Biological Functions and Activities of Rice Bran as a Functional Ingredient: A Review

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ABSTRACT: Rice bran (RB) is a nutrient-rich by-product of the rice milling process. It consists of pericarp, seed coat, nucellus, and aleurone layer. RB is a rich source of a protein, fat, dietary fibers, vitamins, minerals, and phytochemicals (mainly oryzanols and tocopherols), and is currently mostly used as animal feed. Various studies have revealed the beneficial health effects of RB, which result from its functional components including dietary fiber, rice bran protein, and gamma-oryzanol. The health effects of RB including antidiabetic, lipid-lowering, hypotensive, antioxidant, and anti-inflammatory effects, while its consumption also improves bowel function. These health benefits have drawn increasing attention to RB in food applications and as a nutraceutical product to mitigate metabolic risk factors in humans. This review therefore focuses on RB and its health benefits.

KEYWORDS: Bioactive compound, dietary fiber, functional food, gamma-oryzanol, nutrition, protein, rice bran

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Introduction

Rice *(Oryza sativa)* is one of the staple foods globally, especially in Asia. Global rice consumption was approximately 490.27 million metric tons in 2019.[1] Rice provides up to 50% of the calories consumed by populations in Asia.[2] Previous studies indicated that rice by-products from the milling process still contain a variety of nutrients and bioactive compounds, which exhibit beneficial health effects.[3,4] These by-products could be used or added to food products to promote the yield and food sustainability of rice production.[5]

Rice kernels are composed of approximately 70% starchy endosperm (total milled rice), 20% rice husk, and 10% rice bran (RB), depending on the extent of milling and the rice variety.[5,6] Milled rice is sold as food for humans, while broken rice, rice husk, and RB, considered as by-products, are commonly used for industrial applications and feed for animals.[7,8] Owing to its high-fat content and nutritional value, RB oil is also extracted for use in cooking.[9]

A substantial number of in vitro and in vivo studies have shown the benefits of RB for certain health parameters, via its antioxidant activity. Moderate consumption of antioxidant-rich foods is important for scavenging the free radicals that cause oxidative stress, premature cell aging, and heart and muscle damage.[10] However, there is a lack of an updated review study on the effects of RB supplementation on metabolic syndrome. Therefore, this article reviews the health benefits of RB on metabolic indicators.

Nutritional Composition of RB

Rice bran is the brown outer layer of the rice kernel, mainly composed of the pericarp, aleuron, seed coat, and germ. It contains 50% carbohydrate (mainly starch), 20% fat, 15% protein, and 15% dietary fiber (DF), mainly insoluble fiber.[11,12] Nutritional composition on crude RB per 100 g were shown in Table 1. However, the nutrient composition of RB depends on the rice variety and the efficiency of the milling system.[7] Because of these nutrients and bioactive compounds, RB has been tested for its beneficial health effects.[3,4]

Structure of Functional Components of RB

Rice bran dietary fiber

RB contains approximately 12% DF, 90% of which is insoluble DF including cellulose, hemicellulose, and arabinoxylans.[14,15] Pectin and β-glucan, soluble DF, are present in RB at trace levels.[16] However, the amount and composition of nutrients in RB vary depending on the rice cultivar, environmental conditions, degree of milling, and analytical method.[17]

Cellulose. A previous study by Ghodrat et al[18] revealed that RB contains approximately 34% cellulose. Cellulose is a long-chain homopolymer with a high degree of polymerization, ranged from several 100 to over 10 000 monomers, and a large molecular weight.[19,20] The monomer of cellulose is D-glucose linked by a β-(1→4) bond; it is thus a fibrous and highly water-insoluble polysaccharide that cannot be digested by humans.[21]

Table 1. Nutritional information on crude RB per 100 g.[13]

NUTRIENT	AMOUNT
Energy (kcal)	316
Protein (g)	13.35
Total fat (g)	20.85
Saturated fatty acids (g)	4.17
Monounsaturated fatty acids (g)	7.55
Polyunsaturated fatty acids (g)	7.46
Carbohydrate (g)	49.69
Fiber, total dietary (g)	21.00
Minerals	
Calcium (mg)	57.00
Iron (mg)	18.54
Magnesium (mg)	781.00
Phosphorus (mg)	1677.00
Potassium (mg)	1485.00
Zinc (mg)	6.04
Manganese (mg)	14.21
Selenium (μg)	15.60
Vitamins	
Thiamine (mg)	2.75
Riboflavin (mg)	0.28
Niacin (mg)	34.00
Pantothenic acid (mg)	7.39
Vitamin B6 (mg)	4.07
Folate (μg)	63.00
Choline (mg)	32.20
Vitamin E (alpha-tocopherol) (mg)	4.92
Vitamin K (phylloquinone) (μg)	1.90

The effects of cellulose on reducing daily energy intake, glycemic control, and lipid metabolism in humans remain poorly understood. Most studies have consistently reported beneficial health effects of modified celluloses, but not natural celluloses such as high-viscosity hydroxypropylmethylcellulose (HV-HPMC). Previous studies indicated that the characteristics of modified celluloses are similar to soluble fiber, in terms of increasing intestinal viscosity, hindering nutrient absorption, and promoting bile acid excretion.[22-24]

