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Nutritional Significance and Nutrients-related Chronic Diseases Prevention Potential of Brown Unpolished Rice: A Review

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ABSTRACT: The increasing incidence of nutrient-related non-communicable chronic diseases (NCCDs), like type 2 diabetes mellitus, cancers, cardiovascular diseases and hypertension, as the leading cause of morbidity and mortality worldwide, posed researchers in Nutrition and Nutrigenomics to search for the possible link between such diseases and the foods consumed by different communities. Hence, the objective of this paper is to provide a critical review of nutritional significance and nutrient-related chronic diseases prevention potential of brown, unpolished rice using relevant literatures searches from online and library sources. The study, therefore, investigated the various nutritional and health protection potentials of the brown, unpolished rice. The review highlighted the implication of polished, white rice consumption in conditions such as hyperglycemia, dyslipidemia and oxidative stress, as well as the preventive effects of the brown rice consumption against these disease conditions. It can, therefore, be concluded that substitution of the widely consumed polished white rice with the unpolished brown rice may promote healthy living and prevent the risk of various nutrients-related chronic diseases.

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The growing incidences of non-communicable chronic diseases (NCCDs) like type 2 diabetes, obesity, neurodegenerative disorders, and cancers is the major health burden the world experiences today. This situation has been associated with adoption of unhealthy western lifestyles, including the consumption of energy dense and highly processed foods (Imam and Ismail, 2017). About 463 million adults have been reported to be living with diabetes worldwide and it is expected to rise to 578 million by 2030 and 700 million by 2045 (IDF, 2019). Nigeria is the second country in Africa with the highest prevalence of type 2 diabetes, with estimated 2.7 million people living with diabetes mellitus (IDF, 2019). Imam *et al*., (2014) reported an increased risk of insulin resistance in rat offspring whose parents were exposed to white (polished) rice as a staple. Another study reported that white rice consumption worsens antioxidant status in type 2 diabetic rats, while brown rice and germinated brown rice maintain antioxidant status to varying degrees and improved glycaemia (Imam *et al*., 2012). Although effort has been made to prevent the burden of theses NCCDs, there is need for more action to prevent people from

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further suffering from the pandemic. White rice, produced from whole brown rice through series of mechanized processes including hulling and milling, primarily consists of starch and it is the predominant type of rice consumed worldwide (Atkinson *et al*., 2008). The complete milling and polishing processes destroy many nutrients, which may form part of the reasons that the glycemic index values of white rice are higher on average than that of its brown, unpolished counterpart (Foster-Powell *et al*., 2002; Nanri *et al*., 2010). Evidence has been provided that white rice consumption is the primary contributor to dietary glycemic load in populations where rice as the staple food (Nanri *et al*., 2010). It is well known that glucose is generated from dietary carbohydrates and persistent hyperglycemia leads to insulin resistance (IR) and oxidative stress (OS), which have strong correlation to the development of obesity, type 2 diabetes mellitus, cancer, neurodegenerative and inflammatory diseases (Nirmala *et al*., 2015). Astonishingly, consumers often prefer to consume the white, polished rice, perhaps due to its preferred visual and taste appeals than the brown unpolished rice, despite the superior nutritional significance of the later. Several studies reported that white rice consumption can predispose individuals to the diet-related diseases chronic diseases, while the brown rice on the other hand can counteract the effects (Nanri *et al*., 2010). It is, therefore, important to review the nutritional significance and nutrition-related chronic diseases prevention potential of the brown rice, to serve as a baseline for recommending it in the production of nutraceuticals and to consider it as a functional food.

