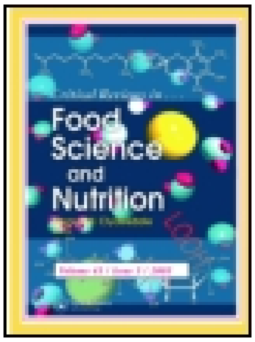

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REVIEW

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Enhancing health benefits of milled rice: current status and future perspectives

Deepak Kasote[a], Nese Sreenivasulu[b], Cecilia Acuin[b]*, and Ahmed Regina[a]

[a]Centre of Excellence in Rice Value Addition (CERVA), International Rice Research Institute (IRRI), South Asia Regional Centre, Varanasi, Uttar Pradesh (U.P.), India; [b]Rice Breeding and Innovation Platform, International Rice Research Institute (IRRI), Los Baños, Laguna, Philippines

ABSTRACT
Milled rice is an essential part of the regular diet for approximately half of the world's population. Its remarkable commercial value and consumer acceptance are mostly due to its promising cooking qualities, appealing sensory properties, and longer shelf life. However, the significant loss of the nutrient-rich bran layer during milling makes it less nutritious than the whole grain. Thus, enhancing the nutritive value of milled rice is vital in improving the health and wellbeing of rice consumers, particularly for those residing in the low-economic zones where rice is the primary source of calories and nutrition. This article provides a critical review on multiple frontiers of recent interventions, such as (1) infusing the genetic diversity to enrich amylose and resistant starch to reduce glycaemic index, (2) enhancing the minerals and vitamins through complementary fortification and biofortification as short and long-term interventions, and (3) developing transgenic solutions to improve the nutrient levels of milled rice. Additionally, the review highlights the benefits of functional ingredients of milled rice to human health and the potential of enhancing them in rice to address the triple burden of malnutrition. The potential merit of milled rice concerning food safety is also reviewed in this article.

KEYWORDS
Milled rice; micronutrients; vitamins; safety; fortification; biofortification bioavailability

Introduction

Rice is the staple food that meets the energy needs of two-thirds of the global population, especially for those rice consumers who have limited opportunity and means for consuming diverse diets (Lei and Yuan 2019; Wani et al. 2012). Despite rapid changes in the global dietary patterns, rice continues to be a crucial staple in large parts of the world. Rice is routinely consumed in nearly 39 countries, mainly of South and Southeast Asia (Juliano 1993). In Asia, rice fulfills 50% of the dietary calorie needs of almost 520 million people (H. Zhou et al. 2016) and provides substantial proportions of key nutrients. The consumption of rice, in one form or another, has been continuously growing in sub-Saharan Africa, the Caribbean, and Latin America regions (Gilbert-Diamond et al. 2011; Muthayya et al. 2014).

In general, rice is a satiating food and considered a quickly available source of energy (Ravichanthiran et al. 2018). After harvesting, paddy is processed for consumption through an initial step of dehulling of paddy to get brown rice, which is constituted by bran layer (6–7%), endosperm (∼90%), and embryo (2–3%). The subsequent milling (or polishing) of brown rice produces the milled or white rice, from which a significant portion of the bran composed of aleurone layer and all of the germ are removed (Ravichanthiran et al. 2018). Bran is generally abundant in lipids, protein, fiber, vitamin B, and E and a range of phytonutrients, whereas the endosperm is mainly composed of starch. Among post-harvesting operations, the degree of milling (DOM), the extent to which bran is removed from kernels during milling, is a crucial parameter in the milling operation that influences the cooking quality, the sensory quality, and the nutritional quality of milled rice (Tong et al. 2019). The higher the DOM, the more significant are the losses in the lipids, protein, fiber, and mineral contents that, in turn, affect the quality features of the milled rice (Puri, Dhillon, and Sodhi 2014). Tong et al. (2019) comprehensively reviewed the impact of DOM on rice appearance, milling, eating, cooking, and nutritional qualities and highlighted several advantages such as it prevents rancidity and enhances shelf life, safety, texture, and palatability of rice, making rice more suitable for consumption.

Brown rice is considered to be nutritionally superior to its milled counterpart, comprehensively reviewed recently (Saleh et al. 2019; Zhao, Lin, and Chen 2020). Several potential health benefits, such as antioxidant, antidiabetic, and anticancer activity, have been attributed to brown rice and its derived fractions or extracts, which make brown rice healthier than milled rice (Saleh et al. 2019). Thus, in recent times, the consumption of brown rice is recommended to achieve nutrition sustainability (Lee et al. 2019). It has been reported that 300 g cooked milled rice (the average intake by an adult male) provides 2–5% of recommended nutrient intake (RNI) of iron (Fe), calcium, and folate, and 12–17%

CONTACT Ahmed Regina a.regina@irri.org Centre of Excellence in Rice Value Addition (CERVA), International Rice Research Institute (IRRI), South Asia Regional Centre, Varanasi 221106, Uttar Pradesh (U.P.), India
*Present address Sustainable Impact Through Rice Cased Systems Platform, International Rice Research Institute (IRRI), Los Banos, Laguna, Philippines.

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of RNI of thiamin and niacin. On the contrary, the same amount of brown rice provides 8–15% of RNI of Fe, calcium, and folate, and 66–67% of RNI of thiamin and niacin (Kennedy, Burlingame, and Nguyen 2003). Moreover, the glycemic index (GI) of brown rice is lower than its well-milled counterpart, mainly due to its high dietary fiber content (Brotman et al. 2021; Trinidad et al. 2013).

Despite nutritional superiority, brown rice has inferior sensory properties and has shorter shelf-life due to rancidity at an ambient temperature that confines its regular use only within a small proportion of health-conscious people and within some cultures (Kaur, Ranawana, and Henry 2016; Saleh et al. 2019). Conversely, consumers' preference toward milled rice is considerably high due to its excellent cooking and sensory properties. Due to the growing consumption of milled rice, preservation and enhancing the nutritional value of milled rice is essential to address the need for nutritional security to millions of rice consumers. Several food-technology based fortification, and agronomy- and genetics-based biofortification strategies have been used to fortify milled rice with essential micronutrients (Fe, Zn, vitamin A) and functional ingredients to furnish some envisaged health benefits to milled rice, especially in the management of metabolic disorders such as diabetes and obesity (Kawakami and Bhullar 2018; Ludwig and Slamet-Loedin 2019).

This article is aimed to provide a comprehensive review on the nutrient components and functional ingredients of milled rice, to outline strategies to overcome the nutritional limitations of milled rice, and to identify optimum holistic strategies to enhance the density of nutrients in the milled rice staple while enhancing consumer acceptability (Figure 1). It underlines the importance of healthier milled rice in addressing the currently prevailing health burdens of undernutrition, obesity, and type-2 diabetes around the world. Moreover, the impact of milling on grain safety, a growing health concern, is also discussed.

Composition of milled rice

Milled rice is mainly composed of starch (~80%), protein (~7%), and with a trace amount of fat (0.66%), dietary fiber (0.2–0.5%), and minerals (0.3–0.8%) (Alhambra, Dhital, et al. 2019; Verma and Srivastav 2017). However, there is significant genetic variability in grain nutrient contents existing amongst different rice cultivars (Bhullar and Gruissem 2013), which could favorably be exploited for improving the nutritive value of milled rice.

Starch

Starch is the major component of the rice grain that defines its GI. It exists as discrete granules consisting of predominantly linear polymers of amylose and branched-chain polymers of amylopectin. The rice starch granules are of different shapes (polyhedral, irregular) with a size of 2–7 μm (Wani et al. 2012). Unlike other major cereal grains such as wheat, rice starch granules exist in compound form, formed by aggregates of smaller granules. The structure and composition of starch play a significant role in determining the cooking quality of rice. The amylose content of rice starch influences its pasting, gelatinization, retrogradation, and texture (Wani et al. 2012). Moreover, amylose is considered the most crucial predictor of sensory quality in rice (Fitzgerald, McCouch, and Hall 2009). In rice, starch granules are smaller than other cereal starches, and the amylose content varies from 0 to >25% (Toutounji et al. 2019; Wani et al. 2012). Based on the percentage of amylose content, rice is classified broadly as waxy (0–2%) and non-waxy (3–>25%) rice (Patindol, Siebenmorgen, and Wang 2015). Waxy rice starches have high swelling and solubility parameters, and larger relative crystallinity values than non-waxy starches (Wani et al. 2012). The non-waxy types can be further classified as very low amylose (3–10%), low amylose (11–20%), intermediate amylose (21–24%), and high amylose >25% (Alhambra, de Guzman, et al. 2019).

