The Role of Pigmented Rice in Reducing Cardiovascular Disease Risk: A Mini-Review of Animal and Human Studies

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ABSTRACT

Higher dietary intake of polyphenols is associated with a reduced risk of cardiovascular disease (CVD) events and mortality. However, these phytochemicals are predominantly present in fruits and vegetables, which are inadequately consumed by some populations, including Filipinos. This narrative mini-review explores the potential role of polyphenol-containing pigmented rice consumption in modulating risk through a range of mechanisms identified in animal studies. Further, human studies have demonstrated promising but inconsistent effects on risk factors associated with the development of CVD, such as dyslipidemia, hyperglycemia, overweight and obesity. Therefore, this review identifies the need for more clinical trials to examine the effect of pigmented rice on CVD risk factors.

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INTRODUCTION

CVDs such as ischemic heart disease, stroke and hypertension are reported to be the leading cause of death in the Philippines.[1] Elevated lipids and glucose, and obesity are linked to the development of CVDs.[2] Alarmingly, there is an increasing prevalence of Filipinos with borderline-to-borderline high total cholesterol (TC) and low-density lipoprotein (LDL) cholesterol and high to very high triglyceride (TG)[3]; high fasting glucose; overweight and obesity.[4] Lipid reduction is, therefore, an important target outcome for the prevention and management of cardiovascular diseases in this population.[5] An 11% reduction in TC can result in a 24% and 21% reduction in coronary heart disease incidence and mortality.[6] Further, a meta-regression analysis of statin and non-statin therapy trials (diet, bile acid sequestrants, ileal bypass and ezetimibe) reported for each 1 mmol/L reduction in LDL, the risk for a major vascular event was reduced by 23% for statins and 25% for non-statins.[7] For diet alone, the relative risk (RR) was 0.83 (95% CI, 0.72-0.96, $P<0.05$). In addition to dyslipidemia, hyperglycemia and overweight/obesity are also identified as risk factors for CVDs.[2] Hyperglycemia contributes to the formation of advanced glycation end products, which damage the endothelium, promoting the development of atherosclerosis and increasing the risk for hypertension and stroke.[8] Overweight and obesity is associated with low-grade chronic inflammation, which contributes to insulin resistance and atherosclerosis.[9] Obesity also results in structural and functional abnormalities, such as an increase in total blood volume, which increases stroke volume and cardiac output leading to ventricular hypertrophy, and alters the metabolic profile contributing to dyslipidemia, glucose intolerance and elevated blood pressure, all of which increase the risk for CVDs.[9,10]

Dietary patterns that are high in polyphenols are shown to reduce the risk for CVD mortality,[11] and dietary intervention with polyphenols is associated with improved CVD risk factors, including reduction of LDL, glucose and obesity.[12] Polyphenol intake is contributed mainly by non-alcoholic beverages such as coffee and tea, as well as fruits and vegetables.[11] While most Filipinos drink coffee, fruit and vegetable consumption is below recommendations.[13] Comparatively, cereals and cereal products account for 39% of food intake and are an essential component of the Filipino diet contributing to 70% of daily energy intake.[13] Polyphenol containing cereals, such as pigmented rice may provide an avenue for increasing intake in this population. Pigmented rice contains polyphenols, such as phenolics and anthocyanins, and are black, red or purple in color.[14] The color of black rice is primarily attributed to its anthocyanin content, while the color of red rice is due to proanthocyanidin, and both polyphenols contribute to the color of purple rice;[14] darker and stronger colors are associated with a higher total anthocyanin content.[15] These bioactive compounds have antioxidant properties.[14,16] This narrative mini-review will summarize the proposed mechanisms by which pigmented rice may provide cardioprotection. It also aims to explore the role of pigmented rice as an intervention in reducing lipids, glucose and weight for the prevention of CVDs.