Rice Taxonomy: Rice grain is the seed of the monocot plant of the genus *Oryza* and of the grass family Poaceae (formally Graminae), which includes wild and cultivated species, such as *Oryza sativa* (Asian rice) and Oryza glaberrima (African rice) (Oko and Ugwu, 2011). The genus *Oryza* is divided into four species complexes, including the *Oryza sativa*, *Oryza officials*, *Oryza widely* and *Oryza granulata* species (Sweeney and McCouch 2007). Sweeney and McCouch (2007) asserted that *Oryza sativa L*. and *Oryza glaberrima Steud* are two cultivated species, whereas *Oryza rufipogon*, *Oryza nivara*, *Oryza barthii*, *Oryza longistaminata*, *Oryza meridionalis*, and *Oryza glumaepatula* are wild species. The origin of *Oryza glaberrima* as African rice is validated by the data from isozyme studies, including simple sequence repeats (SSR) and single nucleotide polymorphism (SNP) (Sweeney and McCouch, 2007). The rice farmers in Africa have ecological knowledge on their local ecosystem and crop varieties, which is passed through generations. This inherited knowledge gave rise to the identification of crops that are grown locally and assigning them vernacular names. Hence, even when improved varieties are introduced, the assigned vernacular names usually outshine the scientific ones (Sweeney and McCouch, 2007).

Anatomy of the Rice Grain: The understanding of the physical and chemical properties of rice is governed by the knowledge of its grain structure. The paddy rice (freshly harvested) grain has a top layer called hull, covering and protecting the caryopsis (brown rice), which is estimated to take about 20% of the weight of the grain (Juliano, 2007). Inside the hull and covering the endosperm and embryo of the mature rice grain is the bran, a layer that contains aleurone, nucellus, seed coat, and pericarp fractions. This layer contains starch, dietary fibers, oils, proteins, vitamins and dietary minerals, making it highly nutritious. Unfortunately, the bran is usually removed during milling process (Park *et al*., 2017). Inside the bran layer lies a very small compartment called germ, which is bounded on one side by the bran and on the other side by the starchy endosperm (Juliano and Tuaño, 2018). The starchy endosperm is made up of the outermost cells located just beneath the aleurone layer, and the central region consisting of the rest of the starchy endosperm (Juliano and Tuaño, 2018).

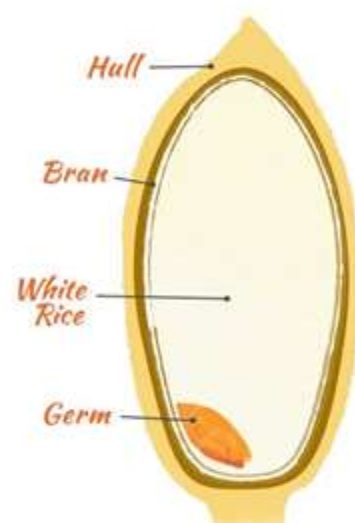

Fig 1. The anatomy of a rice grain (Juliano and Tuaño, 2018).

The Brown, Unpolished Rice: Brown rice is the whole grain rice in which only the hull is removed and retains the bran layer, that differentiates it from the white, polished rice. The nutritional composition of the brown rice gives it several advantages over the white rice, particularly due to the abundance of phytochemicals in the bran layer (Upadhyay and Karn, 2018). It is a common knowledge that the bran layer in the brown rice has several bioactive compounds that promote its nutritional significance. Brown rice and its derived extracts have shown antioxidant activity based on *in vivo* trials on type 2 diabetic rats, where the brown rice and the germinating brown rice both maintained antioxidant status and improved the total antioxidant status (TAS), as well as the radicals' scavenging activity of the kidneys, which may be due to the abundance of antioxidant phytochemicals, such as flavonoids, phenolics, gamma aminobutyric acid and oryzanol (Abubakar *et al*. 2017; Imam *et al*., 2012). It has been suggested that upregulation of superoxide dismutase (SOD) gene is the fundamental mechanism for the antioxidative effect of the brown and germinating brown rice (Imam *et al*., 2012). Therefore, the abundance of bioactive compounds in the brown, unpolished rice makes it a very good option in the prevention of several nutrient-related diseases, some of which are shown in table 1.

Table: Selected bioactive compounds in the rice bran with nutrients-related chronic diseases prevention potentials.