Hemicellulose. RB contains approximately 22% hemicellulose,[18] with arabinoxylans being the most common hemicelluloses.[14] Arabinoxylans also naturally occur in other major cereal grains such as rye, wheat, barley, oats, maize, and millet, which cannot be digested in the human small intestine.[25] Arabinoxylans consist of a β-(1,4)-linked xylose residue backbone, with substitutions of arabinose residues at the second and third carbon positions.[26] Studies have revealed health benefits of arabinoxylans, including immunomodulatory activity and reduction of the glycemic response.[27-31] The mechanism underlying the immunomodulatory activity of arabinoxylans is still unclear, but it was hypothesized that it is mediated by competition with lipopolysaccharides (LPS) from Gram-negative bacteria for the TLR4 receptor of macrophages.[32] The immunomodulatory activity of arabinoxylans depends on several factors, such as the degree of branching, molecular weight, and sugar composition. One type of RB arabinoxylan, known as MGN-3, was shown to be more effective at activating macrophages than wheat bran arabinoxylan due to its higher levels of glucose and galactose side chains.[32,33]

Gamma-oryzanol

Gamma-oryzanol is present in the form of a steryl ferulate, which is a mixture of ferulic acid esters of sterol and triterpene alcohols.[34,35] Gamma-oryzanol is present in approximately 20% of the unsaponifiable fraction in RB oil.[36] In addition, the amount and composition of gamma-oryzanol in RB vary depending on the rice cultivar and extraction method.[4,37] Gamma-oryzanol is considered as one of the most effective natural antioxidants.[38] Functional activities of gamma-oryzanol that have been reported include antioxidant activity, antidiabetic activity, lipid-lowering effect, and anti-cancer properties.[38-42]

Rice bran protein

RB is a good source of high-quality plant-based protein with high digestibility and hypoallergenicity.[43] The protein content of RB is about 10% to 15%, which consists of 37% albumin, 36% globulin, 22% glutelin, and 5% prolamin.[44] However, the distribution of protein fractions in defatted rice bran varies among rice varieties.[44] RB protein has been reported to show good digestibility and biological value, with protein energy ratio, true digestibility, and Protein Digestibility Corrected Amino Acid Score of 2.39, 94.8%, and 0.90, respectively.[45] RB protein is rich in essential amino acids.[45] Moreover, RB is abundant in lysine, a limiting amino acid, compared with other cereal grains.[46] Most previous studies reported that the health benefits of RB protein are related to RB protein isolate, peptides, and hydrolysate. Biological and functional activities of RB protein (Table 2) include antioxidant activity, antihypertensive activity, antidiabetic activity, and a lipid-lowering effect.[47-57]

Biological and Functional Activities of RB

Antioxidant activity of RB

RB possesses high antioxidant activity due to its phytochemical compounds and bioactive peptides.[51,58-60] Previously, an in vitro

Table 2. Summary of functional activities of RB components.