Evidence from Animal Studies

Several animal studies have investigated the possible effect of pigmented rice on health through lowering lipids,[17–21], glucose,[17,22] and body fat,[17,18] and its associated mechanisms of action. Incorporation of pigmented rice (supplement form, extract, germinated) results in a reduction in TC [19–21] and, more importantly, in LDL [17,20,21] which is identified as the major lipid related to the development of CVDs.[5] Lowering TC and LDL may result from changes in the regulation of lipid metabolism. The study of Lo, et al.,[23] which provided germinated purple rice (20% of total diet composition) in the diet of ovariectomized Sprague-Dawley rats, resulted in decreased fatty acid synthase (FAS) and higher carnitoyl transferase (CPT) and β-oxidation activity, resulting in lower plasma TC, LDL and TG. Fatty acid synthase is an enzyme in adipose tissue and liver [24] that catalyzes de novo synthesis of fatty acids that are secreted in very low density lipoprotein (VLDL) or stored as lipid droplets along with TG in the liver.[25] Inhibition of FAS is postulated to reduce atherogenesis.[24] On the other hand, CPT is a rate-limiting enzyme that plays a significant role in fatty acid oxidation. Chung & Kang [17] who fed a high-fat diet including germinated, pigmented, giant embryo rice to obese mice also reported reduced FAS and increased CPT, along with decreased levels of apo-B, insulin and resistin and increased levels of adiponectin and apolipoprotein A-I (apoA-I). apoA-I is a major structural and functional component of HDL, while apolipoprotein B (apoB) is related to increased risk for CVDs as it is essential for the formation of VLDL, intermediate density lipoprotein and LDL,[26] and acts as a ligand for LDL receptors. Adiponectin, produced by adipose tissue but observed to be reduced among obese individuals, is related to increased high density lipoprotein (HDL), decreased TG, improved insulin sensitivity, reduced inflammatory cytokines and protection against atherosclerosis.[27] Using an obese mouse model, Kim, et al.[28] investigated the mechanism by which black rice (administered as an extract for eight weeks) reduced adipose tissue and improved lipids. They observed changes in transcription factors, peroxisome proliferator activated receptors (PPARs); consumption of black rice extract significantly upregulated PPAR-α and down-regulated PPAR-γ. PPARs play an important role in lipid and glucose metabolism; PPAR-α regulates β-oxidation of fatty acids and controls inflammatory processes, while PPAR-γ promotes adipogenesis (lipid storage).[29] These mechanisms observed in various animal studies and their potential effect on CVD risk factors (specifically lipid, glucose and body fat lowering) is summarized in Figure 1. However, results from

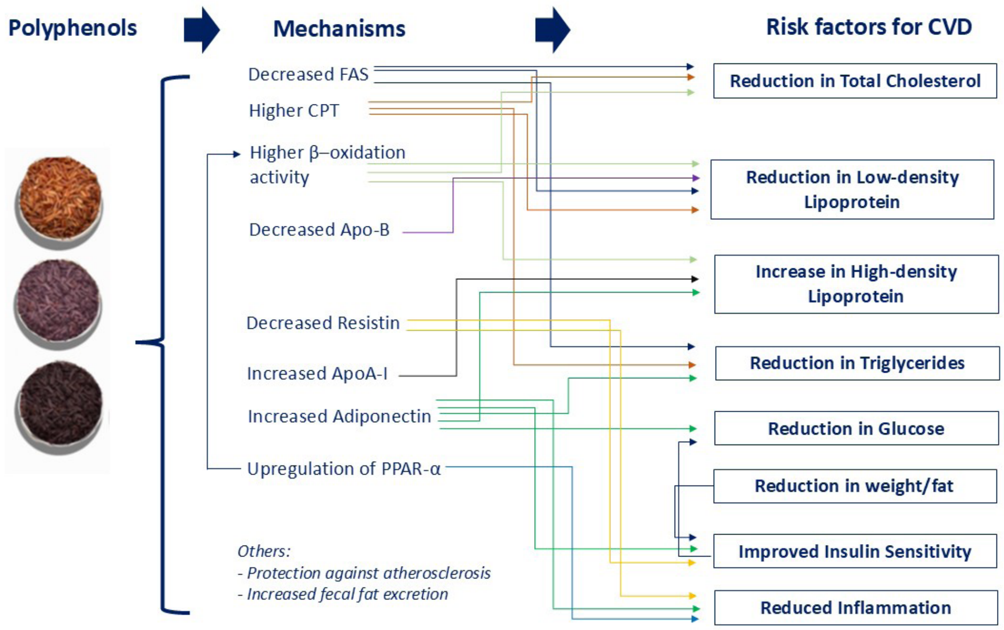

Figure 1. Summary of proposed mechanisms of action of polyphenols from pigmented rice on reducing risk for cardiovascular disease based on animal studies. Each colored line represents the proposed mechanism of action targeting specific risk factors.

animal trials do not always translate in humans as they typically supplement animals with greater doses than in humans and may not entirely capture the complexity of different human metabolic processes and interactions. Nonetheless, these studies test the plausibility of hypotheses and provide insight that can be further developed and used as a basis for human trials.

Evidence from Human Studies

Several human studies have examined the role of pigmented rice in reducing risk factors for chronic disease, specifically CVDs. Given the purported antioxidant activity of polyphenols, various studies evaluated whether consumption of pigmented rice led to increased circulating levels of polyphenols and antioxidant effects. Vitalini, et al. reported that consumption of cooked black rice (100 grams) resulted in higher circulating plasma phenols and flavonoids compared to brown rice among healthy adults.[16] Another study that compared the effect of a supplement containing a 10-gram black rice pigment fraction (BRF) with a white rice fraction (WRF) among coronary heart disease patients observed a significant increase in anthocyanin levels after consumption of the BRF compared to WRF.[30] Both studies observed an increase in polyphenol levels 30 minutes after ingestion of pigmented rice and peaking at 120 minutes. Further, increased antioxidant activity was also observed within 30 minutes, peaking from 60-120 minutes and lasting up to 150 minutes.[16,31] These studies, together with the results from animal studies, contribute to establishing the potential benefits of pigmented rice consumption on chronic diseases through its antioxidant capacity primarily contributed by polyphenols.

