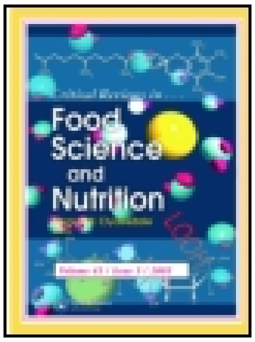

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REVIEW

The journey from white rice to ultra-high hydrostatic pressurized brown rice: an excellent endeavor for ideal nutrition from staple food

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ABSTRACT
Although brown rice (BR) contains significantly higher levels of nutrients than the traditionally used polished white rice (WR), its consumption among the population is still not noteworthy. WR and BR are essentially same grain. The only difference between the two is the application of an exhaustive milling procedure during the processing of WR that removes all other layers of the grain except the portion of its white endosperm. BR, on the other hand, is prepared by removing only the outer hull of the rice seed. Thus, in addition to its inner endosperm, the bran and germ are also left on the BR. Hence, BR retains all its nutrients, including proteins, lipids, carbohydrates, fibers, vitamins, minerals, tocopherols, tocotrienols, γ-oryzanol, and γ-aminobutyric acid (GABA) packed into the bran and germ of the seed. Since BR tastes nutty and takes longer to cook than WR, it is not appreciated by the consumers. However, these problems have been circumvented using non-thermal ultra-high hydrostatic pressure (UHHP)-processing for the treatment of BR. A superior modification in the physicochemical and functional qualities of UHHPBR, along with its ability to curb human diseases may make it a more palatable and nutritious choice of rice over WR or the untreated-BR. Here, we have reviewed the mechanism by which UHHP treatment leads to the modification of nutrients such as proteins, lipids, carbohydrates, and fibers. We have focused on the effects of rice on cell and animal models of different conditions such as hyperlipidemia, diabetes, and hypertension and the possible mechanisms. Finally, we have emphasized the effects of UHHPBR in human cases with rare conditions such as osteoporosis and brain cognition – two age-related degenerative diseases of the elderly population.

KEYWORDS
Ultra-high pressurized brown rice; nutrition; osteoporosis; brain cognition; hypercholesterolemia; hypertension; cardiovascular diseases

1. Introduction

Rice, as a staple food, is splendidly incomparable because it feeds more people (>3.0 billion) than any other crop and grows in wet environments that do not support the sustenance of other crops. Wet environments located abundantly across Asia may be one reason that makes rice the most popular staple food in countries such as Japan, China, Philippines, Thailand, Indonesia, Vietnam, Myanmar, India, and Bangladesh. Japanese people and people from other Asian countries obtain >75% of their daily calorie intake through consumption of polished WR, which is visually more appealing, and discard rice bran (Park, Lee, and Choi 2017). BR, on the other hand, is an unpolished, unrefined whole grain whose hull surrounding the rice kernel has been removed and retains all the essential nutrients that are lost from WR (Behall, Scholfield, and Hallfrisch 2006). However, scientists in Japan have shown that the rice bran, a leftover product of rice processing, provides numerous significant health benefits to humans for ailments such as diabetes, hyperlipidemia, hypertension, depression, osteoporosis, and impairments of cognition; therefore, rice along with its bran layer, *i.e.* the whole grain of the BR, should be consumed (Kayahara and Tsukahara 2000; Ishikawa and Ito 2004). Even though BR provides more nutrients than WR, it's sensory and the long time required for cooking make BR an undesirable option. In a consumer-driven market, therefore, it has been a challenge for the milling industries to develop rice with palatable characteristics desired by the consumers without compromising on the food-safety as well as health and wellness. Numerous methods and approaches have been attempted to alter the sensorial texture and shorten the cooking-time of BR in a pressure cooker. For example, pre-germination (Toyoshima et al. 2004); fermentation (Ilowefah et al. 2015; Zeb et al. 2017); pulse electric field treatment (Barba et al. 2015a); plasma treatment (Chen et al. 2016); ultrasonic treatment (Cui et al. 2010); electrochemical treatment (Feng et al. 2004); radiation treatment (Shao et al. 2013); pre-gelatinization (Thakur and Gupta 2006); partial milling, heating, and cooling (Mohapatra and Bal 2006), soaking and hydrothermal treatment (Zhang et al. 2014); and heat treatment and soaking (Hirokawa et al. 1986). However, these processing systems have numerous noticeable drawbacks including high cost, loss of important nutrients, increased propensity for contamination,

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generation of unwanted off-odors, inferior-quality appearance, and objectionable texture and taste.

Recently, the non-thermal ultra-high hydrostatic pressurized (UHHP) processing system has been receiving an increasing interest for its application in reducing the cooking-time and undesirable palatability of the BR in addition to its ability to avail a rich nutrient content in the rice after treatment (Yoshino and Inoue 2016). The UHHP process defines a condition in which pressure above 400 Mpa is generated using excess of water. In fact, this high-pressure technique has been considered as one of the most important innovations in food processing over the last 50 years (Dunne 2005). Because of the absence of heat in this procedure, the non-thermal UHHP treatment for rice retains not only the sensory and nutritional properties of the food but also conserves its original freshness. Development of UHHPBR, therefore, can be viewed as an attractive upgradation in rice processing. Furthermore, UHHP treatment inactivates a variety of pathogenic and vegetative spoilage microorganisms, ensures a longer shelf-life and guarantees food safety. Therefore, due to the superior nutritive and organoleptic properties of UHHPBR than those of WR or the normal BR, it is not only gaining increasing appreciation among the health-conscious consumers, but an augmented interest is also being generated among the nutritionists, researchers, and scientists due to its effect(s) on different ailments in humans. The aim of this review is to compare the composition of UHHPBR with those of the untreated-BR and WR, and understand the mechanism(s) by which UHHPBR may tend to influence numerous physiological and neurochemical activities in the body. Finally, the areas considered in this review are as follows:

Highlights

- Physiochemical properties and nutritional quality of UHHPBR, BR and WR.
- Functional characteristics of UHHPBR, BR, and WR with respect to proteins, lipids, carbohydrates, fibers, vitamins/minerals, antioxidants, and GABA contents
- Effect of BR on health and diseases like hyperlipidemia, hypertension and diabetes
- Finally, the effect of UHHPBR on human osteoporosis, cognitive functions, and mental health