Tweaking starch quality for high amylose, resistant starch, and lower glycemic response

Besides amylose content, factors such as the lamellar/crystalline structure, the content of long glucan chains, and short-medium amylose chains determine rice starch digestibility (Alhambra, de Guzman, et al. 2019; Gong et al. 2019; Li et al. 2021). It has been found that an elevated amount of long glucan and short-medium amylose chains help to reduce rice starch digestibility (Alhambra, de Guzman, et al. 2019; Gong et al. 2019; Li et al. 2021). Moreover, rice starches with shorter amylopectin chains (degree of polymerization 10–26) showed more perfectly aligned crystalline lamellae and had much slower digestion rates than the other starches (Li et al. 2021). Non-starchy components, such as fiber, protein, amino acid, lipid, and polyphenols, also influence rice starch digestibility either by affecting starch properties or inhibiting digestive enzymes (Khatun, Waters, and Liu 2019; Lu et al. 2021; Ye et al. 2018).

Starch contains a significant portion of digestible starch, and a small amount of indigestible part called resistant starch (RS), mainly contributed from the amylose component of the starch. The digestible portion of starch is further classified into rapidly digestible starch (RDS) and slowly digestible starch (SDS) (Kasote, Nilegaonkar, and Agte 2014). RS escapes digestion in the small intestine, consequently lowers postprandial glucose and insulin responses (Yang et al. 2006). RS also acts as a potential pre-biotic agent by stimulating the endogenous gut microbiota and producing anti-inflammatory products such as short-chain fatty acids (Bird, Brown, and Topping 2000; Walter, da Silva, and Denardin 2005).

Generally, RS is categorized into four types, with different glycemic responses; RS 1- the inaccessible starch to digestive enzymes, RS 2- raw starchy food, RS 3- retrograded starch, and RS 4- modified starch (Haub et al. 2010). RS 5 is another distinct form of RS, wherein the amylose component forms complexes with lipids (amylose–lipid complex) that makes it more thermally and enzymatically stable. Starch-lipid complexes and short glucan chains with degrees of polymerization of 8–12 strongly influence starch digestion

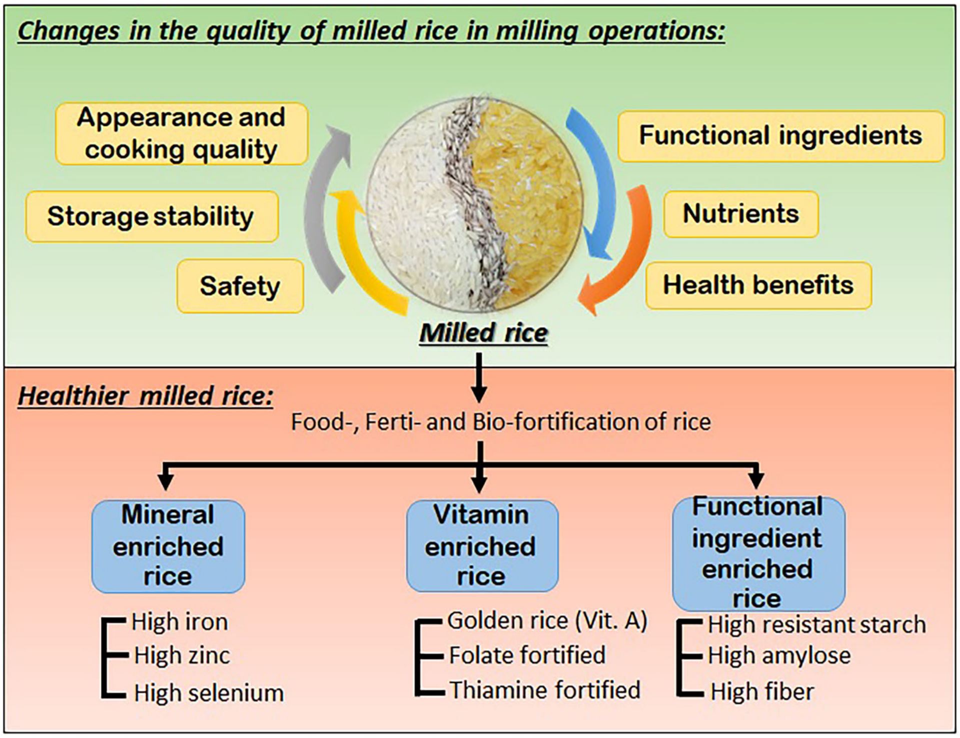

Figure 1. The schematic representation of the journey of milled rice toward healthier rice.

in rice (Shu et al. 2009). RS 5 requires several hours to digest or not at all digested and thus acts as a source of dietary fiber (Ordonio and Matsuoka 2016). The amylose content of starch has a significant impact on its RS content. Amylose is more resistant to enzyme digestion due to its compact linear structure and the presence of more intra-molecular hydrogen bonds (Chang et al. 2014; Sajilata, Singhal, and Kulkarni 2006). In general, the content of RS is increased with increasing amylose (Hu et al. 2004). Thus, waxy rice has a very low RS content than non-waxy rice. The content of RS in cooked milled rice according to traditional domestic methods is always below 3% (Yang et al. 2006). The glycemic and insulinemic responses of rice are influenced by amylose content, amylopectin chain length and branching pattern, starch-lipid complex, and the level of RS (Shu et al. 2009). However, the glycemic index of milled rice is found to be highly variable, mainly depending on the genotype, post-harvest processing, and cooking methods (Boers, ten Hoorn, and Mela 2015; Hu et al. 2012). Post-harvest processing such as parboiling and 'at-home' preparation can also significantly influence the starch digestibility of rice (Boers, ten Hoorn, and Mela 2015). The <3% RS typically contained in cooked rice is quite lower than the recommended daily intake of RS (18–20 g) for health benefits.

In general, the RS content in milled rice grain varies between 0.4% to 3% in the existing germplasm. However, the reduced expression of a starch biosynthetic gene, starch synthase IIa (SSIIa), together with enhanced activity of a second starch biosynthetic gene, the granule bound starch synthase (GBSS) are known to contribute to a moderate increase in RS content (Parween et al. 2020). Using conventional breeding, induced mutations, RNA mediated gene silencing as well as advanced CRISPR/Cas9 based gene-editing technology to target mutations in genes encoding starch branching enzyme (SBE) isoforms, BEI, BEIIa, and BEIIb, various high amylose rice mutants and varieties have been developed such as Goami No. 2, Gongmi No. 3, RS111, and Jiangtangdao 1 (Butardo et al. 2012; Butardo et al. 2011; Gurunathan et al. 2019; Satoko et al. 2021; Zhou et al. 2016). Rice, with RS content of 16%, is found to reduce plasma cholesterol and lipid contents in diabetic rats (Kim et al. 2003). Supplementation with high-amylose rice containing 65% amylose content developed through simultaneous transgenic downregulation of two starch biosynthetic enzymes, BEI and BEIIb, is reported to have a positive effect on lowering the blood glucose response in diabetic Zucker fatty rats (Zhu et al. 2012).

In human intervention studies, the intake of high amylose rice with RS appears to attenuate postprandial blood glucose and insulin response in comparison to the low amylose control rice studied (Zenel and Stewart 2015). Similarly, Mohan et al. (2019) found that high-RS high-fiber rice reduces overall dietary GI and glycemic load. The polished rice of this variety had a five-fold higher dietary fiber and over six-fold higher RS content than conventional milled rice. This rice reduced the GI by 23% compared with traditional milled rice in healthy volunteers (Mohan et al. 2016). Although many of the high amylose/RS rice varieties are generally low-yielding in nature, recently, through higher upper secondary rachis branching, the yield and grain quality traits have been improved in the low GI lines (Pasion et al. 2021).

Proteins

Understanding the protein composition of the milled rice grain is crucial to know its overall influence on human health and to develop premium quality rice for the future, as the protein composition of rice is linked with the rice grain quality and head rice yield (Balindong, Ward, Liu, et al. 2018; Balindong, Ward, Rose, et al. 2018). In rice grain, most of the proteins are concentrated in the bran layer (11–15%). Although milled rice contains relatively low protein (6–8%), it is nutritionally superior to other cereals, mainly in the context of its hypoallergenic properties and balanced amino acid contents (Amagliani et al. 2017a). Unlike wheat and some other cereals, rice protein is free from gluten that underlines its utility in gluten-free diets for people with celiac disease and gluten-sensitivity (Chen et al. 2010; Kasote, Nilegaonkar, and Agte 2014). Rice protein composition mainly includes globulin, glutelin, prolamin, and albumin proteins (Chen et al. 2008). Globulin (about 12%) and glutelin (about 80%) are the main components of rice protein, while albumin (about 5%) and prolamin (about 3%) are minor ones (Ju, Hettiarachchy, and Rath 2001; Juliano 1993). Proteins in rice are stored in the form of protein bodies (PB I and PB II). PB-I (mainly prolamin) is indigestible and negatively affects rice protein quality (Kim et al. 2013; Wani et al. 2012). Rice proteins considerably influence the textural, pasting, and sensory properties of milled rice; however, the exact role of proteins in the physicochemical properties of rice is not yet understood (Sotelo et al. 1994; Zhao, Baxter, and Blanchard 2006). Total protein content and protein composition are found to differ between medium and long grain cultivars (Balindong, Ward, Liu, et al. 2018). The high protein quality of rice is due to its high glutelin-to-prolamin ratio (Sotelo et al. 1994). The comparatively higher lysine content in rice protein provides higher digestibility and nutritional quality (Santos et al. 2013; Shih 2003). Hence, an increase in lysine content in rice protein is one of the targets for nutritional quality improvement of rice. Selective attempts have been made to elevate free lysine content up to 30 fold in rice endosperm through a transgenic approach (Yang et al. 2017). Also, several QTLs, such as *qGPC1-1, qAAC6.1*, and *qAAC7.1* have been identified for increased protein and improved amino acid composition in rice (Jang et al. 2020). Animal study of, rice protein isolated from milled rice has shown to enhance hypercholesterolemia condition, induced by high cholesterol diet, through enhanced fecal excretion of cholesterol (Um et al. 2013).