The results from recent human studies investigating the effect of pigmented rice on lipid levels are inconsistent. Studies by Joo, et al.,[32] Kim, et al.,[33] Seesen [34] and Wang,[30] demonstrated a reduction in TC, LDL and TG following pigmented rice consumption, but were not significantly lower compared to control. Comparatively, a study by Syarief, et al.[35] showed a significant decrease in TC, LDL and TG after the intervention compared to the control. Table 1 presents the key characteristics of these studies and a summary of outcomes. Reductions in lipids ranged from 5 to 30 mg/dL for TC, 1.2 to 8.5 mg/dL for LDL, and 8 to 23 mg/dL for TG. Of the five studies mentioned, only two [33,34] included glucose as an outcome and one [33] included weight. The effects on glucose are also inconsistent. Kim, et al.[33] investigated the effect of energy restricted diets using meal

Table 1. Characteristics of human studies investigating the effect of pigmented rice on lipids, glucose, and/or weight

Reference	Design, Sample size	Age (years)	Sex	Health Status	Intervention	Control	Duration (Weeks)	Outcome of interest	Findings
Joo, et al. 2019 [32]	P-RCT, *n=48*	>50	M, F	Subjective memory impairment	Black rice, extract	Crystalline cellulose	12	TC, LDL, HDL, TG	No between group differences *Within-Group Intervention Effects* Reduction in TC, LDL and HDL (NS) Increase in TG (NS)
Kim, et al. 2008 [33]	P-RCT, *n=47*	20-35	F	Overweight to moderately obese	Black rice, powder	White rice	6	TC, HDL, TG, Glucose, Weight, BMI, Body fat	Greater reduction in weight, BMI and body fat significantly different to white rice (all, p<0.05) *Within-Group Intervention Effects* Reduction in TC and TG (p<0.05) Increase in HDL (<0.05) Reduction in glucose (NS) Reduction in weight, BMI, body fat (p<0.05)
Syarief, et al. 2020 [35]	P-RCT, *n=52*	>40	F	Metabolic syndrome	Black rice, fermented	NR	4	TC, LDL, HDL, TG	Greater reduction in TC (p=0.003), LDL (p=0.002) and TG (p=<0.001) compared to control Greater increase in HDL (p=<0.001) compared to control
Seesen, et al. 2020 [34]	P-RCT, *n=62*	65-74	M, F	Elderly	Black rice, germ	NR	24	TC, LDL, HDL, TG, Glucose	No between group differences *Within-Group Intervention Effects* Reduction in TC (p=0.001), TG (p=0.020) Reduction in LDL (NS) Increase in glucose (NS)
Wang, et al. 2007 [30]	P-RCT, *n=60*	45-75	M, F	Coronary heart disease	Black rice fraction, powder	White rice	24	TC, LDL, HDL, TG	No between group differences *Within-Group Intervention Effects* Reduction in TC, LDL, TG (NS) Increase in HDL (NS)

BMI - body mass index; F - female; HDL - high density lipoprotein; LDL - low density lipoprotein; M - male; NR - not reported; NS - not significant; P-RCT - Parallel randomized controlled trial; TC - Total cholesterol; TG - triglycerides replacement (including black or white rice) among premenopausal overweight-obese women, and reported an 8.2±11.6 mg/dL reduction in fasting glucose levels after six weeks of intervention, along with a significant reduction in weight (-6.75±1.91 kg). The black rice group lost significantly more weight compared to control; however, changes in glucose were not different between the groups. Seesen, et al.[34] reported a non-significant 2.7± 21.74 mg/dL increase in fasting glucose after intervention with black rice germ. Participants from both studies had normal fasting glucose levels at baseline.

A possible explanation for the inconsistencies in results was differences in the study population, duration and design of intervention (ie, with or without concurrent energy restriction), and the form of pigmented rice. Study duration ranged from 4 to 24 weeks, and although all studies used black rice, it varied in form (see Table 1). More pronounced benefit may be seen in individuals with elevated lipids and glucose. Nonetheless, these studies provide preliminary evidence for the possible effect of pigmented rice on lipids, glucose and weight, which may help prevent the development of CVDs.

CONCLUSION AND RECOMMENDATIONS

Animal studies have identified several mechanisms by which pigmented rice may influence risk factors, such as changes to enzymes involved in pathways that regulate fatty acid synthesis, lipid metabolism, inflammation and insulin sensitivity. Several human studies have been conducted with inconsistent results, which may be due to differences in study design and the population investigated. A systematic review and meta-analysis are recommended for a more comprehensive synthesis of the body of evidence. Lastly, more controlled clinical trials are needed to provide additional empirical evidence on the impact of pigmented rice in reducing lipids, glucose and weight.

Conflict of Interest

The authors declare that there is no conflict of interest in the conduct of this review.

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Author's Contribution

D.M-S: Review conception, organization, and execution, and review manuscript preparation.

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