SOURCE	AMOUNT AND DURATION	BIOACTIVITY	REFERENCE
RB enzymatic extract	1% and 5% in obese Zucker rats, 20 weeks	Weight reduction, antidiabetic, hypolipidemic activity, antihypertensive	Justo et al.[77]
RB enzymatic extract	1% and 5% C57BL/6J mice, 16 weeks	Weight control, hypolipidemic activity, antihypertensive, anti-inflammation	Justo et al.[78]
RB polysaccharides	500 mg/kg in ICR mice, 10 weeks	Weight reduction, hypolipidemic activity, antihypertensive	Nie et al.[54]
RB and plant sterols	RB and RB + 2% plant sterols with 25% energy-restricted diet in overweight and obese adults, 8 weeks	Weight reduction, cholesterol-lowering effect	Hongu et al.[75]
RB extract containing acylated steryl glucoside fraction	30-50 mg/day in in obese Japanese men, 12 weeks	Weight reduction, cholesterol-lowering effect	Ito et al.[76]
Brown RB extract containing acylated steryl glucosides	50 mg in post-menopausal Vietnamese women, 6 months	Weight reduction, cholesterol-lowering effect, anti-inflammation	Nhung et al.[80]
RB powder	70 g/day with low-calorie diet in overweight and obese adults, 12 weeks	Anti-inflammation	Edrisi et al.[81]
Black RB ethanol extract	100 mg/kg in diabetic rats, 28 days	Antidiabetic	Wahyuni et al.[85]
Purple and red rice (*Oryza sativa* L.) bran extracts	In 3T3-L1 adipocytes (in vitro)	Antidiabetic	Boue et al.[84]
Egyptian RB extract containing 2% γ-oryzanol	In INS-1 cells (in vitro)	Antidiabetic	Kaup et al.[86]
Stabilized RB	20 g in type 2 diabetes patients, 12 weeks	Antidiabetic, hypolipidemic activity	Cheng et al.[89]
Blended oil (sesame and RB oil)	40 mL/day in type 2 diabetes patients, 8 weeks	Antidiabetic, hypolipidemic activity	Devarajan et al.[90]
RB oil	250 mL/day RB oil-modified milk (18 g of RB oil) in type 2 diabetes patients, 5 weeks	Antidiabetic, hypolipidemic activity	Lai et al.[91]
RB	Diet with 30% RB in male C57BL/6N mice, 7 weeks	Hypolipidemic, antioxidative activity	Kang et al.[95]
RB driselase and ethanol fractions	60 g/kg in stroke-prone spontaneously hypertensive rats, 8 weeks	Antidiabetic, hypolipidemic activity, antihypertensive	Ardiansyah et al. (2007)
RB protein hydrolysates	250 and 500 mg/kg/day in male Sprague–Dawley rats, 6 weeks	Antidiabetic, hypolipidemic activity, antihypertensive, anti-inflammation, antioxidant, restoration of normal endothelial function	Senaphan et al.[56]
RB protein hydrolysates	50 and 100 mg/kg/day in male Sprague–Dawley rats, 6 weeks	Antihypertensive, anti-inflammation, antioxidant, restoration of normal endothelial function	Boonla et al.[51]
RB-derived tripeptide	0.25 mg/kg of peptide in spontaneously hypertensive rats	Antihypertensive	Shobako et al.[101]
RB-contained novel peptide, Leu-Arg-Ala (LRA)	43 µg LRA/day in individuals with high-Normal blood pressure, 12 weeks	Antihypertensive	Ogawa et al.[103]
Defatted RB protein hydrolysates	In Raw 264.7 macrophages (in vitro)	Antioxidant, anti-inflammation	Saisavoey et al.[108]
RB protein hydrolysates	80 mg/kg in male spontaneously hypertensive rats	Antioxidant, antihypertensive	Piotrowicz et al.[109]
RB protein hydrolysates	In vitro	Antidiabetic, antihypertensive	Uraipong and Zhao[52]
Virgin RB oil	2 mL/kg in hypertensive rats, 3 weeks	Antioxidant, anti-inflammation, antihypertensive	Jan-On et al.[110]

study showed that the antioxidant activity of RB was influenced by different treatments, such as hot air and far-infrared radiation (FIR). The inhibition of DPPH (2,2-diphenyl-1-picrylhydrazyl) radical-scavenging activity was increased (to 92.21%) following FIR treatment, compared with the level for raw RB (87.93%). The FRAP also increased from 28.57 μmol $FeSO_4$/g in raw RB to 34.41 μmol $FeSO_4$/g in FIR-treated RB.[60] The antioxidant activity of RB might be attributable to the phenolic and flavonoid compounds in RB, such as hydroxybenzoic acids, hydroxycinnamic acids, and kaempferol, with total phenolic content and total flavonoid content of RB being 3.05 to 4.05 mg/gallic acid equivalent and 3.08 to 3.88 mg retinol equivalents/g, respectively.[60] Furthermore, RB is a good source of γ-oryzanol, with it being present at a rate of 5.3 to 5.7 mg/g. Tocopherols (α- and γ-form) have also been detected in RB, at levels of 63.5 to 95.8 μg/g and 5.0 to 5.1 μg/g, respectively.[60]

Supplementation of RB also showed favorable effects on serum and liver antioxidant levels in rats.[61] Hypercholesterolemia has been shown to stimulate the production of reactive oxygen species (ROS) and decrease serum antioxidant activity.[62] In addition, supplementation with aqueous enzymatic extract of RB (750 mg/kg BW) for 42 days significantly restored serum total antioxidant capacity and superoxide dismutase (SOD) activity in rats fed a high-fat diet, by 36.6% and 83.98%, respectively, compared with the findings in rats fed a high-fat diet only (without RB). Furthermore, RB supplementation in high-fat diet-fed rats increased liver catalase and decreased protein carbonyl content in the liver compared with the levels in rats fed a high-fat diet only due to the antioxidant activity of RB, attributable to oryzanol, tocopherol, polyphenol, and flavonoid compounds.[61] In a clinical study, daily consumption of 30 ml of RB oil containing >4000 ppm of γ-oryzanol for 4 weeks significantly increased plasma oxygen radical absorbance capacity and fluorescence recovery after photobleaching (FRAP) in hyperlipidemic adults.[63] In addition, the antioxidant activity of RB is contributed to by not only polyphenols, flavonoid, oryzanol, and tocopherol, but also bioactive peptides.[51]

Peptide from RB protein hydrolysate (RBP) also showed potential health benefits by exerting antioxidant activity. Boonla et al[51] found that supplementation of RBP (50 or 100 mg/kg) for 6 weeks significantly decreased plasma malondialdehyde (MDA) and protein carbonyl in sham-operated rats.