2. Physicochemical properties of UHHPBR, BR, and WR

Rice is a special type of dry, indehiscent, single-celled, one-seeded fruit in which the seed is cohesively fused with the seed-coat (so-called bran) making it difficult to dislodge the two except by special milling processes. Morphologically, each rice seed consists of a grain of rice enclosed in a hull. The grain mainly comprises the embryo, endosperm, and a surface known as the bran layer, as shown in the Figure 1. BR is generally nuttier and chewier than WR (Vetha-Varshini, Azhagu-Sundharam, and Vijay-Praveen 2013). Depending on the milling procedure, rice of each type can be prepared. Although they are the same seed, one is like a whole grain, which is called BR because of the characteristic brown color of its bran and the other is WR, which looks white because of the whitish color of the inner seed. The inedible dry, coarse, scaly casing known as the chaff is removed from BR, and the WR is actually the same grain with the outer hull, bran, and germ removed. The bran, which is stripped off by polishing the whole rice grain, contains nutrients that polished WR does not. BR comprises of bran layers (6-7%), an embryo (2-3%) and an endosperm (90%) (Chen, Siebenmorgen, and Griffin 1998). The rice bran is a very hard and natural coating that shields its cells and nutrient constituents, and is difficult for humans to consume on a regular basis. BR is not pleasant as a result of the hard bran outer layer and difficulty of cooking, while WR is appreciated due to its characteristics like ease of cooking, tenderness, color, glossiness and translucent appearance after cooking. Recent studies have reported that WR, BR, and germinated-BR differ significantly from each other with respect to their color, odor, and taste, and the qualitative scores of BR were significantly lower than those of WR (Monge-Rojas et al. 2014). UHHPBR, *i.e.* BR after treatment with the UHHP procedure (500 Mpa), demonstrated a significant decrease in its cooking time, which was close to the cooking time required by WR (Yu et al. 2015). When compared to WR, BR and UHHPBR also vary in aroma, whiteness, brittleness and wholeness of the grains.

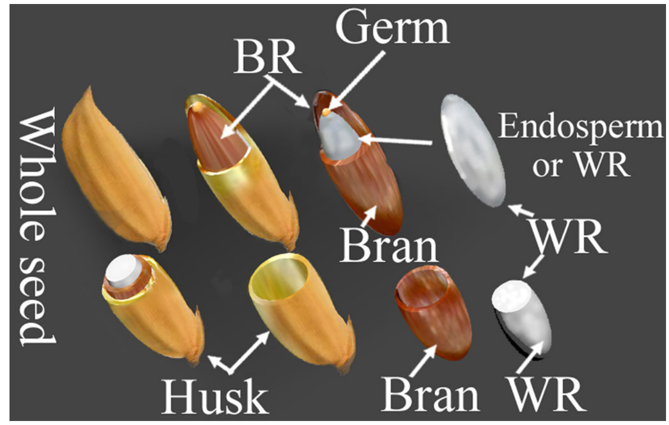

Figure 1. Morphology of rice seed. BR = Brown rice; WR = White rice.

Since the discovery of the UHHP process that reduces bacterial count in milk by Hite (1899) and the pioneering work of Bridgman (1909) on the denaturation/coagulation of egg albumin, many industries have been implementing the UHHP system in food industries. However, its utilization in the rice industry is relatively new. Hence, the mechanism of the UHHP treatment and its effects in enhancing the quality of BR, and its subsequent beneficial effects on human physiology are yet to be known clearly. An improvement in the physical properties of rice with respect to its cooking and eating qualities ultimately depends on its chemical constituents such as the starch (amylose and amylopectin), protein and lipid contents (Juliano, Oñate, and delMundo 1965).

Although not in identical ways as temperature, but pressure, too, influences the biophysical and biochemical characteristics of proteins, lipids, and starches, causing modifications in the quality of the texture of rice. For

Figure 2. Pictures of the WR (A) and ultra-high hydrostatic pressurizing brown rice (UHHPBR) (B) rice. We used these WR and UHHPBR rice to investigate the effects of UHHPBR on bone density mineralization and brain-cognition.

example, high hydrostatic pressure (HHP) affects the secondary/tertiary/quaternary structures of proteins by affecting the void volume of its internal cavities, solvation of the peptide bonds and influencing the non-covalent and electrostatic interactions, leading to either local or overall changes in the protein structures (Mozhaev et al. 1996). Like temperature, high-pressure treatment may also cause a phase transition of the lipids, thereby modulating the lipid-lipid and lipid-protein interactions (MacDonald 1984). In nature, starch occurs as discrete particles called granules and they are packed into the cores of the rice seeds in crystalline and amorphous forms. The UHHP treatment severely agitates the bran and associated aleurone layers, germs and starch granules in the endosperms of the rice grains. UHHP processing helps in availing nutrients to the human body. By changing the structures of amylose/amylopectin in the starch granules, UHHP treatment helps in the gelatinization of starch, improves glossiness, shortens the cooking time and makes UHHPBR more palatable to the consumers (Juliano, Oñate, and delMundo 1965; Jenkins and Donald 1995). The effects and probable mechanisms of UHHP treatment on proteins, lipids, and carbohydrates are discussed below (Figure 2).

3. Focus on the nutritional quality of UHHPBR, BR, and WR

3.1. Proteins

The rice seed stores many essential proteins, enzymes and amino acids essential to its metabolic (biosynthetic and biodegradative) pathways, which are indispensable for its cell cycle during germination and growth. From the standpoint of human nutrition, extracting these essential proteins/amino acids using technological innovations will be highly appreciated. Functional properties of proteins play an important role in determining the texture of the products prepared from rice (Neto et al. 2001). UHHPBR is likely to offer better health-promoting effects than WR or even the

Table 1. Macronutrients of white rice (WR), brown rice (BR) and ultra-high hydrostatic pressurized brown rice (UHHPBR).

Nutrients	WR	BR	UHHPBR
Protein (g)	6.8^{a}	6.8^{a}	7.7^{a}
Carbohydrate(g)	75.3^{a}	73.8^{a}	76.6^{a}
Lipid (g)	1.3^{a}	2.7^{b}	3.0^{b}
Dietary fiber (g)	0.30^{a}	3.0^{a}	7.1^{b}
Kcal	338.8^{a}	344^{a}	361.2^{a}

Results are mean ± SE, each with triplicate determinations. Values in the same raw with different superscript alphabets are significantly different at $P < 0.05$.

untreated-BR as the high quantity of nutrients in UHHPBR, including proteins, will be available for our body-functions. Rice proteins may occur in the germ and bran layers while endosperm protein bodies are present on the surface or interiors of the starch granules of the endosperms and play important roles in the pasting and swelling properties of the starch molecules. Thus, different parts of the rice seed vary in their protein contents. Endosperm proteins of the milled WR consists of 15% albumin and globulin, 5-8% prolamin, and the rest is glutelin (Juliano 1985). Tanaka et al. (1973) reported the presence of 66% albumin, 7% globulin, and 27% prolamin and glutelin in the aleurone protein bodies. Ogawa, Tanaka, and Kasai (1977) reported the presence of 98% albumin in the embryo protein bodies. Liu et al. (2015) reported that approximately 29% of protein is lost during the milling of WR. In our study, 100 gm of UHHPBR, BR, and WR contained 7.7, 6.8 and 6.8 g of proteins respectively (Table 1). The total protein content was higher in UHHPBR by >13% when compared to that of WR, and an increased degree of milling was responsible for the loss of proteins from the bran, germ, and endosperm of WR. The protein content was found to increase in UHHPBR due to disruption induced by the UHHP treatment that led increased the accessibility to the bran, germ, and endosperm layers.The quantity of total protein in UHHPBR was not significantly different from that in the WR. The UHHP treatment is, however, believed to affect the quality of the proteins in the UHHPBR.