Generally, intact rice protein has limited applications due to its poor solubility. However, hydrolyzed rice protein has been increasingly used to formulate hypo-allergenic infant formulations due to its high functionality (Amagliani et al. 2017a). Moreover, hydrolyzed rice protein has been preferentially used as a substitute for animal-based protein not just due to its hypo-allergenic properties (relative to wheat and corn) but also due to its improved functionality enabled through evolving technologies. (Amagliani et al. 2017b). An 8-week trial of whey vs. rice protein involving randomly allocated athletes showed no significant differences in psychometric scores of perceived recovery, soreness, or readiness to train, nor in main outcome indices of body composition and exercise performance (Joy et al. 2013). In a randomized, blinded study, infants having cow's milk protein allergy, when fed with hydrolyzed rice protein formula, showed improvements in the following (1) a reduction of cutaneous manifestations (urticarial, angioedema) from 34% to 4%, and (2) the complete resolution of gastrointestinal symptoms (regurgitations, abdominal pain, diarrhea) while maintaining normal growth during a 3-month follow-up (Solar et al. 2016; Vandenplas, De Greef, and Hauser 2014).

Dietary fibers

Dietary fibers are the portions of plant foods that cannot wholly be digested by human digestive enzymes. They are generally classified as soluble and insoluble fibers based on their solubility in water. Oligosaccharides such as inulin and resistant starches have also been now included under dietary fibers (Anderson et al. 2009). Soluble dietary fibers are fermented by the gut bacteria and produce gases and bioactive metabolites such as short-chain fatty acids. On the contrary, most insoluble fibers have a fecal bulking effect and are slowly fermented in the colon (Makki et al. 2018). In general, milled rice has a lower amount of dietary fiber than its unmilled counterpart. However, the loss of dietary fiber content of milled rice can be minimized by reducing milling and polishing degrees (Ma et al. 2020). Tapping the diversity of genebank lines, enough phenotypic variations were found for enriched pectin, arabinogalactan, and xylan as insoluble dietary fiber in milled rice (Kosik et al. 2020). Milled rice has both soluble and insoluble fibers, including RS, the levels of which vary with genotype, milling operations, and cooking methods (Chiu and Stewart 2013; Longvah and Prasad 2020; Storck, da Silva, and Fagundes 2005). The dietary fiber content of rice has a considerable impact on its GI (Juliano 2016). Dietary fiber and RS enhancements up to 9% can be achieved through mutations in the starch branching enzyme genes involved in the starch biosynthetic pathway (de Guzman et al. 2017). Recently, combined downregulation of specific isoforms of starch synthase and starch branching enzyme utilizing a TILLING approach resulted in enhancing these dietary fiber components to the extent of lowering the hydrolysis index to values as low as 35-40 (Raja 2019).

Lipids

Rice contains starch and non-starch associated lipids. Starch lipids primarily accumulate in the embryo, and non-starch lipids are distributed throughout the grain but concentrated in the aleurone layer of bran (Yanjie et al. 2018). Starch lipids are further divided into free and bound lipids. The free lipids are adsorbed to the surface of starch granules, and bound lipids are complexed with amylose inside the starch granules (Zhou et al. 2003). In milled rice, nearly 0.5–1% of lipids are associated with starch granules (Yang et al. 2008). Lipids from six lipid categories, such as fatty acyls, glycerolipids, glycerophospholipids, sterol lipids, prenol lipids, and sphingolipids, were found in the milled rice (Concepcion et al. 2020). In addition, certain unsaponifiables such as oryzanols, tocopherols, tocotrienols, and squalene are also reported in rice (Ha et al. 2006; Yoshida et al. 2011). Similar to brown rice, oleic acid, linoleic acid, and palmitic acid are the predominant fatty acids in milled rice (Monks et al. 2013). Both brown and milled rice have a much healthier fatty acid profile with the content of unsaturated (oleic acid, linoleic acid) fatty acid roughly three times higher than saturated fatty acids (Deepa, Singh, and Naidu 2008; Monks et al. 2013; Yoshida et al. 2011). Health benefits such as lowering the level of cholesterol and harmful low-density lipoprotein (LDL) and enhancing the level of high-density lipoprotein (HDL) have been attributed to the rice bran fatty acids (Chou et al. 2009; Nicolosi, Ausman, and Hegsted 1991). During milling, free fatty acids are formed on the rice surface. Oxidation of some of these unsaturated fatty acids leads to the formation of off-flavors caused by volatile products such as aliphatic aldehydes, for example, hexanal, although most of these off-flavor compounds are removed during milling operations (Jinakot and Jirapakkul 2019; Wang and Ha 2013).

Phospholipids (PLs)

It is the dominant class of lipids in milled rice endosperm shown to form complexation with amylose, comprising up to 10% of total rice grain lipid content (Liu et al. 2013). The starches of non-waxy rice varieties found to have a much higher content of lipids ($625–1303\,\mathrm{mg.100\,g^{-1}}$) than that of the waxy rice ($16–60\,\mathrm{mg.100\,g^{-1}}$) varieties (Morrison and Azudin 1987), possibly due to the binding of phospholipids to amylose than amylopectin. PL mainly consists of covalently bound phosphate and lipid, primarily present in the endosperm. Natural PLs can be classified into two major categories, glycerophospholipids and sphingophospholipids (Liu et al. 2013). PLs have a beneficial role in preventing hepatic steatosis and cardiovascular diseases (Cohn et al. 2008). The phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol, and their lyso forms are the main PLs in rice (Liu et al. 2013; Yoshida et al. 2011). Specifically, lysophospholipids are the major (50%) starch lipids in the rice endosperm, which complexes with amylose, affecting the physicochemical properties and digestibility of starch, and thereby the cooking and eating qualities of rice (Choudhury and Juliano 1980; Liu et al. 2013). More recently, enhanced redistribution of lysophospholipids in the endosperm due to a low phytic acid gene mutation is suggested to have practical applications in breeding for healthier rice (Tong et al. 2019).

Lipid nutraceuticals and vitamins

Several lipid nutraceuticals such as tocopherol and tocotrienol isomers, γ-oryzanols, squalene, octacosanol, and phytosterols (campesterol, stigmasterol, sitosterol, cycloartenol, and 24-methylcycloartanol) have been reported in milled rice, (Figure 2). The content of some of these nutraceuticals is found to vary with DOM (Ha et al. 2006). The tocopherol and tocotrienol isomers constitute Vitamin E, which is essential for normal neurological function, mainly due to its lipid peroxidation inhibitory potential. The natural vitamin E includes eight chemically distinct molecules: α-, β-, γ-, and δ- tocopherol; and α-, β-, γ-, and δ- tocotrienol (Sen, Khanna, and Roy 2004). Amongst these, tocotrienols (specifically, γ- tocotrienol and δ- tocotrienol) have received considerable attention recently due to their health benefits in chronic diseases, based on their antioxidant, neuroprotective, cholesterol-lowering, anti-inflammatory, and anticancer properties (Montagnani Marelli et al. 2019). In milled rice, α-tocopherol is the major tocopherol, and γ-tocotrienol and α-tocotrienol are the major tocotrienols (Ha et al. 2006). Roughly, rice contains more tocotrienols than tocopherols (Ha et al. 2006; Shammugasamy et al. 2015). Black-pigmented rice has significantly higher levels of α-tocopherol, β-tocopherol, and α-tocotrienol than non-pigmented brown rice and red-pigmented rice. In contrast, red-pigmented rice has considerably lower levels of γ-tocotrienol and total vitamin E than non-pigmented rice (Shammugasamy et al. 2015). The γ-oryzanols are another set of major natural antioxidants found in rice, especially in its bran layer. Chemically, γ-oryzanols are a mixture of ferulic acid esters of sterol and triterpene alcohols (Scavariello and Arellano 1998). Several health beneficial properties such as antioxidant, anti-inflammatory, hypocholesterolemic, antidiabetic, and anti-cancer activities have been reported for γ-oryzanols (Sohail et al. 2017). Milling operations appear to reduce nearly 94% of γ-oryzanol of the brown rice (Tuncel and Yı lmaz 2011). Four different types of γ-oryzanols such as 24-methylenecycloartanol ferulate, campesterol ferulate, cycloartenol ferulate and β-sitosterol ferulate have been reported in milled rice (Pereira-Caro et al. 2013).