Compound	Disease Prevention Activity
Ferulic acid	Antioxidant, chemo preventive, anti-inflammatory and lipid-lowering effects
γ-Oryzanol	Antioxidant, chemo preventive, anti-inflammatory and lipid-lowering effects
Inositol hexaphosphate	Blocks cancer growth and signaling
GABA	Antioxidative effects and glucose-lowering activity
β-Sitosterol	Blocks cholesterol
Linoleic acid	Anti-inflammatory
α-Tocopherol	Inhibit lipid peroxidation and intracellular signaling
Tocotrienol	Inhibit lipid peroxidation and intracellular signaling
Salicylic acid	Anti-inflammatory
ASG	Antidiabetic effects
Caumaric acid	Antimutagenic, inhibit cell cycle, antioxidant, and chemo preventive
Tricin	Antimutagenic, inhibit the cell cycle, antioxidant, and chemo preventive

GABA= Gamma aminobutyric acid. ASG= acylated steryl β-glucoside. Source: (Chaudhari et al., 2018)

The Insulin Signaling: Insulin action is mediated by cascaded of three main pathways: the phosphatidyl inositol 3-kinase (PI3K)/protein kinase B (Akt) pathway, the Cbl associated protein (CAP)/Cbl pathway, and the Ras/mitogen-activated protein kinase (MAPK) pathway. These pathways regulate glucose uptake, protein synthesis, and the expression of genes involved in cellular proliferation and differentiation (Litvinova *et al*., 2014). The pathways are triggered by the binding of insulin to the Tyrosine Kinase, a transmembrane insulin receptor, composed of α and β chains. The Tyrosine Kinase pathway is activated by the insulin itself and the IGF I and IGF II (Færch *et al*., 2016). The binding of insulin to the α subunits leads to conformational change in InR and IGF-IR that activate the kinase activity in the β subunits. This results in transphosphorylation among β subunits, further activating the kinase and allowing the recruitment of main cytoplasmic adaptor molecules, which are involved in transducing extracellular signals from receptors to downstream proteins, known as IRSs. The most studied IRSs are IRS 1-6, which act as a ladder to organize and mediate signaling complexes and are activated by different insulin-induced kinases, such as, PKC, SIK2, AKT, S6K1, mTOR, ERK1/2, and ROCK1(Shaw, 2011). The activated IRS-1 triggers subsequent signal transduction by binding to phosphoinositide 3-kinase (PI3K) and activating it, which in turn, catalyzes the conversion of phosphatidylinositol 4,5-bisphosphate (PIP2) (an inositol phospholipid in the plasma membrane) to phosphatidylinositol 3,4,5-triphosphate (PIP3) (Ho *et al*., 2016). PIP3 is a potent inducer of activation of various protein kinases, mostly protein kinase B (PKB), otherwise known as AKT, and 3-phosphoinositidedependent protein kinase–1 (PDK1) to the plasma membrane, where PDK1 activates PKB (Ho *et al*., 2016; White, 2003). PKB facilitates glucose entering into cells by translocation of GLUT-4, and it inhibits serine–threonine protein; glycogen synthase kinase, which is an inhibitor for glycogen synthase, thereby promoting glycogen synthesis (Koeppen and Stanton, 2017).

Effects of the Brown Rice on Insulin Signaling: The consumption of brown rice during pregnancy and lactation was shown to prime the genes of rats' offspring towards an enhanced insulin sensitivity, as reported by Adamu *et al*., (2017). The authors observed improvements in high fat diet (HFD)-induced metabolic perturbations, when rats were fed with brown rice and GABA, in addition to the HFD during pregnancy, which was evidenced by downregulation of the PRKCZ, MTOR, MAPK, SOCS1 and IKBKB genes, and followed by a concomitant increase in expressions of IRS1 and insulin receptor (INSR) genes. Another study showed that brown rice diet can downregulate some downstream molecules of the IRS1/PI3K/AKT insulin signaling pathways, including phosphorylated GSK3β protein expression and FOXO1 gene expression (Gao *et al*., 2019). On the contrary, numerous studies reported that polished white rice consumption predisposes individuals to the risk of insulin resistance, perhaps due to its high glycemic index. White rice consumption has been reported to worsen glucose tolerance test due to hyperglycemia (Imam *et al*. 2014). Shen *et al*., (2015) have reported hyperglycemia to play a critical role in insulin signaling via the downregulation of INSR, IRS-1, PI3K, GLUT-4, AMPK, and glucokinase (GCK) and high expression of GSK and serine/threonine kinase in muscle and liver. Similarly, white rice has also been shown to modulate MAPK1, MAFA1 and SLC2A2, as suggested by Abubakar *et al*., (2020). These changes in gene expression could collectively lead to insulin resistance, which in turn causes some metabolic perturbations in the body, and consequently predisposing the individual to many chronic diseases.