Pressure in the UHHP treatment favors a reaction that leads to a decrease in the volume of proteins. Proteins possess plenty of void volume due to numerous internal cavities in their tertiary/quaternary structures. Thus, the UHHP treatment is likely to compress the protein volume and cause its denaturation. Silva and Weber (1993) reported that pressures of 100-200 Mpa were sufficient to dissociate the oligomeric, multi-protein complexes. Heremens (1982) reported that monomeric proteins are denatured by pressures ranging from 400 to 800 Mpa. Since covalent bonds are insensitive to pressure (up to 1000 Mpa), it is inferred that the pressure of 500 Mpa used during the preparation of our UHHPBR did not have any effect on the composition of the proteins (Knorr, Heinz, and Buckow 2016). In this regard, UHHPBR would be more beneficial to the consumers than WR. For example, proteins responsible for rice allergies (Satoh et al. 2019) located in the rice endosperm (Matsuda et al. 1988) or aleurone layers (Kurokawa et al. 2014) of the bran are likely to be denatured and inactivated into non-allergens. As a result, by lowering the allergen proteins, the UHHP treatment may reduce the allergic response to proteins (Meng et al. 2017) and also maintain a high food quality by inactivating the enzymes (Tanimoto et al. 2005). Hayashi et al. (1990) reported that the rate of protein hydrolysis increases with an increase in the pressure, thus demonstrating that the UHHP treatment may also increase the number of free amino acids in UHHPBR. The *amino acid score* is the highest for the bran layers of rice, and the score is higher for BR than WR (Juliano 1985).

Thus, it is anticipated that UHHP treatments will augment the amino acid scores of UHHPBR compared to that of the milled WR and/or untreated-BR. However, it may appear conflicting that the proteolytic enzymes, which are themselves believed to be damaged/inactivated after UHHP processing, are found to increase the degree of hydrolysis upon treatment. De Maria, Ferrari, and Maresca (2017) recently reported that the HHP treatment at pressures <400 Mpa increased the hydrolysis of bovine serum albumin (BSA) by the protease enzyme. They proposed that the HHP treatment ruptured the non-covalent bonds of the BSA protein and induced an unfolding which in turn increased the accessibility of the hydrolytic enzyme to sites of the BSA-protein backbones hidden previously, thus increasing hydrolysis of the protein. It is not clear whether similar mechanisms are active in UHHPBR; however, numerous reports support that UHHP treatment increases the proportion and number of free amino acids in BR (Xia et al. 2017). Thus, a clear mechanism to explain the effect of UHHP treatment on BR is required.

The levels of the non-protein amino acid, GABA, also increased greatly after the UHHP treatment (Table 2). We conclude that though UHHP treatment could not quantitatively increase the protein content to a very large extent, it affected UHHPBR qualitatively by denaturing the in situ molecular structures and properties of the proteins and enzymes thereby affecting the palatability and cooking time of the BR. These evidences strongly suggest that UHHP treatment improves the taste, nutrition, as well as the bio-accessibility and bio-functionality of the proteins/amino acids and might help in the prevention of hypertension and mental stress, for example, by its elevated GABA content (Kinefuchi et al. 1999).

Table 2. Vitamins, minerals, GABA, Inositol, Ferulic acid and other micronutrient contents of WR, BR and UHHPBR.

	WR	BR	UHHPBR
Vitamin B1 (mg)	0.12	0.41	0.51
Vitamin B2 (mg)	0.03	0.04	0.04
Vitamin B3 (mg)	1.40	6.3	7.46
Vitamin B6 (mg)	0.05	0.45	0.32
Vitamin E (mg)	0.40	1.3	ND
Calcium (mg)	2.0	9.0	9.0
Magnesium (mg)	20	110	110
Phosphate (mg)	140	290	290
Potassium (mg)	110	230	230
Sodium (mg)	2.0	1.0	1.8
Iron (mg)	0.5	2.1	2.1
Zinc (mg)	4.0	1.8	1.8
GABA (mg)	2.2	4.4	9.1
Inositol (mg)	ND	–	202
Ferulic acid (mg)	ND	–	12-50

Values are shown for 100 g WR, BR and UHHPBR. GABA, γ-aminobutyric acid. ND, not detected. Nutritional data was obtained from Shimane institute for industrial technology, Japan Food Research Laboratories (JFRL) and Shimane Environment & Health Public Corporation.

3.2. Lipids

The concentrations of lipids in WR, BR, and UHHPBR were found to be 1.3%, 2.7%, and 3.0% (Hashimoto et al. 2017), respectively, suggesting that the lipid levels in rice depend on its degree of milling (DOM). Though the lipids comprise only a tiny percent (1%) of the composition of rice as compared to the high abundance of carbohydrates (75 ~ 80%) and proteins (6-8%), rice lipids do contribute to its nutritional, sensory and functional qualities (Fujino 1978). The effects of lipids on the quality of rice are conceivable from the rancidity-induced bad odor of BR during storage.

Lipids are chiefly located in the aleurone and sub-aleurone of bran layers and as spherosomes in the embryos of the rice seeds. These are known as the non-starch lipids (Godber and Juliano 2004). Lipids that remain associated with the starch granules either at their surface or interior regions are referred to as the starch lipids. These lipids play crucial roles in the pasting and swelling properties of the amylose and amylopectin molecules of starch in the rice seed, which ultimately determine the palatability of rice after cooking. Though it has not been understood clearly, non-starch lipids were negatively correlated with the amylose contents (Choudhury and Juliano 1980). The non-starch lipids constitute the majority of lipids in the rice seed, while the starch lipids have substantial effects on its functionality (Morrison 1995). Starch granules are considered to be one of the target places where the UHHP treatment exerts its effects and modifies the structural features of the starch molecules, and hence, the quality and texture of the rice. Compared with other biomolecules such as proteins and DNA, lipid layers respond more sensitively to hydrostatic pressure (Winter and Dzwolak 2004). The intermolecular distance between the acyl chains and the volume of water in the bilayer is reduced by high pressure (MacDonald 1984). The total fat content, fatty acid composition, and ratios of saturated and unsaturated fatty acids vary with the degree of milling (Yoshizawa, Ishikawa, and Noshiro 1973). The iodine and saponification numbers of the non-starch lipids suggest that the fatty acids existing in the bran layers vary in their molecular weights and degree of unsaturation. The major fatty acids of these lipids are linoleic, oleic and palmitic acids (Hemavathy and Prabhakar 1987; Taira, Nakagahra, and Nagamine 1988). Essential fatty acids in the rice oil constitute about 28-53% linoleic acid and 0.2-1.6% linolenic acid (Gopala Krishna et al. 2006). Rice bran contains lipases, which increase free fatty acid (FFA) levels. Therefore, caution needs to be exerted regarding the deleterious effects of FFAs like the acceleration of lipid hydrolysis by lipases and subsequent occurrence of a number of auto- or enzyme-induced oxidation reactions due to the UHHP treatment (Jaisut et al. 2009; Wang et al. 2012). If the enzymes, like other proteins, are inactivated by UHHP treatments, enzymatic oxidations do not take place.