Milled rice has the least amounts of vitamin B complex and E isomers, compared to its unmilled counterpart. The rice genotype and DOM determine the levels of vitamins in milled rice (Ha et al. 2006; Shammugasamy et al. 2015). In rice, the vitamin B complex includes thiamin (B1), riboflavin (B2) and niacin (B3) pantothenic acid (B5), pyridoxine (B6), and folic acid (B9) (USDA 2019).

Minerals

In rice grain, the distribution of minerals is mainly regulated by distributing their ligands and transporters (Ram et al. 2020). In milled rice, over 16 different elements (Calcium (Ca), Cadmium (Cd), Cobalt (Co), Copper (Cu), Iron (Fe), Potassium (K), Phosphorus (P), Nickel (Ni), Magnesium (Mg), Molybdenum (Mo), Manganese (Mn), Sodium (Na), Sulfur (S), Lead (Pb), Zinc (Zn), and Selenium (Se)) have been reported in trace amounts (Liu, Zheng, and Chen 2017; Reddy et al. 2017). The true retention (TR) of Zn and Fe in milled rice was 63.8–89.6% and 21.1–44.5%, respectively (Taleon et al. 2020). Milled rice was reported to contribute significantly to the recommended dietary allowances (RDA) of Mn (14%) (da Silva, Paim, and da Silva 2018). Parboiled rice has higher mineral content than non-parboiled milled rice, as solubilization and migration of minerals toward rice endosperm may occur during parboiling (da Silva, Paim, and da Silva 2018). During the process of

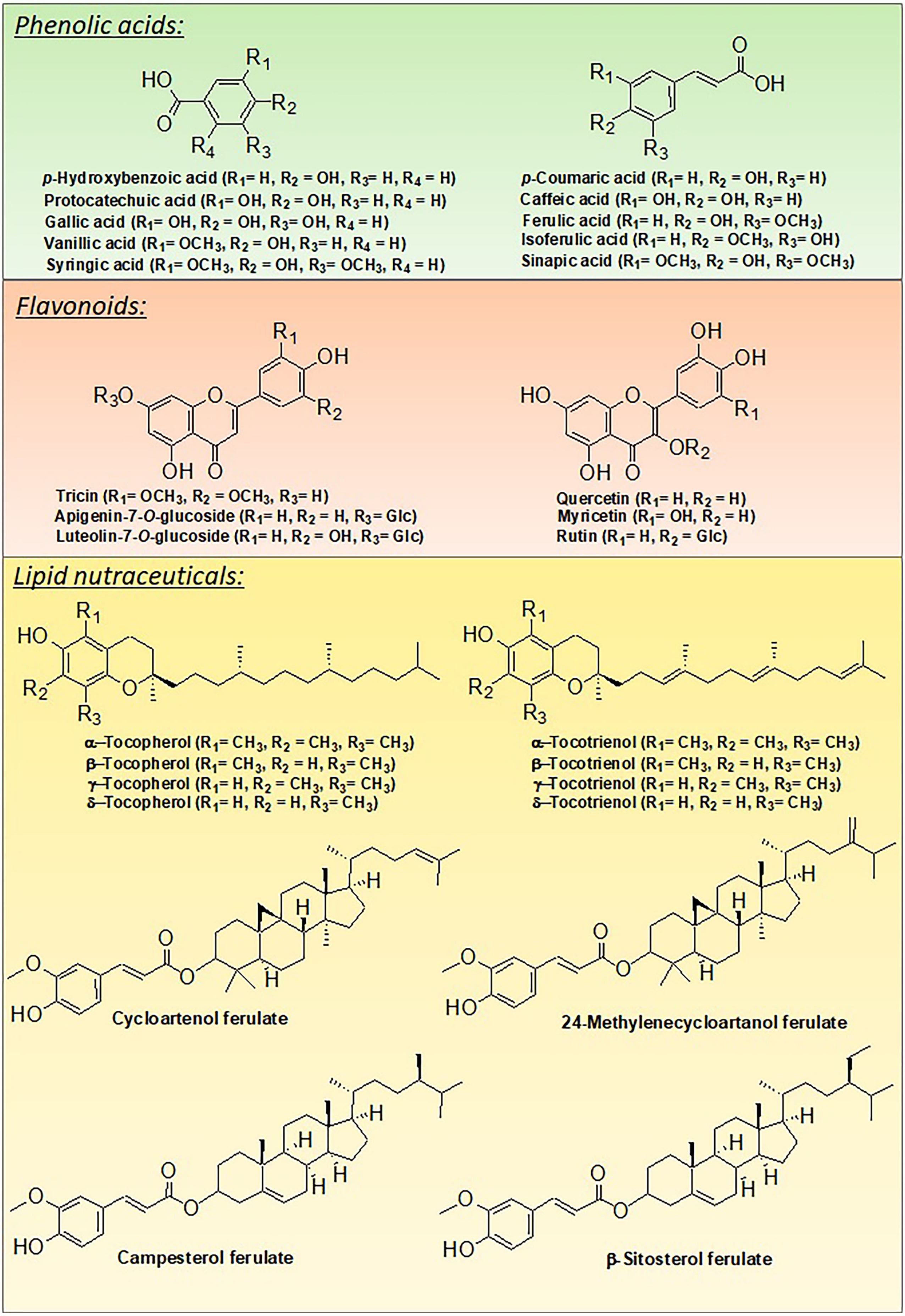

Figure 2. Structure of some phenolic acids, flavonoids, and lipid nutraceuticals reported in milled rice.

Table 1. Phenolics, flavonoids, γ-oryzanols, and carotenoids reported in milled rice.

Sr. No.	Class of compounds	Name of compound	References
1.	**Phenolic acids**	Caffeic acid	(Ti et al. 2014; Zhang et al. 2018)
		Ferulic acid	(Ti et al. 2014; Zhang et al. 2018)
		Gallic acid	(Ti et al. 2014; Zhang et al. 2018)
		Isoferulic acid	(Shao et al. 2014)
		p-Coumaric acid	(Ti et al. 2014; Zhang et al. 2018)
		p-Hydroxybenzoic acid	(Vichapong et al. 2010)
		Protocatechuic acid	(Setyaningsih et al. 2015; Ti et al. 2014)
		Sinapic acid	(Finocchiaro et al. 2007)
		Syringic acid	(Shao et al. 2014; Zhang et al. 2018)
		Vanillic acid	(L. Liu et al. 2015)
2.	**Flavonoids**	Apigenin 7-*O*-glucoside	(Goufo et al. 2014)
		Apigenin 6/8-C-pentoside-8/6-C-hexoside	(Pereira-Caro et al. 2013)
		Catechin	(Liu et al. 2015)
		Luteolin 7-O-glucoside	(Goufo et al. 2014)
		Luteolin 6/8-C-pentoside-8/6-C-hexoside	(Pereira-Caro et al. 2013)
		Myricetin	(Prathepha, Siriamornpun, and Sakdakham 2017)
		Quercetin	(Liu et al. 2015)
		Rutin	(Prathepha, Siriamornpun, and Sakdakham 2017)
		Tricin	(Goufo et al. 2014)
3.	**Other phenolic compounds**	Chlorogenic acid	(Ti et al. 2014)
		3,5-Xylenol	(Vichapong et al. 2010)
		o-Cresol	(Vichapong et al. 2010)
		Diferulic acid	(Zaupa et al. 2015)
		Triferulic acid	(Zaupa et al. 2015)
		Sinapic acid *O*-dihexoside	(Zaupa et al. 2015)
		Ferulic acid *O*-dihexoside	(Zaupa et al. 2015)
4.	**γ-Oryzanols**	24-Methylenecycloartanol ferulate	(Pereira-Caro et al. 2013)
		Campesterol ferulate	(Pereira-Caro et al. 2013)
		Cycloartenol ferulate	(Pereira-Caro et al. 2013)
		β-Sitosterol ferulate	(Pereira-Caro et al. 2013)
5.	**Carotenoids**	Lutein	(Pereira-Caro et al. 2013)
		Zeaxanthin	(Pereira-Caro et al. 2013)

parboiling, 18% mineral enrichment can be achieved, especially of K and P. However, some of the essential minerals such as Mn, Ca, and Zn are significantly lost during parboiling of milled rice (Heinemann et al. 2005). The mobilization of Zn from the inner endosperm toward the outer layers has been reported during parboiling (Taleon et al. 2020). In milled parboiled rice, the observed TR of Zn and Fe was 49.8–72.2% and 23.4–36.7%, respectively (Taleon et al. 2020). Parboiled rice also contributes to 45% to RDA of Cu (da Silva, Paim, and da Silva 2018).