Several epidemiological studies revealed the association between oxidative stress and NCDs. Moreover, antioxidant-containing foods have also attracted a lot of attention due to their beneficial health effects.[64-66] Previous studies indicated that the intake of antioxidants and antioxidant-containing foods is associated with a reduced risk of NCDs.[67-69] These previous studies show that RB possesses antioxidant ability, which may be important for alleviating the risk of NCDs associated with oxidative stress. Therefore, further research is needed to investigate the antioxidant activity of RB in order to obtain a better understanding of its mechanism of action and effect in humans.

Effect of RB on weight management

Obesity is one of the risk factors of many diseases, such as cardiovascular diseases, type 2 diabetes, certain types of cancer, and hypertension.[70] It is increasingly prevalent not only in adults, but also in children. Childhood obesity increases the risk of obesity in adulthood, as well as other obesity-related diseases.[71] Shifting dietary patterns, economic growth, and globalization have contributed to the increasing prevalence of obesity globally. Economic transitions have also resulted in the intake of more processed foods, which have been shown to be related to obesity.[70,72]

Previously, Giacco et al[73] concluded that higher whole-grain intake leads to a lower body weight by lowering the glycemic index, lowering energy density, producing short-chain fatty acids (SCFAs), and modulating gut microbiota. However, recent clinical studies found a lack of evidence to support the beneficial effects of whole grains on weight loss, despite possible mechanisms by which the consumption of whole grains could promote weight loss, such as increasing chewing, reducing energy density and availability, reducing postprandial glycemic response, increasing fermentation, and promoting gut microbiota in the colon.[74]

As a component of whole grains, the effect of consuming RB on weight management has been investigated in animal and human studies.[54,56,75,76] Justo et al[77] investigated the effects of RB enzymatic extract (1% and 5% supplemented diet) on metabolic, biochemical, and functional adipose tissue changes related to diet-induced obesity in mice. The results showed that a high-fat diet significantly increased body weight compared with a standard diet. Mice fed a high-fat diet supplemented with 1% and 5% RB extract did not show any differences in body weight compared with mice consuming a high-fat diet. Mice fed a high-fat diet had an adipocyte size distribution (100-400 μm^2) larger than that of mice fed a standard diet (<100 μm^2).[77] Interestingly, supplementation with 1% RB in the high-fat diet of mice restored the adipocyte size distribution as well as the inflammatory cytokines to normal levels.[77] These effects could have been mediated by oryzanol as the main active component of RB by upregulating Peroxisome Proliferator-Activated Receptor (PPAR)-γ expression in adipocytes.[78] In addition, in a high-fat-diet animal model, mice intragastrically administered 500 mg/kg RB polysaccharide solution for 10 weeks had significantly reduced body weight compared with the control group.[54] It was suggested that RB polysaccharides prevented weight gain by regulating the expression of lipid metabolism-related genes including PPAR-α, PPAR-γ, PPAR-δ, Sterol Regulatory Element-Binding Protein (SREBP)-1C, Fatty Acid Synthase (FASN), Acetyl-CoA Carboxylase Alpha, Sirtuin (SIRT), and CD36.[54]

In contrast, RBP (500 mg/kg/day) did not affect body weight in rats fed a high-carbohydrate and high-fat diet.[56]

Studies on humans have reported inconsistent effects of RB consumption on weight loss.[75,76,79,80] Rice bran extract reduced abdominal circumference and subcutaneous fat area following the consumption of 30 to 50 mg/day of RB extract for 12 weeks in obese Japanese men with high low-density-lipoprotein (LDL) cholesterol.[76] In addition, supplementation with RB extract (50 mg) for 6 months in post-menopausal Vietnamese women with high LDL cholesterol did not significantly alter body mass index.[80] However, in that study, body fat percentage, hip circumference, and abdominal circumference significantly decreased at month 6 when compared with the levels at baseline, although there were no significant differences when compared to a placebo.[80] Another study investigated the effect of pigmented RB bar consumption with or without plant sterols for 8 weeks in obese adults receiving a 25% calorie-restricted diet.[75] Each participant consumed 3 RB bars, which contained 16.7% RB per serving (30 g), with or without 2% plant sterol daily. The results showed that body weight decreased by 4.7 ± 2.2 kg ($P < .001$) and body fat decreased in all participants, but these weight losses were not significantly different between the plant sterol groups.[75] However, it is unclear whether the body weight and body fat reductions were due to the pigmented RB or the calorie deficit.[75] In a randomized controlled trial of 105 overweight and obese adults, the participants received a low-calorie diet with RB (70 g/day), a low-calorie diet with rice husk (25 g/day), or a low-calorie diet alone for 12 weeks.[81] The results demonstrated that body weight, body mass index, and waist circumference were significantly reduced in all groups. The study concluded that the reduction of anthropometric indices of obesity in this study might be explained by the energy-restricted diet combined with RB and rice husk supplementation.[81] More studies are needed to clarify the effect of RB on body weight management.