Rice bran lipid/oil is healthier than any other vegetable-based edible oil because of its unsaponifiable lipid fraction comprising largely of γ-oryzanol, tocopherols, tocotrienols, and a broad spectrum of phytosterols. All these compounds, in principle, demonstrate strong anti-oxidative effects (Kim and Godber 2001; Patel and Naik 2004). Among them, γ-oryzanol has received huge attention from the basic research and clinical scientists because of its numerous health and nutrition benefits. Contrary to previous assumptions in which γ-oryzanol was considered to be made up of a single component, it is now known that the compound comprises of at least 10 components including β-sitosterol, cycloartenol, campesterol, 24-methylenecycloartenol, stigmasterol, and ferulic acid esters (Akihisa et al. 2000). As the UHHP treatment increased the total lipid content in UHHPBR compared to those in BR and WR, it is likely that the quantities of these bioactive compounds are higher in UHHPBR, as can be presumed from the differences in the compositions of ferulic acid and inositol (Table 2).

3.3. Carbohydrates

Carbohydrates in rice can be categorized into two major types of polysaccharides as follows: (a) starch-polysaccharides comprising amylose, amylopectin, and simple sugars and (b) non-starch polysaccharides that include fibers such as cellulose, hemicellulose, and pectin. Products of starch hydrolysis constitute majority of the digestible carbohydrates in the human diet (Orford et al. 1987). Therefore, increasing the digestibility of carbohydrates by treating rice with the UHHP system would prove to have an additional advantage. The UHHP technology has great potential for its use in modifying different textural characteristics with minimum effects on flavor, color, and nutritional value without leading to any thermal degradation (Ahmed et al. 2007).

Thus, an understanding of the complex internal organization of the amylose and amylopectin molecules in starch granules is crucial for revealing the mechanisms by which UHHP treatment affects their physicochemical/functional properties. The highly-branched amylopectin molecules with their external branched chains fold into a double-helical crystalline structure, and primarily linear amylose molecules present themselves in the amorphous form in the starch granules. Amylose and amylopectin molecules are synthesized in apposition and appear in radial lamellar arrangements that are interspersed and oriented perpendicular to the surface of starch granules. Because of their partially crystalline structures, starch granules are insoluble in water at temperatures below the gelatinization temperature of the starch (French 1984; Jane et al. 2003) (Figure 3).

Guilbot and Mercier (1985) reported that UHHP treatment disrupts the orders of amylose and amylopectin molecules in the native organization of starch granules and causes gelatinization. The degree of disorder and process of gelatinization are a consequence of the breaking of inter- and intra-molecular hydrogen bonds and an interruption in the hydrophobic interactions occurring between the amylose and amylopectin molecules of the starch granules. The broken hydrogen bonds are then replaced with the water molecules introduced from the UHHP treatment that penetrate the structures and cause extensive hydration. Hydration leads to a loss of the anisotropic order of the amylose molecules. The helix-helix dissociation and transition from helixes to random coils also occurs in the amylopectin molecules, resulting in the loss of their crystallinity. In this way, the water molecules induced as a result of the UHHP treatment allow the amylose and amylopectin to move freely, disrupting the helical form of the amylopectin chains and eventually destroying their native molecular organization in the starch granules. Finally, this leads to a structural disruption of the starch granules and the formation of gelatin. Previously, Ahromrit, Ledward, and Niranjan (2006) have reported that high pressure treatments accelerate the uptake of water in the rice grains. Along these lines, Yu et al. (2015) reported that the HP treatment causes damage to the pericarp and aleurone layers of the brans, decreases the cooking time significantly and increases the palatability of BR. UHHPBR, BR, and WR contained, 76.6%, 73.8%, and 75.3% carbohydrate, respectively, indicating again that the qualitative effects of BR are mediated by the UHHP treatment. For example, by changing the qualitative properties of the starch, UHHP treatment increased the palatability and decreased the cooking time of the BR.

3.4. Fibers

Consumption of foods rich in dietary fiber are known to improve health. One of the most noticeable effects of UHHP treatment was observed on the non-starch polysaccharide component of the BR, *i.e.* on its fiber contents. WR contained only 0.3% (wt/wt) dietary fibers. Untreated-normal BR had a 10-fold higher dietary fiber content than that of WR. More interestingly, the amount of dietary fiber in UHHPBR was higher by 20-folds and 2-folds than that of WR and BR respectively, indicating that the content of total edible dietary fibers was highest in UHHPBR among the three. Majority of the dietary fiber from plant sources, including cereal bran, is mainly composed of cellulose, hemicelluloses and lignin,