Polyphenols

In rice, polyphenols (phenolic acids and flavonoids) are distributed as free, soluble-conjugated, and bound forms in the endosperm and bran/embryo (Ti et al. 2014). The amounts of free and bound phenolics in rice vary depending on the genotype. Pigmented rice generally has higher polyphenols than non-pigmented rice (Huang and Ng 2012). In cereals, including rice, most of the polyphenols are in insoluble forms and bound to cell walls (Finocchiaro et al. 2007). The distribution of bound and free phenolic acids in rice grain is not clearly understood. The bound phenolic acids are mainly present in bran, while free phenolic acids are highly concentrated in the endosperm (Kong and Lee 2010; Liu et al. 2015). The percentage of bound polyphenols in milled rice decreases with an increase in the DOM (Liu et al. 2015). In general, milled rice is characterized by the presence of specific phenolic acids, flavonoids, and γ-oryzanols (Pereira-Caro et al. 2013), as shown in Figure 2 and tabulated in Table 1. However, certain milled rice is also reported to contain carotenoids and phenolic compounds other than phenolic acids (Table 1). Rice polyphenols are mainly responsible for the observed antioxidant activity of milled rice. Other molecules with antioxidant activity in milled rice include tocopherols, tocotrienols, γ-oryzanol, and phytic acid (Goufo and Trindade 2014). Milled rice is found to have lower free radical and total antioxidant capacities compared to whole grain rice. The empirical contribution of rice endosperm in their whole-grain antioxidant capacity of white, red, and black rice is only 1%, 3%, and 3% in radical scavenging activity measurement assay, and 18%, 4%, and 4% in total antioxidant assessment assay, respectively (Shao et al. 2014). Moreover, cooking causes a further loss of antioxidants (Finocchiaro et al. 2007).

Phenolic acids

Rice endosperm contains soluble free, soluble conjugated, and insoluble bound phenolic acids. The concentration of phenolic acids decreases from the aleurone layer to endosperm in rice. The bran and embryo show higher free and bound phenolic acid content than rice endosperm (Liu et al. 2015). The hydroxycinnamic and hydroxybenzoic acids are the most common forms of phenolic acids occurring in rice (Setyaningsih et al. 2015). Among the cereal grains, rice contains higher levels of certain hydroxycinnamic acids, such as ferulic, coumaric and caffeic acids, which are not present in significant amounts in fruits and vegetables (Bunzel et al. 2001; Setyaningsih et al. 2015; Ti et al. 2014). In *Indica* and *Japonica* brown rice, protocatechuic acid, caffeic acid, and chlorogenic acid only exist in their free form, and on the

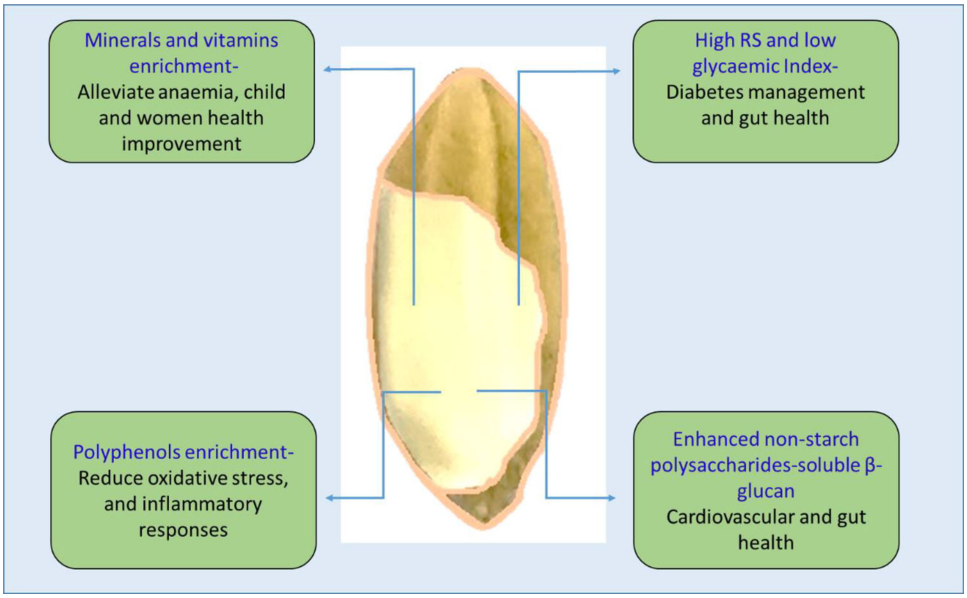

Figure 3. Potential health benefits from biofortified healthier milled rice.

contrary to this, vanillic acid, ferulic acid, and isoferulic acid predominantly present in their bound form (Liu et al. 2015; Zhang et al. 2018). Among these phenolic acids, ferulic acid, the most abundant phenolic acid in rice, is found to be beneficial in the treatment of type 2 diabetes through its capacity to regulate blood glucose levels, as shown in mice, by elevating glucokinase activity and production of glycogen in the liver (Jung et al. 2007).

Flavonoids

Similar to phenolic acids, rice also contains free, soluble-conjugated, and bound forms of flavonoids (Liu et al. 2015). The total flavonoid content of milled rice is lower than that of the total phenolic acid amount, as they are mainly accumulated in the bran layer (Kong and Lee 2010; Liu et al. 2015). The bound form of quercetin and free and bound form of (+)-catechin have been reported in *Indica* and *Japonica* rice (Liu et al. 2015).

Nutrient density enhancement in milled rice: fortification and biofortification strategies

Fortification

Milled rice being a highly consumed processed cereal grain, its fortification is typically advised due to its low levels of micronutrients and vitamins (de Pee 2014). Fortification is the practice of deliberately increasing the content of essential micronutrients in food to improve the nutritional quality of the food supply and provide a public health benefit with minimal risks to health (WHO 2019a). Thus far, milled rice has been fortified with minerals (Fe, Zn, Ca, Se, and I) and vitamins such as thiamin and folic acid (Saha and Roy 2020; Tiozon et al. 2021). In general, rice fortification involves (1) whole grain fortification, in which the nutrients are applied externally or mixed with rice kernels; (2) powder type fortification, where nutrients added in rice flour followed by extrusion (Kyritsi, Tzia, and Karathanos 2011); and (3) parboiling based nutrient enrichment.

In whole-grain fortification, rice kernels are fortified using coating or extrusion technologies, following which these fortified kernels are blended at a 0.5–2% percent ratio with nonfortified rice (de Pee et al. 2018). Four different technologies, such as hot extrusion, cold extrusion, coating, and dusting, are used for rice fortification (Piccoli et al. 2012). The coating and dusting are somewhat old techniques but still in practice for the enrichment and fortification of rice (Atungulu and Pan 2014). The more advanced hot- and cold-extrusion techniques are gaining prominence for the fortification of rice (Hackl, Speich, et al. 2017). These methods provide a range of desired properties to the final product, for instance, wash stability, shelf stability, cooking behavior, visual appearance, and favorable cooked rice texture (Steiger et al. 2014). The cost of fortifying rice is only 1.5–3% of the current retail price of rice (Muthayya et al. 2012). Pinkaew et al. used hot extrusion technology to fortify rice grain with zinc, iron, and vitamins (Pinkaew et al. 2013). They also demonstrated the efficiency of Zn fortification of extruded rice grains and its potential to improve Zn status in school children. Rice has also been fortified with thiamin (Vitamin B1) and folic acid (Vitamin B9), and different cooking methods are reported to have distinct effects on the stability of fortified thiamin and folic acid in rice (Della Lucia et al. 2013; Silveira et al. 2017). Folic acid is found to be more stable than thiamin in cooking operations (Silveira et al. 2017). The addition of ferric-EDTA and zinc sulfate to soaking water during parboiling also increases the zinc and Fe contents of milled rice (Hotz et al. 2015; Prom-U-Thai et al. 2011). Interestingly, it has been found that zinc sulfate can be a preferable zinc co-fortificant for optimal iron bioavailability of iron-fortified extruded rice (Hackl, Zimmermann, et al. 2017). Rice fortified with micronized ferric pyrophosphate (developed by Ultra Rice® Technology) showed high iron bioavailability, whereas the addition of yacon flour at 7.5% fructooligosaccharides was found to reduce iron bioavailability (Della Lucia et al. 2013). Rice fortified with microencapsulated iron pyrophosphate is found to be beneficial in improving the iron status of women in Mexico (Hotz et al. 2008). The following levels (in mg.100 g^{-1}) are recommended to meet daily dietary requirements of micronutrients and vitamins for rice consumers, when a quantity of 150–300 g.cap^{-1}.day^{-1} of rice is consumed: iron, 7; folic acid, 0.13; vitamin B12, 0.001; vitamin A, 0.15; zinc, 6; thiamin, 0.5; niacin, 7; and vitamin B6, 0.6. These concentrations can be achieved at a 1:100 blending ratio of fortified: unfortified kernels (de Pee 2014). Despite several success stories about the fortification of milled rice, the impact of fortification of milled rice on sensory quality, appearance, and consumer acceptability needs to be thoroughly investigated (Saha and Roy 2020).