Effects of Brown Rice Consumption on Metabolism: The consumption of rice can impact metabolism positively or negatively. Some details on the impact of rice consumption on the two most important insulin dependent metabolic pathways, i.e., carbohydrate and lipid metabolism are discussed in the succeeding section:

Carbohydrate Metabolism: Brown Rice has been found to improve the secretion of insulin and the expression of some genes responsible for glycolysis, like the INSR, IRS 1 and 2, PI3K, which are the most important insulin signaling genes, by Yen *et al*. (2017). They also found increase in the expression of GLUT 1 and 4, GCK, and peroxisome proliferator-activated receptor γ (PPAR-γ), which are important regulators of glucose uptake, glycolysis and glycogenesis (Yen *et al*. 2017). Reports of the suppression of gluconeogenesis, mediated via the downregulation of FBP1 and PCK1 genes, linked to the presence of bioactive compounds like GABA, oryzanol and phenolics in brown rice also abounds (Azmi *et al*., 2013). Park *et al*. (2017) reported that supplementation of diabetic rats with Germinating Waxy Black Rice reduced the expression of SGLT1 and GLUT2 genes, which code for glucose transporters responsible for intestinal glucose uptake and transfer to blood circulation. They also found increases in the expression of GLUT4 and PI3K, and AKT protein phosphorylation in muscles. Expression of these genes collectively balance the glucose homeostasis (Park *et al*., 2017).

Lipid Metabolism: Brown rice was reported to decrease the levels of SREBP-1 (regulator of both cholesterol and fatty acids metabolism and synthesis), SCD-1 (an important enzyme in the synthesis of monounsaturated fatty acids from dietary fats) and liver triglycerides (TG) as well as HMG-CoA reductase (HMGCR), an enzyme that catalyzes the rate limiting step of cholesterol synthesis and increases the levels of LDLR, CYP7α1 and PPAR-α and also increases the fecal excretion of triglycerides, total cholesterol and bile acids (Yen *et al*., 2017). Diabetic rats have been reported to show high levels of TGs, TC and LDL cholesterol, as well as low levels of HDL cholesterol, which were then reversed by 5% germinating brown rice to normal levels (Park *et al*., 2017). Hypocholesterolemia effect of the brown rice were also seen in the report with significant decrease in the concentrations of TC, TG and LDL-C in plasma and increased HDL-C in hypercholesterolemia rats (Hossain *et al*. 2019). In the latter study, the decrease in TC and TG in the liver were associated with decreased intestinal absorption or increased excretion of cholesterol from the liver.

Antioxidant Activity of the Brown Rice: Brown, unpolished rice and its extracts have shown a substantial antioxidant activity in both *in vitro* assays and *in vivo* trials. Numerous studies investigating the antioxidant effects of the brown rice, germinating brown rice and white rice reported that consumption of brown and germinating brown rice improved, whereas consumption of white rice worsen, the total antioxidant status in type 2 diabetic rats. Similarly, brown rice consumption preserved liver enzymes and serum creatinine levels (Imam *et al*., 2012). The superoxide dismutase (SOD) gene was upregulated, suggesting a possible mechanism underlying the antioxidant effect of brown rice (Imam *et al*., 2012). In another study, diets supplemented with brown rice exhibited greater effects on increased antioxidant enzyme activity and vitamin E levels, as well as reduced lipid peroxidation in hypercholesterolemia rabbits (Mohd Esa *et al*., 2013). The antioxidant activity of the brown rice extracts *in vitro,* varies depending on factors, such as the extraction method, bioactive compound content, brown rice cultivar and fractionation of the bioactive compounds into free or bound (Gao *et al*., 2018). In contrast, the low antioxidant activity of white polished rice compared to the brown rice could be attributed to the removal of the outer bran layer during milling, which contains higher levels of phytochemicals with antioxidant properties (Pang *et al*., 2018). Brown rice consumption also enhanced the antioxidant properties and immune function in aged mice compared to the white rice (Wu *et al*., 2013).