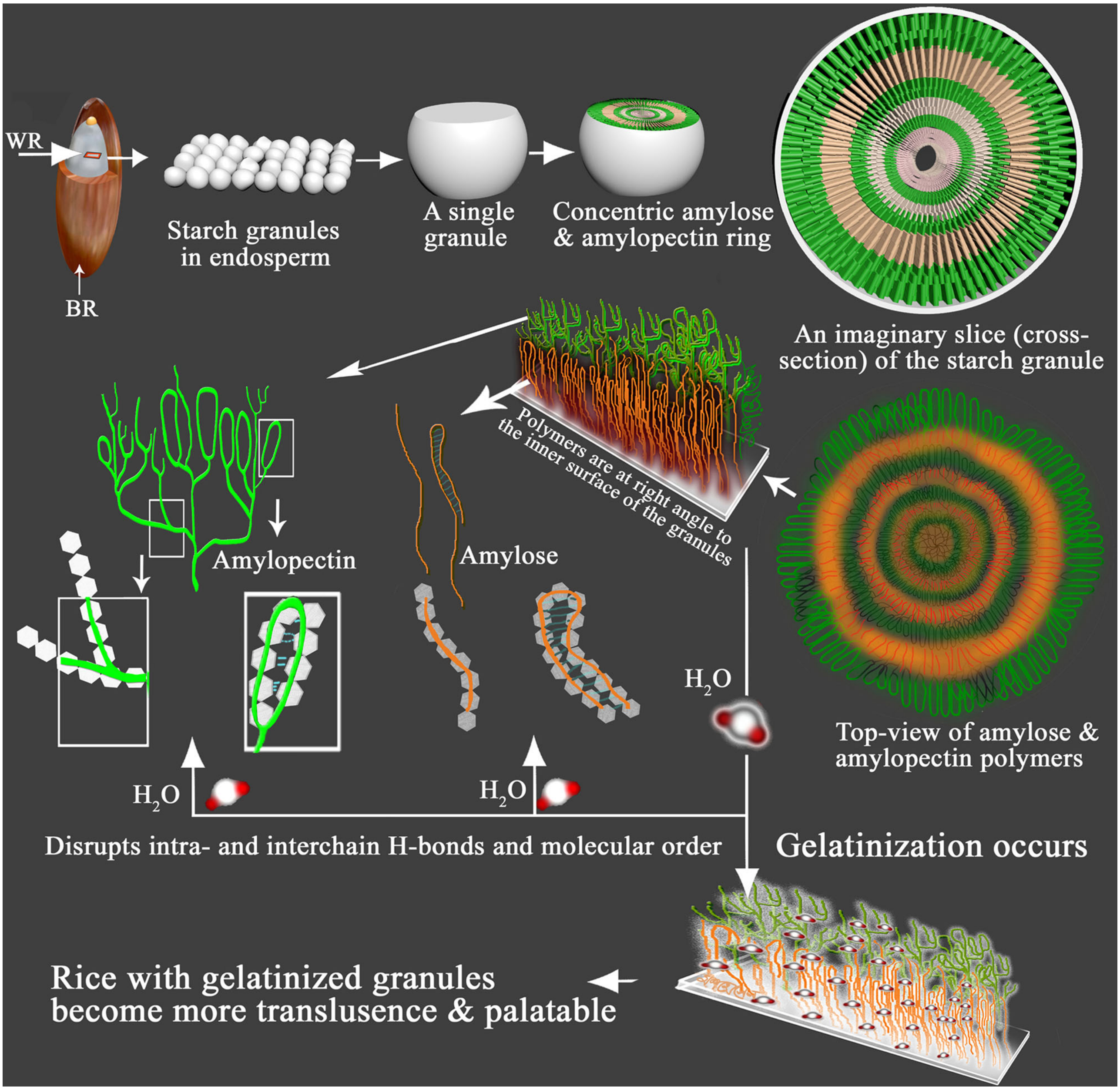

Figure 3. Scheme of the morphology of starch granules and their internal organization of amylose and amylopectin polymers. Rice starches vary in shape and size. They are polyhedral, oval, irregular, angular, or smooth in shape. The sizes vary from 2-7 µm. The amylopectins are believed to form the semicrystalline layer by partial alignment of their molecular chains, while the amylose forms the amorphous layers in an alternating fashion, which looks like a tree growth rings. The glucose chains might be both straight and helical chains. The helical chains are stabilized by H-bonds. The helical chains again can be associated to form a helix-helix duplex. Ultra-high hydrostatic pressure forces the water molecules to penetrate into the lamellar regions of the amylose and amylopectin molecules. As a result, the anisotropic orders of the polymer molecules are lost. Amylopectin molecules lose their crystallinity. These processes ultimately lead to the formation of gel-like consistency of the starch granules, i.*e.* gelatinization. Finally, the palatability of the UHHPBR increases.

which contain functional groups such as alcohols, aldehydes, ketones, carboxylic acid, and phenolic and ether linkages. These groups have a strong affinity to bind water. However, it is required for the water molecules to penetrate these functional groups. Thus, UHHP treatment is an excellent technique by which brans of BR can be exposed. Qi et al. (2015) reported that rice bran is composed of approximately 27.5% insoluble dietary fiber and 18.9% soluble dietary fibers. Though we do not have the data of the soluble versus insoluble fibers, both have been regarded as important. Since the UHHP treatment increases the levels of total dietary fibers, the levels of both soluble and insoluble fibers in UHHPBR are expected to be higher than those in WR or BR. This may be due to the effect of UHHP treatment on the fiber-filled bran layers of the BR. Soluble fiber is resistant to digestion and absorption in the small intestine (Almeida, Chang, and Steel 2013). Soluble fiber reduces the absorption of cholesterol and glucose, thus, decreasing the risk of ischemic heart disease and postprandial glycemia. The functional properties of dietary fiber such as its water-holding capacity, cation binding, and absorption of bile acids play a significant role in the prevention of diet-dependent diseases like obesity, atherosclerosis and colon cancer (Dziedzic et al. 2012). The insoluble fraction of dietary fiber that activates intestinal peristalsis is capable of binding bile acids and water and can act as a stool-bulking agent (Tomlin and Read 1988). We again speculate that UHHP treatment increased the penetration of water into the complex polysaccharide structures of the brans and damaged their structures, thus increasing the extractable total dietary fiber contents in UHHPBR. Finally, the influence of UHHP treatment improves the texture-quality and palatability of the BR, which otherwise would have been harder and less digestible. The fiber in BR helps lower blood cholesterol while the glucose moves the waste through the digestive tract and may help prevent hypercholesterolemia and diabetes, respectively.

3.5. Vitamins and minerals

Since BR contains more vitamins and minerals than WR, the macro- and micronutrients of BR have become an important topic for active research. Sufficient vitamin and mineral nutrition is essential for optimal growth and development (Shenkin 2006). Deficiency of vitamins and minerals is known to cause birth defects (Oakley, Bell, and Weber 2004), stunted growth (Branca and Ferrari 2002), diminished mental development, decreased cognition and learning ability, weak immune system and high mortality rates (Grantham-McGregor and Ani 1999; Verhoefa et al. 2003; Gernand et al. 2016). Particularly, the risks of death during childbirth are high among pregnant women lacking or deficient in key vitamins and minerals (Ramakrishnan et al. 1999). Therefore, consuming grains fortified with micronutrients is considered as one of the best ways to replenish the malnourished population (Alavi et al. 2008). Humans need approximately 15 types of macro- and microminerals. Most of the dietary elements are obtained from the intake of grains like rice, wheat and maize (Gai, Dong, and Fu 2004). Macrominerals usually include Ca, P, K, S, Na, CI and Mg, while the microminerals or trace dietary elements include Fe, Co, Cu, Zn, Mo, Mn, Se, I and Ni. The mean concentrations of minerals in BR were in the following order: P > K > Mg > Ca > Fe > Na. Except Zn, the concentrations of all other elements were found to increase significantly in both, UHHPBR and BR, as compared to those in WR. The vitamins and minerals found in rice are mostly bound to important proteins, forming metalloproteins, particularly enzymes (Housten and Kohler 2000). The levels of Mg, Ca and Fe increased significantly in UHHPBR than those in WR. Thus, in UHHPBR, it is difficult to relate the bio-accessibility of the divalent cations directly to its phytate content, since all divalent cations could have otherwise been decreased. Briones-Labarca et al. (2011) also reported that bio-accessibility to minerals shows no essential relationship with their concentration. Thus, a decrease in the absolute concentrations of Zn in UHHPBR might not be the exclusive reason for its reduced bio-accessibility. Yet, the reasons for lower levels of Zn in UHHPBR/BR than those in WR remains to be understood clearly. One approach to avail minerals is that, prior to milling, the rice may be steeped under pressure in order to transfer all the vitamins and minerals from the bran layers into its white kernel itself, and/or all the vitamins and minerals in the cooked rice should be assembled from its bran layer. UHHP processing is one of the approaches that can be implemented for availability of all vitamins and minerals in the rice. Alternatively, the milled and polished WR can be submersed in a solution of vitamins and minerals in order to coat its grains. Once the vitamins and minerals have been absorbed into the grains, they should be allowed to dry. However, the processes will undoubtedly be time-consuming, labor-oriented and costly. Consequently, rice processing by the UHHP treatment for withholding the vitamins and minerals into the grains is a better way. The bio-accessibility of minerals is reduced by their binding to phytic acid and dietary fibers but can be increased by indigestible polysaccharides (Vitali, Dragojević, and Šebečić 2008). Since UHHPBR increases the levels of both soluble and insoluble (indigestible) fibers, it can be considered as a better option to derive the maximum vitamins and minerals from rice. Accordingly, UHHPBR can contribute to and substantially fulfill the daily recommended intake of important vitamins and minerals.