Parboiling is a hydrothermal pre-milling treatment to gelatinize starch components of rice in a three-stage process, namely soaking, steaming, and drying (Kwofie and Ngadi 2017). In this process, paddy is submerged in water at a temperature above 58 °C, followed by autoclaving for total or partial starch gelatinization, and finally dried (Giniani Carla Dors, de Almeida Pinto, and Badiale-Furlong 2009; Pascual et al. 2013). This process leads to physical, chemical, and organoleptic changes in the rice grain that affect milling, storage, cooking, and eating qualities (Kwofie and Ngadi 2017). Parboiling also affects the color of milled rice. The nonenzymic browning and pigments from the husk and bran are responsible for the amber color of parboiled rice (Lamberts et al. 2006). Usually, parboiling is a value addition technique used for nutritional and organoleptic improvements in rice grain (Arendt and Zannini 2013). Parboiled white rice is 80% nutritionally similar to brown rice (Atungulu and Pan 2014). Moreover, parboiling improves the milling quality and shelf-life of milled rice (Rosentrater and Evers 2017). The parboiling technique is used for the fortification of micronutrients and vitamins in milled rice and its products (Hotz et al. 2015; Kam, Arcot, and Ward 2012). It has been found that the bioaccessible form of Zn in the unmilled Zinc fortified parboiled rice (*komal chawal*) ranged between 4.24 and 11.07 mg.100 g^{-1}, which was significantly higher than the milled and unfortified parboiled rice (Wahengbam et al. 2019). Fortification of rice with calcium and iron by limited-water soaking parboiling was found to retain approximately 66% of calcium and 71% of the iron in the rice (Jannasch and Wang 2020). Similarly, the limited-water soaking parboiling method improved the fortification of folic acid and water-soluble forms of β-carotene or vitamin A in milled rice (Jannasch et al. 2020). However, rice parboiling also has certain disadvantages, such as it destroys natural antioxidants, promotes rancidity, and migrates mycotoxins into starchy rice endosperm (Arendt and Zannini 2013; Dors, de Almeida Pinto, and Badiale-Furlong 2009).

Biofortification of milled rice

The biofortification of food is different from fortification. It is the process by which the nutritional quality of food crops is improved through agronomic practices, conventional plant breeding, or modern biotechnology (WHO 2019a). Several agronomy- and genetics-based biofortification strategies have been used to fortify milled rice with essential micronutrients (Fe, Zn, vitamin A) and functional ingredients to obtain some envisaged health benefits, as shown in Figure 3. The agronomic biofortification mainly includes soil and foliar fertilizer applications (Ludwig and Slamet-Loedin 2019). In contrast, genetic biofortification consists of conventional breeding and genetic engineering approaches (Kawakami and Bhullar 2018).

High iron rice

Fe is an essential component of hemoglobin and myoglobin, and its deficiency leads to anemia. Nearly 20–25 mg of Fe is needed daily for the production of red blood cells and cellular metabolism (Lopez et al. 2016). Fe content of milled rice is around 2 $\mu g.g^{-1}$ (Trijatmiko et al. 2016). The recommended concentration of Fe for its fortification in rice is 15 $\mu g.g^{-1}$ dry weight of milled rice (Bouis et al. 2011). Thus far, agronomic, conventional breeding, and transgenic approaches have been used for Fe biofortification in rice. The biofortification of Fe in rice is challenging, mainly due to the presence of intrinsic high phytate content that affects its bioavailability (Steiger et al. 2014). Fertilizer (Ferti)-fortification or foliar fertilization approaches are not found to be very useful in Fe biofortification in rice, because of absorption issue of Fe fertilizers (Jin et al. 2008; Sperotto et al. 2012). The variety IR68144 is a Fe fortified rice developed using a conventional breeding approach (Majumder, Datta, and Datta 2019). However, the lack of sufficient genetic variability available in rice germplasm is often a challenge for Fe fortification through conventional breeding (Kawakami and Bhullar 2018; Sperotto et al. 2012). Classical breeding can modify the contents of Fe absorption inhibitors (Sperotto et al. 2012). Numerous QTLs, such as *qFe3:1, qFe3:2, qFe7:1, qFe9:1, qFe9:2, qFe10:1, Fe11:1, qFe3.3,* and *qFe7.3* related to the Fe content in the rice, have been identified (Pradhan et al. 2020). Various transgenic approaches are used to generate Fe-fortified cultivars that efficiently increase the uptake and translocation of Fe, including Fe storage capacity of grains (Boonyaves et al. 2017; Masuda, Aung, and Nishizawa 2013). It has been demonstrated that the introduction and expression of ferritin genes from soybean in rice under the control of endosperm-specific promoters can increase the concentration of Fe in polished grain of a popular rice variety, IR64, and in its progenies without compromising the agronomic traits and grain quality of the transgenic plants (Oliva et al. 2014). Similarly, the concomitant introduction of the ferritin gene and mugineic acid biosynthetic genes such as *HvNAS1* and *HvNAAT-A,-B* and *IDS3* from barley also sufficiently increased the Fe content in rice grain (Masuda, Aung, and Nishizawa 2013). Recently, in genetic engineered rice line, concerted expression of *AtIRT1*, *AtNAS1*, and *PvFER* gene cassettes led to the highest iron increases of up to 10.46 $\mu g.g^{-1}$ dry weightin the polished grains of Japonica (Boonyaves et al. 2017).

High zinc rice

Zn is an essential micronutrient for prenatal and postnatal development, and its deficiency contributes substantially to the morbidity and mortality in young children due to diarrhea, pneumonia, and malaria throughout the world (Yakoob et al. 2011). Most of the world's arable soils are deficient in Zn, which leads to its deficiency in plants (Hefferon 2019). Milled rice has low-level of Zn ranging from 12 to14 ppm of zinc and provides only one-fifth of the daily recommended zinc requirement of ~15 mg (though varies across sex and age) (Neeraja et al. 2018). Several ferti-fortification, conventional breeding, and genetic engineering approaches have been used for Zn biofortification in rice. Ferti-fortification of rice with Zn through foliar application showed 1.6 times more Zn in brown rice than in its husk part (Dhaliwal et al. 2010). Appropriate phosphorus fertilizer application is also found to increase Zn and Fe in rice grain (Su et al. 2018). The use of zinc-solubilizing bacteria, *Enterobacter cloacae* strain ZSB14, is also found to be beneficial in rice Zn fortification (Krithika and Balachandar 2016). However, agronomic biofortification of Zn in rice has shown inconsistent results. The combination of genetic and agronomic biofortification strategies is more successful and thus effective (Swamy et al. 2016). Unlike Fe, there is enough genetic variation for Zn in the rice germplasm, which has been used for breeding high Zn rice varieties (Swamy et al. 2016). Several Zn enriched rice varieties released in Bangladesh, such as BRRI dhan72, BRRI dhan84 and DRR Dhan 45 developed by conventional breeding, were found to have two times more bioavailability than IR64 (Sanjeeva Rao et al. 2020). For Zn and Fe biofortified rice breeding, QTLs *qZn7* and *qFe7* effectively provided phenotypic variance for grain Zn and Fe contents (Jeong et al. 2020). The Co-localized QTLs on Chr 01 and Chr 06 having genes such as *OsPOT, OsZIP4, OsFDR3,* and *OsIAA5* may also influence the grain Fe and Zn accumulation (Dixit et al. 2019). It has been found that the overexpression of nicotianamine synthase gene increased grain Zn content in rice (Kawakami and Bhullar 2020). Similarly, the high activity of influx transporter, OsZIP9 is also found to be important for the uptake of Zn (Yang et al. 2020). Transgenic biofortification of Fe through overexpression of nicotianamine synthase gene *HvNAS1*, the Fe(II)-nicotianamine transporter gene *OsYSL2* and the Fe storage protein gene *SoyferH2* resulted in 1.3 fold (from 29.5 to 39.2 μg.g^{-1}) higher accumulation of Zn along with to 3.4 fold (from 1.46 to 5.02 μg.g^{-1}) increase in Fe accumulation compared to non-transformed rice (Aung et al. 2013). Other studies also showed similar results of increased Zn accumulation with attempts to enhance Fe accumulation in rice grain (Paul et al. 2014)