Effect of RB on glycemic control

RB and its components have demonstrated the ability to alleviate hyperglycemia and its associated complications.[82,83] Many in vitro studies have suggested that RB extracts inhibited α-glucosidase and α-amylase activity, and increased glucose uptake in 3T3-L1 adipocytes, so they may lower glucose absorption and postprandial glycemic response.[84,85] RB extracts also stimulate glucose uptake into cells by inducing the messenger ribonucleic acid (mRNA) expression of glucose transporters (GLUT1 and GLUT4) and insulin-signaling pathway proteins, such as insulin receptor gene (INSR) and insulin receptor substrate (IRS)1,[84,85] as well as inducing the release of insulin in INS-1 cells.[86] In addition, reduction in blood glucose and enhancement of hepatic glucokinase activity by the phenolic acid fraction of RB were reported in C57BL/KsJ db/db mice after 17 days of oral administration.[87] Glucokinase is an important regulator of blood glucose, which promotes glucose utilization in the liver by facilitating the phosphorylation of glucose into glucose-6-phosphate.[87]

The effects of RB on blood glucose have also been studied in humans.[88-91] A low-fiber diet supplemented with RB fiber (40 g/day) for 7 days showed greater effects in lowering fasting and postprandial serum glucose levels in diabetic patients than a low-fiber diet alone.[92] A 12-week intervention of stabilized RB (20 g/day) in type 2 diabetic patients resulted in significant reductions in fasting blood glucose, postprandial glucose, and glycated hemoglobin (HbA1c) when compared with baseline levels.[88] The results also suggested that stabilized RB may affect insulin secretion as fasting insulin and area under the curve insulin were increased when compared with the levels with a placebo. This suggests that RB supplementation may improve insulin resistance because the levels of adiponectin, which has been linked to whole-body insulin sensitivity, were also increased. However, RB supplementation did not significantly alter Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and no clear effect of RB on adiponectin was observed in this study.[88] In a similar vein, another study showed significantly reduced fasting and postprandial blood glucose levels among type 2 diabetes mellitus (DM) patients who were on RB supplementation of 20 g/day for 30 days, compared with their baseline levels.[93]

RB oil is widely produced in Thailand and India and is utilized as cooking oil. RB oil is rich in gamma-oryzanol, which confers many health benefits. A combination of 80% RB oil and 20% sesame oil as daily cooking oil (consumption less than 35-40 ml per day) for 8 weeks significantly reduced fasting plasma glucose, postprandial plasma glucose, and HbA1C in type 2 DM patients when compared with the baseline.[90] The effect was greater with the administration of glibenclamide; this implies that RB oil blend works synergistically with glibenclamide to lower blood glucose response in type 2 DM patients.[90] It is possible that gamma-oryzanol in RB oil attenuates pancreatic beta-cell dysfunction and promotes glucose-stimulated insulin secretion.[90] In contrast, a study found that fasting and postprandial blood glucose levels were increased following supplementation of 18 g of RB oil in milk consumed daily for 5 weeks, compared with a placebo (18 g of soybean oil in milk). The researchers stated that the higher amount of palmitic acid in RB oil than in soybean oil may have induced insulin resistance in L6 skeletal myotubes.[91]

Lipid-lowering effect of RB

Studies on mice fed an RB diet showed that they exhibited significantly lowered total blood cholesterol and liver cholesterol concentrations, mainly via an increase in fecal lipid excretion and the regulation of lipogenic enzyme activities.[94,95] Malic enzymes and fatty acid synthase were found to be significantly reduced following RB supplementation (30% of diet) for 7 weeks in mice fed a high-fat diet.[95] Malic enzymes were shown to contribute to cellular nicotinamide adenine dinucleotide phosphate (NADPH) production, which is involved in fatty acid and cholesterol biosynthesis, while fatty acid synthase is a co-factor of NADPH.[95] Furthermore, the supplementation of RB and RB oil in high-fat diet-fed rats also downregulated the expression of β-hydroxy β-methylglutaryl (HMG)-CoA reductase mRNA, a rate-limiting enzyme of cholesterol synthesis, and hepatic malondialdehyde.[96]

Several studies on humans have also been conducted to investigate the effect of RB on blood lipids. In a 12-week intervention with stabilized RB (20 g/day), significant reductions in serum levels of total cholesterol, LDL, and LDL to high-density lipoprotein (HDL) ratio were found in type 2 diabetic patients.[88] Gamma-oryzanol supplements with PUFA n-3 and vitamin E significantly restored a normal lipid profile in dyslipidemic patients after 4 months of intervention, compared with the placebo and PUFA n-3 with vitamin E groups.[97] A randomized controlled trial showed that serum triglyceride levels were significantly reduced and HDL levels were significantly increased, with a tendency for (non-significant) decreasing trends in total cholesterol and LDL in type 2 diabetic patients after receiving 20 g/day of soluble RB for 30 days.[93] In obese Japanese men with high LDL cholesterol, the consumption of RB extract at 30 to 50 mg/day for 12 weeks significantly reduced total cholesterol, LDL cholesterol, and non-HDL cholesterol levels.[76] Supplementation with RB extract (50 mg) for 6 months also significantly reduced LDL cholesterol and the risk of atherosclerosis compared with placebo in post-menopausal Vietnamese women with high LDL cholesterol.[80] In another study, the consumption of pigmented RB with or without plant sterols for 8 weeks also reduced total cholesterol in obese adults who consumed a 25% calorie-restricted diet. The effect was greater in subjects who consumed RB with plant sterols.[75]