3.6. Gamma-aminobutyric acid (GABA)

GABA is a non-protein, bioactive amino acid of the plant cells. The level of GABA increases in response to stress, such as cold, heat, salinity, oxygen deficiency, and mechanical damage (Kinnersley and Turano 2000; Palanivelu et al. 2003). It plays an important role in the defense against stress in plant cells including cereal grains like the rice seed (Al-Wadei, Ullah, and Al-Wadei 2011). Interestingly, GABA causes hyperpolarization of the plant cells and provides defense against stress in the plant kingdom. More interestingly, in animals, GABA also provides an anti-stress defense by acting as an inhibitory neurotransmitter in the brain (Curtis and Johnston 1974) and takes place by hyperpolarization-induced brakes in the excitation. As a result, GABA plays a significant role in inducing sleep, calmness, and the treatment of anxiety and depression in humans. GABA is also found in the peripheral tissues (Erdo 1985).

Over time, GABA contained in BR helps to lower blood pressure, improves kidney function, reduces insomnia and helps to prevent the onset of Alzheimer's disease (AD) (Itoh and Ishikawa 2004). Interest has stemmed regarding the effects of GABA-rich rice on the aging population suffering from AD and other age-related conditions leading to a decline of cognition. It has been noted that the amount of GABA in the germinated BR was 10 times higher than that in the milled WR and twice as high in the regular BR. We found that the concentration of GABA is approximately 2-folds higher in BR and 5-folds higher in UHHPBR as compared to that of WR. Soaking and subsequent imbibition and germination of the rice seed stimulates the synthesis of GABA from glutamic acid by glutamate decarboxylase (GAD) via the GABA-shunt (Saikusa, Horino, and Mori 1994). The function of GABA is required for proper growth of the rice seed in response to abiotic stresses such as low light (Michaeli et al. 2011) or hypoxia (Crawford et al. 1994). The level of GABA was reported to vary among different varieties of BR due to differences in the soaking time and temperature, their genetic make-up (Karladee and Suriyong 2012) and the degree of activation and accumulation of GAD (Komatsuzaki et al. 2007). However, the mechanism(s) underlying the increase in levels of bio-accessible GABA in UHHPBR than that in the untreated-normal BR remains unknown. The primary level of GABA was higher in the untreated-BR as compared to that in WR. This demonstrates that the GABA probably remains in the protein bodies of the germs and bran layers of the grain. Since the levels of GABA increased further in UHHPBR, it can be elucidated that the UHHP treatment caused ruptures and swelling of the germs and brans by allowing penetration of water into these layers resulting in greater bio-accessibility of GABA, and hence, the levels of GABA increased quantitatively in these grains. In other words, the increased levels of GABA in UHHPBR might be an additive benefit of the UHHP treatment. The intake of GABA or GABA-rich BR suppresses blood pressure and improves conditions like sleeplessness and autonomic disorders experienced during menopause or the presenile period (Okada et al. 2000).

3.7. Antioxidants

Reactive oxygen and nitrogen species (RONS), which are indispensably produced by all aerobic cells, cause oxidative damage to cellular membranes, proteins, lipids, carbohydrates and DNA (Salisbury and Bronas 2015). The free radical theory of aging postulates that age-associated functional losses occur as a result of damages to these biomolecules induced due to the accumulation of RONS (Venkataraman, Khurana, and Tai 2013). Increased levels of RONS transform 'normal cells' into 'senescent cells' (Pole, Dimri, and Dimri 2016; Chandrasekaran, Idelchik, and Melendez 2017). Cellular senescence is associated with many acute and chronic pathological processes such as cardiovascular diseases (CVDs), diabetes, hypertension, osteoporosis and hyperlipidemia as well as neurodegenerative diseases like AD. Therefore, it is very crucial to prevent chronic diseases and mitigate the risks associated with the aging processes.

Antioxidants may potentially defuse the free radicals resulting in the reduction of RONS- and age-related chronic diseases, leading to improvements in cognition and mental health (Zhang et al. 2010). Antioxidative effects of BR are mediated by phenolics, triterpenes, nicotinic acid, γ-oryzanol, ferulic acids, tocopherols, sterol (ergosterol), vitamin E (tocopherol) and tocotrienols (Komatsuzaki et al. 2007). Recently, Sarkar et al. (2019) reported that the presence of higher contents of total polyphenols, flavonoids, β-carotene, and lycopene in the BR compared to those of WR were linked to the diminishing of oxidative- and pro-inflammatory stresses in the liver tissues of hypercholesterolemic rats. Indeed, rats fed with BR also demonstrated significantly reduced levels of urinary 8-OHdG (8-hydroxy-2′ –deoxyguanosine), a marker of oxidative stress to DNA, and total antioxidant status essentially noted during hypertension (Subash et al. 2010). Oxidative stress is one of the risk factors for age-related neurodegenerative vascular dementia (VD) and AD (Hashimoto et al. 2002, Luca, Luca, and Calandra 2015). Finally, a high content of antioxidants in UHHPBR can potentially contribute in inhibiting the progression of diseases resulting from oxidative stress to a greater extent than WR. However, the mode of action for the increase in total antioxidants in BR after UHHP treatment compared to that of WR remains to be clarified. Since the covalent bonds of larger biomolecules and some other small molecules are insensitive to UHHP treatments (Balasubramaniam, Martínez-Monteagudo, and Gupta 2015), UHHP-derived disruption of the cell walls and organelles might enhance the extraction and release of antioxidants into the extracellular milieu, causing an increase in the levels of total antioxidants in UHHPBR. This speculation was consistent with other reports (Barba et al. 2015b). In our previous studies, a significant increase in the content of ferulic acid was observed in the BR after UHHP treatment. Xia et al. (2017) also reported that high hydrostatic pressure increases the bio-accessibility of antioxidants in the BR. Bio-accessibility of antioxidants also increased in other foods such as plantain pulp and apple when subjected to pressures of 500 Mpa, (Briones-Labarca et al. 2011; Jiménez-Martínez et al. 2017).

4. Effects of UHHPBR, BR and WR on different common disorders

4.1. Effects of UHHPBR, BR and WR on hyperlipidemia

Hyperlipidemia is a high-risk cardiovascular disease (Niswender 2010; Nordestgaard and Varbo 2014). Numerous studies report that the cholesterol-lowering statin drugs can cause adverse effects on different organs of the body such as liver dysfunctions or myalgia (Ohtsubo et al. 2005; Bays 2006; Nichols and Koro 2007). Therefore, drop in the blood cholesterol levels via a non-drug approach, particularly by the consumption of staple foods like rice containing bioactive compounds with hypolipidemic potentials, would be an interesting and excellent choice. An individual consuming polished WR for fulfilling the carbohydrate requirement of their body is, in fact, depriving the body from optimum health benefits of the BR.