Insulin Resistance and Oxidative Stress: The Link: Several evidence have associated oxidative stress with the development of insulin resistance and other metabolic diseases, through excessive production of reactive oxygen and/or nitrogen species, or deficiency of antioxidants (Rodrigo *et al*., 2007). The induction of insulin resistance by oxidative stress can also be through impairment in insulin signaling pathways leading to dysregulation of adipokine (Houstis *et al*., 2006), or by IRS degradation through the activation of Serine-Threonine Kinase pathways, such as the Janus Kinase (JAK) pathway, which phosphorylate the IRS proteins (Evans *et al*., 2005). Furukawa *et al*., (2017) reported an increase in free radicals and biomarkers of oxidative damage, carbohydrate metabolites and 8-hydroxy-2′-deoxyguanosine (8-OHdG) in adipocytes and skeletal muscles, which predispose to insulin resistance. The major effect of insulin resistance is hyperglycemia, a condition capable of inducing oxidative damage to cells, as shown by Lee *et al*. (2010). In chronic hyperglycemia, reactive oxygen species are produced in various ways including an increase in the production of advanced glycation end products (AGEs), activation of the polyol pathway and activation of Protein Kinase C (PKC) (Halliwell, 2009). This phenomenon elicits the reciprocal link between insulin resistance and oxidative stress.

Antidiabetic Activity of Brown Rice: Type 2 diabetes mellitus (T2DM) is one of the most prevalent diet-related chronic diseases world over. It is, therefore, imperative to identify a functional food that can be effective as a dietary intervention in the prevention and/or management of T2DM. Several studies have explored the underlying mechanisms of the brown rice's antidiabetic effects. A study demonstrated that brown rice-specific γ-oryzanol acts as a molecular chaperone, mitigating endoplasmic reticulum stress in the hypothalamus, protecting β-cells against apoptosis, and inhibiting DNA methyltransferases in the brain's reward system, in mice and cell cultures (Abubakar *et al*., 2018). These findings suggest that consumption of brown rice may reduce high fat diet preferences, through the epigenetic modulation of the striatal dopamine D2 receptor, thereby promoting insulin sensitivity and fuel homeostasis (Masuzaki *et al*., 2018). The inhibition of high fat diet preferences may help in avoiding most of the junk foods, implicated in insulin resistance, obesity and other risk factors of T2DM (Abubakar *et al*., 2018). In another study, germination enhances the antidiabetic potential of the brown rice, as evidenced by the reducing glycemic index, insulin index, hypercholesterolemia, OS, and TNF-alpha levels. Grown brown rice significantly lowered plasma glucose levels and body weight in rats more effectively than normal brown rice and metformin, with white rice showing adverse effects on glycemia (Imam and Ismail, 2013). Moreover, clinical trials involving human subjects revealed that brown rice induces slower gastric emptying rates than white rice, irrespective of variations in amylose content and starch digestion rates *in vitro*, resulting in a reduced glycemic response (Pletsch and Hamaker, 2017). Also, ingestion of parboiled brown rice pudding resulted to a significant decrease in plasma glucose levels in healthy men, over a 90-minute period compared to a control, accompanied by reduced plasma insulin response. This indicated that parboiled brown rice can be effective in combatting type-2 diabetes mellitus and obesity (Poquette *et al*., 2012).

Anti-obesity Effects of Brown Rice: Another diet-related condition bedeviling the world, especially in the developed nations is obesity. Obesity constantly is accompanied by the increased risk of developing chronic diseases, such as diabetes mellitus, hypertension, cardiovascular disease, cancer and inflammation (Lim *et al*., 2014). Brown unpolished rice consumption is reported in several studies to have positive effects on mitigating obesity. For example, diets enriched with 50% brown rice were found to be more effective in reducing weight gain and improving lipid parameters, including ox-LDL and F2-isoprostane levels, in rats with hypercholesterolemia. Conversely, diets supplemented with white, polished rice demonstrated detrimental effects on these parameters (Imam *et al*., 2014). Similarly, methanolic extract of germinating brown rice exhibited anti-adipogenic effects, by reducing lipid accumulation via inhibition of adipocyte differentiation, down-regulation of adipogenic transcription factors and expression of mRNA of adipogenic genes in 3T3-L1 adipocyte cells (Ho *et al*., 2013). Oral administration of γ-oryzanol has also been reported to improve DNA hypermethylation of the promoter region of the dopamine D2 receptor in the striatum of mice, fed with a high fat diet, suggesting its potential as novel epigenetic modulator and anti-obesity compound (Kozuka *et al*., 2017). These effects can be attributed to the combination of dietary fiber, vitamins, minerals, and various bioactive compounds such as GABA, γ-oryzanol, phytosterols, polyphenols, tocotrienols, and α-tocopherol of the brown rice (Lim *et al*., 2016).