Selenium-enriched rice

Se is an essential mineral element for both human and animal nutrition, but not for plants (White 2016). Nearly one billion people are estimated to be Se-deficient in the world (Carey et al. 2012). In humans, Se deficiency leads to hypothyroidism, cardiovascular disease, weak immunity, male infertility, and increased incidence of various cancers (White 2016). In rice, four species of Se, such as selenomethionine (SeMet), selenocysteine (SeCys), selenate, and selenite, have been reported (Gong et al. 2018). Organic forms of Se have more bioavailability than the inorganic Se species. Foliar fertilization approach with sodium selenate is used to prepare Se-enriched-rice, and consumption of such rice is found to increase the serum selenium levels and glutathione peroxidase activity in healthy women (Giacosa et al. 2014). Foliar application of 10 mg.L^{-1} sodium selenite exhibited most organic selenium (0.03 mg.kg^{-1}) in polished rice, and interestingly, 75–85% of the Se found in polished rice and embryo was organic (Farooq et al. 2019). In addition to this, the application of selenite in the soil during the booting stage is also found to be helpful in the accumulation of Se at higher levels in rice grain, depending on rice genotypes (Huang et al. 2018; Lidon et al. 2018). However, very few reports are available in the literature on breeding or transgenic-based biofortification of Se in rice. In rice, several QTLs such as *qSe1.1, qSe1.2, qSe3, qSe6, qSe7,* and *qSe9*, influencing Se accumulation in rice grain, have been identified (Norton et al. 2010). Feeding Se-rich rice (Z3055A/R363) to naturally aged mice showed significantly better growth performance and improved immunity and antioxidation abilities compared with the inorganic Se source (G-725 + Se) and general rice G-725 supplemented (Zeng et al. 2019). Moreover, the treatment of selenoprotein extracted from selenium-enriched rice was found to have a positive effect on liver hepatocytes and biochemical features in mice, highlighting its application as a potential diet in scavenging oxidative injury and supporting enzymatic antioxidant system (Zeng, Farooq et al. 2019).

Golden rice (pro-vitamin A enriched rice)

Golden Rice is a genetically engineered rice variety that produces carotenoids (pro-vitamin A) in the endosperm of the rice grain (Paine et al. 2005). In the initial work, golden rice-1 was developed by transforming rice using a construct containing a phytoene synthase (*Psy*) gene from daffodil, which had 1.6 μg.g^{-1} of total carotenoids (X. Ye et al. 2000). Later on, Golden Rice 2 was developed by expressing the phytoene synthase gene from maize resulting in rice lines with further elevated levels of carotenoids of up to 23-fold (37 μg.g^{-1}) compared to the Golden Rice-1 (Paine et al. 2005). The reported carotenoids in provitamin A biofortified GR2E rice mainly include, β-cryptoxanthin, *all-trans*-α-carotene, *all-trans*-β-carotene and 9′-*cis*-β-carotene (Swamy et al. 2019). The β-Carotene derived from Golden Rice is found to be converted into vitamin A in humans (G. Tang et al. 2012). It has been reported that the mean provitamin A concentrations (5.88 mg.Kg^{-1}) in milled rice of GR2E can contribute up to 89–113% and 57–99% of the estimated average requirement for vitamin A for preschool children in Bangladesh and the Philippines, respectively (Swamy et al. 2019). Recently, Marker-free carotenoid-enriched rice was generated by targeted insertion of a 5.2 kb marker-free DNA fragment at two genomic safe harbors using CRISPR-Cas genome editing (Dong et al. 2020). Golden Rice came into the limelight nearly 20 years ago, but still, it has been a flashpoint in debates over GM crops (Stokstad 2019). Following extensive biosafety assessments by IRRI and regulatory approvals from the respective countries, Golden Rice is now registered as safe in the Philippines, Australia, New Zealand, Canada, and the USA (Saha and Roy 2020). Application for regulatory approval for cultivation and consumption is pending in Bangladesh (Owens 2018).

Folate fortified rice

Milled rice is a poor source of folate (vitamin B9). Using metabolic engineering approach, folate biofortification in rice is achieved by overexpressing two *Arabidopsis thaliana* genes of the pterin and para-aminobenzoate branches of the folate biosynthetic pathway from a single locus. In this study, over 100 times of folate enhancement is achieved compared to wild type, which is almost four times the adult daily folate requirement (Storozhenko et al. 2007).

Thiamin fortified rice

Thiamin is required to synthesize thiamin pyrophosphate (TPP), an essential cofactor of enzymes of central metabolism (Minhas, Tuli, and Puri 2018). Biofortification of rice grain by engineering the thiamin biosynthetic pathway leads to a 5-fold increase in thiamin content in unpolished rice grains (Goyer 2017). However, polished seeds that retain only the starchy endosperm had similar thiamin content as that of non-engineered plants, suggesting that enriched thiamin in bran is lost upon milling.

Purple endosperm rice

Anthocyanins and proanthocyanidins are flavonoids and colored pigments mainly found in pigmented rice such as black, red, and purple (Limtrakul, Semmarath, and Mapoung 2019). The kernel of black rice is characteristically rich in anthocyanins, whereas the kernel of red rice is characterized by the presence of proanthocyanidins (Granström et al. 2016). These pigments are primarily accumulated in the bran layer of whole grain rice. DOM determines the anthocyanins and procyanidins contents in black and red rice (Paiva et al. 2014). During milling operations, most of these pigments are either completely removed or remain in trace amounts. Recently, genetic engineering approach has been used to enrich anthocyanins in rice endosperm as a value addition to milled rice, considering the significance of anthocyanins in human health. Anthocyanin fortified rice is termed as “purple endosperm rice” (called “Zijingmi” in Chinese). To develop purple endosperm rice through engineering anthocyanin biosynthesis, a construct containing eight anthocyanin-related genes (two regulatory genes from maize and six structural genes from Coleus) driven by the endosperm-specific promoters, plus a selectable marker and a gene for marker excision is generated and used for transforming rice by *Agrobacterium*-mediated transformation (Q. Zhu et al. 2017).

Low phytic acid rice

Phytic acid (myo-inositol hexaphosphate), is the most abundant storage form of phosphorus in seeds. It acts as a potent chelator of metal cations to form phytate and reduces the bioavailability of micronutrients in rice, for both human and livestock (Perera, Seneweera, and Hirotsu 2018). Hence, the reduction of phytic acid content is essential for enhancing bioavailable micronutrients in cereal grains (Kumar et al. 2017). In rice, about 80% of the total seed phosphorus (P) is found in the form of phytic acid, and the remaining is present as soluble inorganic phosphate, and the P present in nucleic acids, proteins, lipids, and sugars (Kuwano et al. 2006). Generally, high inorganic P-containing genotypes have low phytic acid content. Induced mutants exhibiting increased seed inorganic P have been identified in rice and used for conventional breeding-based fortification (Kim et al. 2008; Zhao et al. 2016). However, conventional breeding strategies using mutants cause poor agronomic characteristics, such as decreased germination and reduced seedling emergence (Kuwano et al. 2009). Conversely, transgenic technology is found to be useful in developing low-phytic acid rice without hampering plant growth or seed development (Perera, Seneweera, and Hirotsu 2018). Around 68% of phytic acid content in rice seeds has been reduced by antisense repression of the rice Ins(3)P1 synthase gene *RINO1* using the 18-kDa oleosin promoter (Kuwano et al. 2009).

Safety of milled rice

Proper nutrition requires safe food (FAO 2019). Consumption of unsafe food impacts health and nutrition through the prevention of optimal nutrient uptake leading to delays in growth and development, particularly in children, as well as through rendering susceptibility to diseases. Over 200 acute and chronic diseases are known to occur due to foodborne hazards, ranging from digestive tract infections to cancer (Kraemer et al. 2016). Toxic contaminants observed in rice, negatively impacting nutrition and health, include heavy metals such as arsenic, mycotoxins, and pesticide residues.

Arsenic (As) poisoning in humans is directly linked to malnutrition, as revealed by the studies on children between 7 and 14 years of age (Minamoto et al. 2005) and on women of childbearing age (Milton et al. 2010). As is highly toxic in its inorganic form, and its prolonged exposure can cause cancer and skin lesions (WHO 2019b). The carcinogenicity of As is related to the inorganic arsenicals exposure, namely, arsenite (AsIII) and arsenate (AsV), which are classified as Group 1. Group 2B comprises much less toxic arsenicals such as methylated organic species (monomethylarsonic acid and dimethylarsinic acid). Certain organic arsenic compounds, such as arsenobetaine and arsenocholine, are practically nontoxic to living entities (Oteiza et al. 2020;

Platanias 2009). The WHO and the European Commission have set a maximum residue limit (MRL) advisory levels of 200 μg.kg^{-1} for inorganic As, including AsIII and AsV, in polished rice (Codex Alimentarius Commission 2013; Oteiza et al. 2020). In recent years, arsenic has been detected in rice grain well above the MRL, which raised a significant health concern about the safety of rice consumption around the world. The recent study using femtosecond Laser Ablation-Inductively Coupled Plasma- Mass Spectrometry (fs LA-ICPMS) imaging shows that arsenic is highly distributed in the rice bran layer and milling of whole rice grain reduce the arsenic content of rice substantially (Choi et al. 2019). Moreover, the inorganic As content is also further found to be reduced during cooking operations. It has been found that cooking in excess water reduces inorganic As by 40% from long-grain polished rice (Gray et al. 2016). On the contrary, partial cooking methods such as parboiling are not substantially reducing the arsenic content from contaminated rice (Duxbury et al. 2003).

