight weeks) of a tocotrienol-rich fraction of RBO (200 mg/kg body weight per day) reduced the fasting blood glucose, HbA1c, and serum nitric oxide levels in type 1 DM rats. Moreover, supplementation of a tocotrienol-rich fraction of RBO protected the kidney tissues of experimental DM animal from nitrosative and oxidative damages by reducing the urine nitric oxide levels and increasing the antioxidant enzyme levels, respectively[62]. Chou *et al*[63] also reported the protective effect of

RBO using streptozotocin/nicotinamide-induced type 2 DM rats. Supplementation of RBO (150 g RBO per kg diet for five weeks) showed an increase in HDL-cholesterol, and excretion level of fecal bile acid and neutral sterols, and reduction in hepatic cholesterol, atherogenic index, and hyper-insulinemic response in type 2 DM rats. Jung *et al*[64] reported the induction of hepatic glucokinase activity and blood glucose lowering ability of phenolic acid fraction of RB (17 days intervention) in C57BL/KsJ *db/db* mice.

The intervention (11 days) of oryzanol (50-100 mg/kg body weight) extracted from crude RBO improved the antioxidant capacity by increasing the antioxidant enzyme level in the liver of the streptozotocin-induced DM rats. Reduction in blood glucose levels and dose-dependent reduction of lipid peroxidation was observed in oryzanol supplemented diabetic rats[65]. Thai purple sticky rice bran supplementation (50 g/kg; 8 weeks) improved the health status of streptozotocin-induced diabetic rats by reducing the plasma glucose, free fatty acids, and triglyceride level and enhancing the insulin sensitivity[66].

Supplementation of Thai pigmented rice bran oil (5.0 or 7.5 or 15% of RBO) for 12 weeks showed reduction in serum MDA level, and improved the levels of catalase, coenzyme Q_{10}, glutathione peroxidase, superoxide dismutase, and oxygen radical absorbance capacity in streptozotocin-induced diabetic rats fed with high-fat diet. The intervention of RBO reversed the damages caused in the heart, kidney, liver, and pancreas to its normal state in RBO treated rats fed with high-fat diet[67]. The regulation of hepatic glucose-regulating enzyme by RBO is one of the key mechanisms behind the anti-diabetic property of RBO. High glucokinase activity, reduced phosphoenolpyruvate carboxykinase and glucose-6-phosphatase activity were observed in high-fat-diet-fed C57BL/6N mice supplemented with RBO (30% RBO supplemented for seven weeks)[68]. Kozuka *et al*[69] claimed that both γ-oryzanol (20 or 80 μg/g body weight; 13 weeks intervention) and brown rice (Chow diet containing 30% of brown rice) improved the metabolic rate of glucose and reduce hypothalamic endoplasmic reticulum stress in high-fat-diet-fed C57BL/6J mice model. Oryzanol influences the insulin secretion, serum glucose level, hepatic glucose regulating enzyme activities, and reduced the risks of hyperglycemia[70,71]. Ohara *et al*[72] revealed that oryzanol regulates the adiponectin secretion by preventing the activation of NF-κB.

Wahyuni *et al*[73] reported the mechanism of the anti-diabetic property of ethanolic extract of black rice bran in alloxan (150 mg/kg body weight)-induced Sprague Dawley rats. The intervention of ethanolic RB extract (100 or 200 mg/kg body weight) for 4 weeks showed high glucose lowering ability and insulin levels by regenerating the pancreatic beta cells in the DM rats[73].

4.3. In vitro studies

Ethanol extract of black rice bran showed inhibition of α-glucosidase with the IC_{50} of 121 mg[73]. The *in vitro* study suggested that the RB extracts inhibited α-glucosidase, α-amylase activity, and also accelerated glucose uptake in 3T3-L1 adipocytes. The molecular regulation study proved that RB extract induced the mRNA expression of glucose transporters (GLUT1, and GLUT4), and insulin-signaling pathway components (INSR, and IRS1)[74]. Kaup *et al*[75] investigated the antidiabetic property of Egyptian stabilized RB extract and reported the dose-dependent activity of RB extract on inducing the release of insulin in INS-1 cells[75].

5. Conclusion and future prospects

RB is rich in essential nutrients and known for its health-promoting activities. The γ-oryzanol, tocols, dilatory fibers, and other crucial fatty acids are attributed for the bioactivities of RB. The studies proved that supplementation of RBO, RBE, γ-oryzanol fraction significantly reduced the hyperglycemic state and its associated consequences by regulating the hepatic glucose-regulating enzyme activity, and proteins involved in the insulin signaling pathway. However, the therapeutic nature of RB was not utilized properly. The detailed research on dose, treatment period, and other allied nutraceutical procedures are obligatory. The development of RB based functional food and creating awareness to the people to use RB-derived products in their daily life may help to manage the hyperglycemia more efficiently in developing and developed countries.

Conflict of interest statement

The authors declare that there is no conflict of interests.

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Authors contributions

Bhagavathi Sundaram Sivamaruthi and Periyanaina Kesika contributed to conception and design, acquisition, manuscript preparation, and critical revision of the manuscript. Chaiyavat Chaiyasut involved in the review and finalization of the manuscript. All the authors agree with the content of manuscript.

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