Effect of RB on hypertension

A meta-analysis and systematic review on the association of dietary protein intake and blood pressure indicated that plant protein and animal protein are effective macronutrients for lowering blood pressure.[98,99] RB is an inexpensive by-product with an abundance of proteins, DF, and bioactive phytochemicals, which may be a useful nutritional factor for managing hypertension.[100] Several mechanisms by which RB protein may reduce blood pressure have been proposed, including activity to inhibit angiotensin-converting enzyme (ACE), upregulation of endothelial nitric oxide synthase (eNOS) protein, and antioxidant activity, leading to the improvement of endothelial function and blood pressure.[51,101,102] Boonla et al[51] investigated the antihypertensive effects of peptides derived from RBP in a rat model of 2 kidney–one clip (2K-1C) renovascular hypertension. In that study, rats were intragastrically administered either 50 or 100 mg/kg of RBP or distilled water (control) for 6 weeks. Blood pressure and peripheral vascular resistance were significantly decreased in 2K-1C rats treated with RBP compared with those in control rats ($P < .05$).[51] RB protein hydrolysates also significantly reduced plasma ACE, decreased superoxide formation, reduced plasma MDA, increased plasma nitrate/nitrite, and increased eNOS protein expression ($P < .05$), which are associated with the restoration of endothelial function.[51] Moreover, supplementation with RB protein hydrolysates alleviated the effects of a high-carbohydrate/high-fat (HCHF) diet, namely, hyperglycemia, insulin resistance, dyslipidemia, hypertension, increased aortic pulse wave velocity, aortic wall hypertrophy, and vascular remodeling, by mitigating these alterations.[56] RBP also significantly reduced ACE, decreased plasma MDA, decreased superoxide production, increased plasma nitrate/nitrite, upregulated eNOS expression, and increased nitric oxide production in blood vessels of HCHF-diet-fed rats.[56] This study suggests that RBP has beneficial effects against vascular alterations and the risk of cardiovascular disease through several mechanisms involving enhanced NO (nitric oxide) bioavailability, and anti-ACE, anti-inflammatory, and antioxidant effects.[56] Another study found novel bioactive peptides derived from RB protein, Leu-Arg-Ala (LRA), to be a vasorelaxant.[103] In that study, LRA significantly relaxed the mesenteric artery of spontaneously hypertensive rats (SHRs) with $EC_{50} = 0.1\ \mu M$, which is claimed to be the most potent vasorelaxant derived from grain peptides.[103] The tripeptides relaxed the endothelial cells via the endothelial NO system by inducing the phosphorylation of eNOS in endothelial cells without altering eNOS expression. LRA also decreased systolic blood pressure 4 hours after oral administration in SHRs.[104]

A recent clinical trial of 100 individuals with high-normal blood pressure or grade 1 hypertension investigated the effect of processed RB containing peptide Leu-Arg-Ala (43 μg/day) or placebo for 12 weeks on blood pressure.[103] The results showed that subjects who consumed RB had significantly lower systolic blood pressure than those with placebo at the end of the study ($P = .0497$), without any serious adverse effects.[103] Peptides used in the study (Leu-Arg-Ala) promoted vascular smooth muscle relaxation by activating eNOS, which synthesized NO in endothelial cells.[103] Nitric oxide plays an important role in vascular smooth muscle tone. Decreased NO availability leads to endothelial dysfunction and raises blood pressure.[105] These findings reveal that RB protein may be an important component for the preventing and treating hypertension. Therefore, further research is required to investigate the hypotensive effect of RB protein in humans.

Effect of RB on inflammation

The effect of RB on inflammation has been studied in vitro and in vivo. In 2013, Hou et al[106] investigated the effect of anthocyanin-rich black RB extract (200, 400, or 800 mg/kg) for 7 weeks in tetrachloride (CCl_4)-treated mice. The results showed that anthocyanin-rich RB extract normalized liver enzymes, increased plasma antioxidants (SOD and glutathione peroxidase), as well as reduced thiobarbituric acid reactive substances

(TBARS, expressed as MDA) and 8-hydroxy-2′-deoxyguanosine (8-OHdG) . 8-OHdG is a biomarker of oxidative stress as guanine in DNA is transformed into 8-oxo-Gua by a repair process and removed from the body as 8-OHdG; thus, its levels are increased in certain disease conditions, such as atherosclerosis and DM.[42] Meanwhile, MDA is a secondary product of lipid peroxidation and widely used as a biomarker of oxidative stress. The amount of MDA is increased in various diseases related to inflammation, such as cardiovascular diseases, cancer, DM, Alzheimer's disease, liver disease, and Parkinson's disease.[107] Similarly, peptides derived from Thai RB decreased superoxide formation, reduced plasma MDA, and improved endothelial function in 2K-1C hypertensive rats.[51] Moreover, RBP exhibited anti-inflammatory activity as evidenced by reductions of IL-6 and TNF-α (proinflammatory cytokines) and an increase of IL-10 (anti-inflammatory cytokine) in Raw 264.7 macrophage cells.[108] Protein hydrolysate from defatted RB was found to exert antioxidant and ACE inhibitory properties.[51,52,56,109] Rice bran protein was hydrolyzed with alcalase or flavorzyme to obtain RBP. The results showed that RBP fractions lower than 3 kDa possessed the strongest antioxidant activity, and had the highest level of total phenolic compounds and most potent ACE inhibitory properties.[109]