Scientists in Japan and other Asian countries have shown that BR decreases the levels of lipids in the blood of hypercholesterolemic mice (Oh et al. 2005), rats (Roohinejad et al. 2010), rabbits (Shimabukuro et al. 2014) and humans with metabolic syndromes such as diabetes, cardiovascular disease and baseline cancer (Sun et al. 2010). It has been recently reported that germinated BR reduces the total cholesterol (TC), triglycerides (TG) and LDL-C in the blood as well as TC/TG in the liver with concomitant increases of fecal TC in the rats fed with the BR (Sarkar et al. 2019). Our results were consistent with the above reports. Multiple mechanisms underlying the hypocholesterolemic effect(s) of BR have been proposed. In brief, the active compounds of BR, such as phytosterols (Ghatak and Panchal 2011), GABA (Kritchevsky and Story 1974), oryzanol (Turley, Daggy, and Dietschy 1991)[119] and antioxidants like phenolics (Lin et al. 2009) have been ascribed to the up-regulation of LDL-R and Apo-1 (carrier of HDL-C) (Imam et al. 2013; Walldius and Jungner 2007). High fiber contents also are also linked to the hypocholesterolemic effect due to its increased ability to excrete fecal cholesterol (Sarkar et al. 2019). All these reports suggest that BR is better than WR for its hypolipidemic attributes. However, the effects of UHHPBR on hypercholesterolemia still need to be determined although numerous reports on the hypocholesterolemic effects of BR are available. It was found that the lipid profile of the subjects was not affected in our human study involving normolipidemic and normotensive elderly Japanese population fed with UHHPBR for 24 months (Kuroda et al. 2019). Thus, the results support that further studies are essential, particularly on subjects with normolipidemia.

4.2. Effects of UHHPBR, BR and WR on diabetes

The International Diabetes Federation (IDF) reported that approximately 425 million adults (age group of 20-79 years) were living with diabetes, in the year of 2017, and by 2045 the number is predicted to rise to 629 million (Cho et al. 2018). The worldwide spike in type 2 diabetes (DM2) in the recent decades is supposed to parallel a shift in diets away from staple foods rich in natural ingredients like whole grain BR to highly refined carbohydrates such as WR, indicating that the effect of the consumption of WR on diabetes is huge (Yu et al. 2013 and Liu et al. 1999). Hu et al. (2012) reported that the consumption of WR was associated with an elevated risk of DM2 particularly in the Asian population. In a study based at the Japan Public Health Center (JPHC), it was reported that rice consumption was positively associated with the risk of DM2 in women but not in men (Nanri et al. 2010). In a study conducted in the USA, it was reported that the replacement of WR with BR each day reduces the risk of type 2 diabetes by 16% (Sun et al. 2010). BR has glucose-lowering effects in normal and diabetic subjects (Panlasigui and Thompson (2006). BR was also associated with a lower risk of DM2 (Shimabukuro et al. (2014). In contrast, some studies showed an inverse association between the risk of diabetes and WR consumption (Dong et al. 2015; Yu et al. 2011). These reports thus suggest that WR impacts positively on the manifestation of DM2 while BR impacts negatively since the former increases the risk of diabetes whereas the latter decreases it.

Several conceivable reasonings are possible to explain why consumers of BR remain at lower risk for DM2. In general, rice is considered to be a high glycemic index (GI) food but varies depending on the type and differences in their degree of milling. Reports show that the GI of rice ranges from 48-93 (Boers, Seijen Ten Hoorn, and Mela 2015). The values of low, medium and high GI foods are $\leq$55, ~56-69, and 70-100, respectively. The average GI for BR is $\leq$ 55 whereas that for WR is $\geq$64 (Sun et al. 2010). Foods with a high GI increase the risk of type 2 diabetes and deteriorate the condition further, while an opposite effect is indicated for those with a low GI (Hodge et al. 2004)· Thus, a low GI of BR might be the reason behind its hypoglycemic and anti-diabetic effects when compared with that of WR. Foods with a lower GI, like BR, are digested more slowly leading to a "slower and steadier change in the blood sugar levels. This may also be related to the increased contents of resistant starch and fiber contents in the BR. From this point of view, the fiber content was highest in UHHPBR suggesting that it has a better effect than either BR or WR.

In addition to a lower GI value than WR, BR also contains Mg in high amounts that is stripped off during the refining process of WR (Table 2). Levels of Mg in the plasma have a significant impact on the development of DM2 in the general population (Kao et al. 1999). This is further supported by the fact that the concentration of Mg is consistently reduced in the subjects with DM2 when compared to their non-diabetic counterparts (Resnick et al. 1993). Although the mechanism has not been clearly understood, a deficit of ATP may help to understand the decrease in cellular Mg observed in patients suffering from DM2 (Barbagallo, Dominguez, and Resnick 2007). Magnesium is a mineral nutrient indispensable for life. What we call 'ATP' actually exists in the cells in the form of the Mg-ATP complex, demonstrating that Mg is responsible for the stability of all polyphosphate compounds in the cells. Consequently, a decrease in the cellular Mg^{2+} will impair the formation of the Mg-ATP complex. We thus consider that an increased concentration of Mg in BR is also attributable its antidiabetic actions. The level of Mg in UHHPBR was over 5 times greater than that of WR, indicating that it is likely to affect the diabetic state significantly.

4.3. Effects of UHHPBR, BR and WR on hypertension

Hypertension, an indicator of cardiovascular diseases, is the foremost cause of morbidity and death, and a positively preventable disease. Multiple tactics could be employed for the control, prevention and treatment of hypertension. Animal studies, epidemiologic studies, meta-analyses and randomized controlled trials have demonstrated that consumption of sodium, cholesterol, saturated fats, alcohol, and cigarette smoking are related to the occurrence of hypertension, while potassium, magnesium and fiber play a significant role in its prevention (Bazzano et al. 2013). Therefore, besides drugs, many research endeavors are being undertaken for the detection of bioactive components, particularly in the staple foods, that can contribute to decreasing the risk and/or prevention of CVDs. The initiatives to encourage people to eat the healthier BR instead of the traditional WR is one such approach that can be employed to reduce the risk of hypertension. BR significantly lowers blood pressure (Okada et al. 2000) in rats. Kawakami et al. (2018) reported that, in spontaneously hypertensive rats, the systolic blood pressure (SBP) decreased by 15 mmHg 12 weeks after consumption of BR, but not the diastolic blood pressure (DBP). Oral administration of pre-germinated BR for 8 weeks decreased the SBP by 50 mmHg (Ebizuka, Ihara, and Arita (2009), indicating a strong antihypertensive action of the germinated BR.

Numerous studies have also reported an anti-hypertensive effect of BR on the spontaneously hypertensive rats (SHRs) (Choi et al. 2006; Yasui et al. 2004). In the studies with Chinese hyperlipidemic patients, consumption of germinated BR reduced both the SBP and DBP (Geng et al. 2016). Jung, Cho, and Chae (2018) reported a reduction in the blood pressure of hospitalized Korean hypertensive patients after serving them with BR. Whole-grain diets containing BR also reduced the blood pressure in mildly hypercholesterolemic men and women (Behall, Scholfield, and Hallfrisch 2006). Sugiyama et al. (2008) reported that BR vinegar with a high concentration of GABA is useful for controlling the blood pressure in mild hypertensive subjects without any adverse effects. The molecular mechanism by which BR reduces blood pressure is still far from clear. Utsunomiya et al. (2011) reported that the extract prepared from the sub-aleurone layers of the bran of BR reduces high blood pressure by inhibiting the binding of angiotensin-II to its receptors and/or by interfering with the signals involved in the elevation of intracellular $Ca2^{+}$ ($[Ca2^{+}]_i$) of the vascular smooth muscle cells. Some studies also reported that the mode of action of the BR extract is similar to the most commonly prescribed drugs like the angiotensin-1 converting enzyme (ACE) inhibitors for decreasing the blood pressures (Chen et al. 2007; Nishibori et al. 2013).