Among the food safety issues, the occurrence of mycotoxins (toxins produced by molds) such as aflatoxin in agro-food products has received considerable attention in recent years, because they can cause severe health threats to humans and livestock (Moretti, Logrieco, and Susca 2017; Moss 2002). Mycotoxin contaminated rice, in addition to its carcinogenic effects, can aggravate malnutrition (Maresca et al., 2008) and contributes to stunting in children (Smith, Stoltzfus, and Prendergast 2012). Good agricultural and manufacturing practices are highly advisable during harvest, storage, and distribution of rice to minimize aflatoxins contamination in the final product (Ali 2019). In general, mold growth is possible when the moisture content exceeds 13–15% (Aydin, Aksu, and Gunsen 2011). Mycotoxin contamination in rice is generally lower than in other cereals (Sun, Su, and Shan 2017). However, even the lower levels of fungal and mycotoxin contamination in rice can be of concern considering the high consumption of rice (Gonçalves et al. 2019). In rice, mycotoxins are produced by molds of genera *Aspergillus, Penicillium,* and *Fusarium* (Sun, Su, and Shan 2017). Aflatoxins, ochratoxin A, trichothecenes, and *Fusarium* toxins (fumonisins, deoxynivalenol, trichothecenes (T-2, and HT-2), and zearalenone) are the common mycotoxins present in moldy rice (Aydin, Aksu, and Gunsen 2011; Sun, Su, and Shan 2017; Tang et al. 2013). In tracing the sources of mycotoxin contamination in food, one must consider the different parts of the supply chain. One of the critical points for monitoring is storage. Fungi producing mycotoxins thrive in high humidity and high-temperature conditions, in locations with insect and rodent infestation when crops are inadequately dried and improperly stored, and where water infiltrates the storage area (Gong et al. 2002; Wild, Miller, and Groopman 2015). The tropics, where rice is consumed as a primary staple, is, therefore, a potential breeding ground for mycotoxins. Another critical point for monitoring is on-farm adverse climate conditions before harvesting may encourage fungal growth and mycotoxin production (Unnevehr and Grace 2013). Most of the mycotoxins on paddy are removed during the milling process (Takashi et al. 1984). Pressure cooking or cooking in rice cooker of milled rice further significantly reduces mycotoxins (Park and Kim 2006; Sani et al. 2014).

Pesticide exposure is associated as a risk factor for child stunting (Kartin et al. 2019). The possibility of long- term neurotoxic damage and adverse effects on malnutrition is reported in developing countries due to prenatal exposure of pesticide (Grandjean et al. 2006). Pesticide exposure and stunting are found as independent predictors of neurobehavioral deficits in Ecuadorian school children. According to WHO, over 1000 pesticides are used around the world, and each of these pesticides has different properties and toxicological effects. Thus, to protect food consumers from adverse effects of pesticides, WHO set internationally-accepted MRLs for these pesticides (WHO 2019c). Pesticide residues have been found in almost all parts of the rice grain (Giniani C Dors et al. 2011). Lipophilic pesticides are frequently found in brown rice, whereas fungicides mainly occurred in milled rice. Carbendazim, malathion, iprodione, tebuconazole, quinclorac, and tricyclazole are the pesticides that are most commonly found in milled rice (Pareja et al. 2011). It is important to note that, during hulling, milling, or parboiling, many of the pesticides are lost (Pareja et al. 2011). In household cooking processes such as rice washing, boiling, and steam cooking, the amount of the pesticide residues in the grain is further reduced by 21–100% (Shakoori et al. 2018).

Opportunities and challenges of enhancing nutrient density and safety in milled rice

Undernutrition, micronutrient deficiency, overweight, and obesity are overlapping faces of malnourishment that take our globe through a triple burden of malnutrition (Peng and Berry 2018). Statistics show approximately two million people in the world suffering from micronutrient deficiency, and more than 190 and 600 million adults facing overweight and obesity, respectively (Nair, Augustine, and Konapur 2015; WHO 2017). Tackling this heavy load on human health care necessitates concerted multidisciplinary efforts at various scales depending on country level skews on prevailing issues. Dietary supplementation and fortification have recorded successes in addressing some of the nutrient deficiencies. However, limiting drawbacks of these strategies are also reported, such as the side effects of dietary supplements, affordability, and altered taste, appearance, and shelf-life of fortified foods (Kawakami and Bhullar 2021; Lind et al. 2004; Manwaring, Bligh, and Yadav 2016; Prom-U-Thai et al. 2009).

Delivering nutritional benefits through biofortification to improve the inherent nutritional quality of staple food crops is a more sustainable approach to addressing regional malnutrition. Rice being the staple food for two-thirds of the global population, it provides a viable platform for nutritional enrichment to benefit its consumers. Developing low GI, high RS, and high fiber rice could help address metabolic disorders, such as overweight, obesity, type II diabetes, and bowel disorders (Lee and Lee 2016; Trinidad et al.

2013). Biofortification efforts to enhance various micronutrients such as minerals (Fe, Zn, I and Se) and vitamins (folic acid and pro-vit A), in milled rice grain is a feasible way of addressing malnutrition, and nutritional disorders amongst rice consumers, who constitute a larger portion of the global population residing in the low-economic zones (De Steur et al. 2014). Considering the broader impact economic viability and sustainability, a substantial investment of time and money had been made in conventional breeding and transgenic approach-based rice improvement programs. Excellent progress has been made recently in understanding the genetic basis of nutrient uptake, transport, distribution, and loading in rice grain. For example, the manipulation of some essential element transporters, especially those localized in the node for allocation of mineral elements to the grain, is found to be valuable in generating rice with a higher density of essential elements in grain, particularly with less accumulation of toxic elements (Huang et al. 2020). However, several post- biofortification challenges have been emerging, especially concerning consumer acceptability of the biofortified varieties. Changing the inherent grain composition to derive nutritional benefits may be associated with changes in the organoleptic properties that hamper consumer appeal. For example, high amylose (and potentially low GI) rice shows inferior textural properties after cooking, lower hedonic rating for sensory attributes, and poor consumer acceptability (Patindol et al. 1995; Suwannaporn, Pitiphunpong, and Champangern 2007). Moreover, the bioavailability of the value-added nutrients in the rice grain is key to determining its efficacy in improving health and nutrition. Thus, the strategies for utilizing rice as a medium for delivering nutritional and health benefits should wisely be determined, designed, and deployed considering the feasibility, efficiency and, pros and cons of all biofortification approaches.

Both safety and nutritional value of food are integral to food security as per the UN Food and Agriculture Organization (Shaw 2007). Thus, protecting rice from toxic contaminants from farm to fork is also essential to enhance the contribution of rice to food security. Although milling, washing, and cooking processes reduce the level of consumed toxic contaminants through milled rice, more evidential data need to be generated on risk mitigation during production and post-harvest handling across the supply chains with respect to the different types of contaminants and the nature of health hazards they pose.

Conclusions and future perspectives

Although promoting whole grain consumption to tackle non-communicable diseases and to meet the daily requirement of micronutrients is a preferred option for improved nutrition security, the rice-growing areas contaminated with heavy metals and, in part use of pesticides prevents the promotion of brown rice consumption. Nevertheless, from the safety point of view, milled rice is much safer to consume than unmilled rice, as the majority of toxic contaminants such as As, mycotoxins, and pesticide residues are removed during milling operations. In this context, milled rice is the most favored form of rice for consumption around the world but requires strategies to enrich nutritional density through bio(fortification). While fortification strategies can be valuable short-term interventions to enhance the nutritional aspects of milled rice, genetics-based biofortification of rice is a sustainable way to enhance nutrient density in milled rice. However, challenges of biofortification such as consumer acceptability, safety, cost, and sustainability need to be critically studied and addressed in the long run. To address the growing non-communicable diseases in Asia, lowering the glycemic index without altering texture is critical to ensure consumer acceptance. In addition, overcoming the yield barrier and incorporating high RS/dietary fiber-rich traits as part of edible milled rice can be targeted to make rice products for breakfast, which includes flakes, bread, noodles, and other processed products.

To enhance the nutritional content of milled rice, mining the traditional rice landraces as valuable genetic resources is critical for introgressing economically and nutritionally relevant traits in high-yielding backgrounds. Deploying artificial intelligence tools for genome-phenome analysis provide novel opportunities for allele mining in traditional landraces to identify essential donors for the nutritional enrichment of milled rice. Human intervention studies have shown the potential of nutritionally enhanced and biofortified rice in alleviating micronutrient deficiencies and improving metabolic disease conditions. However, pieces of evidence are yet to be built on engineering starch metabolism to lower glycemic index and enhance the bioavailability of micronutrients and ensure the food safety aspects of fortified rice to address triple burden nutrition challenges.

Disclosure statement

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