Recently, it was found that virgin rice brain oil reduced oxidative stress and inflammation in rats with hypertension induced by N(omega)-nitro-L-arginine methyl ester.[110] Decreased NO bioavailability has been linked to increased production of ROS and leads to endothelial dysfunction and hypertension.[111] Virgin RB oil is rich in oleic acid, linoleic acid, γ-oryzanol, phytosterols, tocopherols, and tocotrienols, which upregulate eNOS and downregulate gp^{91phox} and P-NF-κB protein expression in aortic tissue. As eNOS protein expression is upregulated by virgin RB oil, it would increase the availability of NO and thus reduce inflammation.[110]

In a randomized trial of 105 overweight and obese adults, RB (70 g/day), rice husk (25 g/day), and placebo with an energy-restricted diet were administered. After 12 weeks of intervention, serum levels of high-sensitivity C-reactive protein (hs-CRP) were significantly decreased in the RB and rice husk groups compared with the baseline. The reductions of hs-CRP and IL-6 in the RB group were significantly greater than those in the placebo group, whereas no significant change was found in the placebo group.[81]

Effect of RB on gastrointestinal functions

Fiber consumption is known to promote gut health.[112] However, excess amounts of fiber may cause bloating and gastrointestinal disturbance due to the fermentation of fiber in the colon by gut bacteria.[113] Daily supplementation with RB (30/g) in colorectal cancer patients for 4 weeks helped to meet the recommended amount of DF without causing gastrointestinal discomfort and changing the stool consistency.[114] In another study, supplementation of arabinoxylan derived from RB for 4 weeks in inflammatory bowel syndrome (IBS) patients was found to improve reflux, diarrhea, and constipation.[115] The improvement in gastrointestinal functions in IBS patients could be mediated by the immunomodulatory effect as the levels of inflammatory biomarkers were also reduced. Fermentation of RB shifts the gut microbiota and stimulates the mucosal balance in the intestinal tract.[115] Hence, the consumption of RB, as a source of DF, could improve gut health and wellbeing.

Prebiotic properties of RB

RB contains a large amount of DF, which has shown prebiotic properties in some studies.[116-119] In 2015, Kurdi and Hansawadi[117] reported that hydrothermal-treated RB (0.22 MPa, 135°C, 0.5-3 hour) produced a mixture of oligosaccharides that stimulated the growth of *Bifidobacterium* and *Lactobacillus*. Similarly, oligosaccharides from RB were found to increase the production of SCFAs and change the population of gut microbiota, mainly *Bacteroides, Dorea*, and *Prevotella*, following fermentation in fecal samples over 24 hour; the effect was comparable to that of fructo-oligosaccharide. Furthermore, the combination of a polyphenol fraction and oligosaccharides from RB increased the population of *F. prausnitzii*, without affecting the production of SCFAs.[119] Recently, Zhang et al[116] conducted in vitro gastrointestinal digestion and colonic fermentation of the DF fraction of RB (RBDF) and phenolic-removed RBDF (PR-RBDF). The results showed that RBDF, but not PR-RBDF, increased the population of *Lactobacillus* spp. after 24 and 48 hour. In addition, the populations of *Bifidobacterium* spp., *A. muciniphila*, and *F. prausnitzii* were higher in RBDF than in PR-RBDF following colonic fermentation. This indicated that not only the fiber fraction of RB, but also phenolic compounds in RBDF, contributed to the prebiotic properties of RB. In an animal study, enzyme-treated RB (4% of diet) for 6 days prevented colitis in a murine model by decreasing *Clostridium* and *Eubacterium* and increasing the production of SCFAs, mainly acetate and butyrate, which contributed to reducing inflammation in colitis.[118]

RB also showed a prebiotic effect in human studies and improved gut health.[120,121] Six months of RB supplementation (1-5 g/day) in weaning Malian and Nicaraguan infants (aged 6-12 months) improved the incidence of diarrheal episodes compared with the level in the control group. This effect was mediated by the changes in the composition of gut microbiota, such as *Lachnospiraceae, Bifidobacterium, Veillonella, Bacteroides*, and *Lactobacillus*, in infants receiving RB. In addition, as the incidence of diarrheal episodes was decreased by RB supplementation, the growth of infants was also improved.[121] Previously, 4 weeks of RB supplementation in healthy adults was shown to increase *Bifidobacterium* and *Ruminococcus* populations. Furthermore, RB supplementation increased the levels of branched-chain fatty acids and secondary bile aids.[120] It was reported that branched-chain fatty acids could be utilized by gut microbiota, such as *Ruminococcus*, contributing to intestinal health.[120]