Anticancer Effect of Brown Rice: Cancer is the leading cause of death worldwide, especially in developing countries (WHO, 2017). Therefore, reducing the cancer risk factors through nutritional strategies, such as consumption of functional foods that have the potential to lower the cancer incidence is imperative. Brown rice has been reported to exhibit anticancer properties, as revealed by several studies. The effects of parboiled brown rice may be attributed to the combination of bioactive compounds, such as ferulic acid, p-coumaric acid, γ-oryzanol, γ-tocotrienol, and GABA. These compounds have the potential to reduce the risk of liver cirrhosis and cancer, perhaps due to their synergistic effects (Wunjuntuk *et al*., 2016). The extract from a mixture of brown rice and rice bran, fermented with *Aspergillus oryzae* (FBRA) reduced human cell viability, in a concentration- and time-dependent manner. Also, the FBRA extract triggered an apoptotic cell death in human acute lymphoblastic leukemia cells, possibly via the death receptor-mediated pathway or the truncated Bid-mediated mitochondrial pathway or both (Horie *et al*., 2016). Brown rice and rice bran were also found to reduce the expression of cyclooxygenase-2 significantly, in the middle colon of rats compared to the white rice. This suggests that the bran layer may be the potent fraction of the rice that protect against early carcinogenesis, induced by colon 1,2-dimethylhydrazine, hence lending credence to its use as a dietary supplement for prevention of colon cancer (Li *et al*., 2011; Lin *et al*., 2019).

Effect of Brown Rice in Prevention of Neurodegenerative Disorders: Neurodegenerative disorders are a group of conditions that affect the brain and nervous system caused usually by aging, resulting in progressive damage of brain cells over time. Several studies conducted to investigate the effect of brown rice consumption on neurodegenerative diseases, like Alzheimer's disease (AD) and Parkinson's disease as the most prevalent neurodegenerative disorders, demonstrated potential neuroprotective effects against these diseases. The cytotoxicity test results indicated that extract of germinating brown rice did not induce damage to human neuronal cells at concentrations up to 20 ppm (Chompoopong *et al*., 2016), and morphological analyses revealed that the extract (up to 10 ppm) prevented H_2O_2-induced apoptotic changes in the neuronal cells. Interestingly, brown rice mixed with the regular diet of rats induced with rotenone-induced Parkinson's-like disease exhibited neuroprotective effects at a dose of 1.5 mg/kg every 2 days (Chompoopong *et al*., 2016). The protective effect of the extract on these cells is associated with its capacity to induce transcriptional alterations in antioxidant and apoptotic genes, as demonstrated by multiplex gene expression analyses (Azmi *et al*., 2013). In a different study, administration of a diet of water pressurized brown rice (HPBR) to Alzheimer's disease mice models enhanced cognitive dysfunction and decreased the levels of amyloid-β, a major protein associated with Alzheimer's disease in the brain (Okuda *et al*., 2018). As there are no known drugs or medications that can prevent these disorders presently, the adoption of brown rice diet to mitigate the effects of aging processes and enhance neuronal functions is highly recommended.

Conclusion: Consequent upon the fore going, it can be concluded that substitution of the commonly consumed polished, white rice with the unpolished brown rice can be beneficial in promoting health and preventing the prevalence of nutrients-related non-communicable diseases (NCCDs) and other diet-related diseases in the community.

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Data Availability Statement: Data are available upon request from the corresponding author

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