Effect of RB on kidney and liver function

Kidney plays an important role in maintaining the water and electrolyte balance.[122] Meanwhile, the progression of various metabolic diseases, such as DM and cardiovascular diseases, was shown to influence the kidney function by generating ROS and inflammatory cytokines.[123] Diabetic nephropathy is one of the most common complications in kidney diseases marked by increased albumin and creatinine levels in urine. Diabetic mice supplemented with RBP (100 or 500 mg/kg/day) for 8 weeks showed significant decreases in urine albumin and creatinine compared with diabetic control mice, which improved the diabetic nephropathy.[55] Similarly, purified γ-oryzanol or the combination of γ-oryzanol and RB oil was reported to improve liver and kidney function in rats treated with cisplatin and a high-fat/sucrose diet.[124] Cisplatin injection was found to induce kidney dysfunction in high-fat/sucrose-fed rats, marked by increases of plasma creatinine and urea, and urine volume, along with decreases of urinary creatinine and creatinine clearance. Supplementation with γ-oryzanol (50 mg/kg) with or without RB oil (300 mg) significantly restored the kidney function.[124] It was suggested that the mechanisms were mediated by γ-oryzanol through its inhibition of inflammatory markers, such as prostaglandin E2 (PGE2), which is involved in the progression of kidney dysfunction.[124,125]

Furthermore, RB also showed a hepatoprotective effect against a high-fat diet.[124] A high-fat diet causes lipotoxicity, which increases the risk of non-alcoholic fatty liver disease (NAFLD) in combination with a rise of liver enzymes.[126] The pathogenesis of NAFLD begins with the accumulation of free fatty acids and triacylglycerids in the liver, followed by oxidative imbalance, mitochondrial dysfunction, and activation of proinflammatory cytokines.[126] Supplementation of γ-oryzanol (50 mg/kg) with or without RB oil (300 mg) was also reported to improve liver function by decreasing the rises of alanine transaminase and aspartate transaminase levels in rats treated with cisplatin and a high-fat/sucrose diet.[124] Furthermore, supplementation of 0.5% oryzanol for 7 weeks also increased liver glucokinase, while reducing glucose-6-phosphatase (G6pase) and phosphoenolpyruvate carboxy kinase (PEPCK) in mice fed a high-fat diet.[127] Consequently, the use of blood glucose for energy or storage as glycogen was increased, while hepatic glucose production was decreased, thus improving blood glucose homeostasis.[127]

Toxicological Effect of RB

Rice bran products, including RB oil and fiber, have been used for human consumption and are safe since no mutagenic and teratogenic effects were observed.[128] Recently, RB extract has been utilized as a food additive and considered to be safe for use given it being assigned Generally Recognized as Safe (GRAS) status by The United States Food and Drug Administration in 2018.[129] Based on GRAS Notification Number 884, the RB extract can be used as a food additive at a maximum level of 1.5% (w/w), which is equivalent to 0.71 and 1.50 g/day for those aged 2 and older, respectively.[129]

The toxicity of RB extract has been evaluated in several animal studies.[130-132] The injection of RB oil (0.1 ml) into chicken embryo did not significantly affect embryo morphology and no toxicity was observed, so it was considered safe for human consumption.[132] In 2015, El Askary et al. evaluated the acute effects of RB extract and the effects of its repeated administration for 28 days in albino rats. A dose of 2000 mg/kg was administered to evaluate the acute toxicity; meanwhile, repeated oral toxicity was evaluated at concentrations of 100, 500, and 1000 mg/kg. The results showed that there were no significant effects on mortality or pathological abnormalities following the acute administration of 2000 mg/kg. However, the administration of RB extract daily for 28 days at concentrations of 500 and 1000 mg/kg significantly affected the liver and kidneys. The higher maximum dose of RB extract was previously reported by Al-Okbi.[130] Hexane extract of RB was acutely administered orally at increasing doses from 1 to 12 g/kg to mice. The results revealed that doses up to 12 g/kg were safe in mice, which corresponds to 93 g in a human weighing 70 kg.[130]

Conclusions

The above review of evidence from both animal and human studies shows that RB exerts glycemic control, hypocholesterolemic, hypotensive, and anti-inflammatory effects, as well as promoting bowel function. As a nutrient-rich by-product from the milling process, RB and its derivatives provide nutrients and bioactive compounds that confer these beneficial health effects. Given that there is evidence pointing to the value of this by-product in attenuating metabolic risk factors, RB and its derivatives can potentially be used as nutritional supplements for the control of metabolic syndrome in humans. RB has potential for improving health outcomes, but studies on the effects of its daily consumption are lacking. Further research is required to investigate the effect of RB and its components on functional food development and health outcomes.

Author Contributions

Suwimol Sapwarobol and Weeraya Saphyakhajorn are responsible for preparation, creation of the initial draft. Suwimol Sapwarobol oversight and responsible for the research activity planning and execution, including mentorship external to the core team. Junaida Astina is responsible for critical review and revise manuscript.

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