The antihypertensive effect of germinated BR has also been attributed to its abundant GABA content. The mechanism of action of GABA on blood pressure is more complex than perceived, and has not yet been fully elucidated. The blood-brain barrier (BBB) restricts the permeation of GABA into the brain (Kuriyama and Sze 1971). This was consistent with the fact that the concentration of GABA administered via an intravascular (*i.v*) injection did not change (Tsukada et al. 1960). GABA can modulate cardiovascular functions by acting not only within the central nervous system (Gillis et al. 1980) but also in the peripheral tissues (DeFeudis et al. 1981). GABA also modulates the vascular tone by suppressing the release of sympathetic noradrenaline in the isolated rabbit ear artery and rat kidney, and in the mesenteric arterial bed via presynaptic GABA-B receptors (Fujimura et al. 1999). Therefore, the manifestation of antihypertensive effects following a direct administration of GABA in animals (Takahashi et al. 1955) and humans (Elliott and Hobbiger 1959) or after dietary administration of GABA-rich BR (Kawakami et al. 2018) and GABA-added WR (Nishimura et al. 2016) seemed to mediate its actions on the peripheral tissues and presumably on the blood vessels and related autonomic neurocircuitry system.

Among other components of the BR, ferulic acid was shown to lower the blood pressure in streptozotocin-induced diabetic rats (Suzuki et al. 2002) and spontaneously hypertensive rats (Balasubashini, Rukkumani, and Menon 2003). Dietary fiber decreases the blood pressure indirectly by reducing the levels of blood cholesterol (in fact, by increasing the levels of excretory cholesterol). γ-oryzanol, because of its antioxidant (Xu and Godber 1999), anti-hypercholesterolemic (Rong, Ausman, and Nicolosi 1997) or anti-platelet aggregation activity (Seetharamaiah, Krishnakantha, and Chandrasekhara 1990), has also been reported to exhibit antihypertensive effects. Due to higher levels of GABA or γ-oryzanol in UHHPBR, it is believed to act as a better antihypertensive staple food item than WR. Besides these, the increased levels of K and Mg in UHHPBR or BR may contribute, at least partially, to the reduction of hypertension, as there is an emerging recognition for potassium (Geleijnse et al. 2003) and magnesium (Jee et al. 2002) as a potential agents demonstrating antihypertensive effects.

4.4. Effects of UHHPBR on osteoporosis

Osteoporosis is a condition in which the bones become porous, thereby presenting a risk of wrist, hip and spine fractures. The bone has both, a structural function providing support for mobility, and a storehouse function which is called-upon in times of need by the body for a supply of Ca and P. This called-upon process is referred to as bone resorption as opposed to bone mineralization, the process by which the bony skeleton deposits minerals (Ca/P) from the body. Bone formation outpaces resorption until the peak bone mass is reached, typically by the late 20 s. After that time, aging accelerates the resorption and decelerates the deposition making the bones porous and weak and leads to the most common bone disorder, osteoporosis and subsequent fractures (Figure 4).

Osteoporosis has been a serious public health concern. Over 200 million people worldwide suffer from osteoporosis (Cooper, Campion, and Melton 1992). Approximately 30% of all postmenopausal women have osteoporosis in the USA and Europe (Melton et al. 1992). There are an estimated 12,800,000 patients with osteoporosis in Japan, which has become a great social burden, and since one-third of the Japanese population would be classified into the elderly group by 2030, the prevention of osteoporosis has become an urgent issue (Ding et al. 2008). There is a scarcity of reports on the effects of BR or WR on human osteoporosis. Very recently, we (Hashimoto et al. 2017, Matsuzaki et al. 2019) reported that the long-term dietary intake of UHHPBR exerts a beneficial effect on the bone mineral density (BMD) of the Japanese elderly population. Though the mechanism of this effect was not clear, however, the improvement of BMD in UHHPBR-intake group was attributed to the high concentrations of Ca, P, Mg, K, Fe, and other functional ingredients, namely polyphenols, vitamins B1, B6, and niacin, fibers, GABA and ferulic acid. Other mechanisms for the improvement of BMD have also been described. Postmenopausal osteoporosis, the most common type of age-related osteoporosis in women, is associated with the ovarian estrogen hormone deficiency (Raisz 2005). Among many functional ingredients, the content of ferulic acid content in BR has been ascribed to significantly increase the bone mineral density. Sassa et al. (2003) reported that ferulic acid-induced bone formation in ovariectomized rat models is mediated by an estrogen-independent mechanism indicating that ferulic acid promotes bone remodeling by predominantly affecting the osteoblastic phase that is responsible for the mineralization of bones besides inhibiting the bone resorption by osteoclasts. Kang et al. (2015) examined the preventive effect on osteoporosis in ovariectomized mice by feeding them BR rich and low in phytate contents. The results suggested that phytic acid regulates osteoporosis in in vivo animal models.

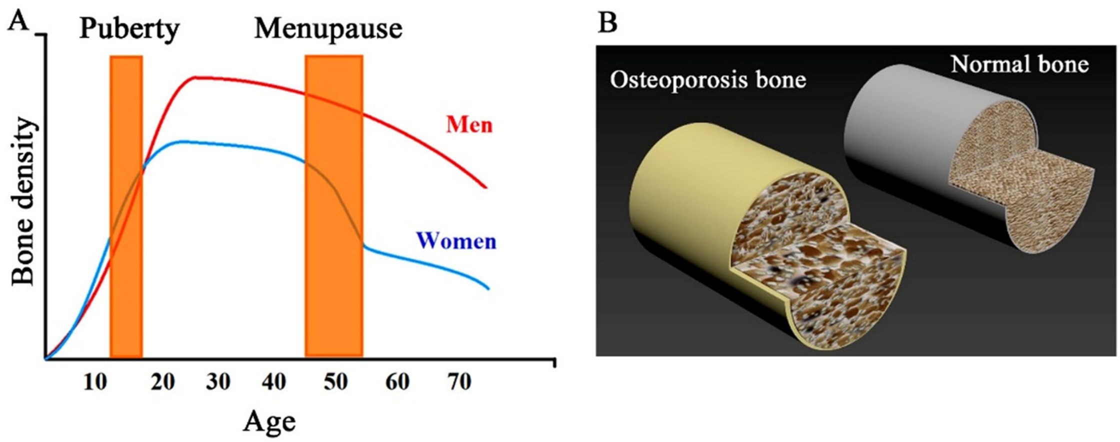

Figure 4. Scheme of the general characteristics of osteoporosis. Osteoporosis is a systematic skeletal disorder characterized by low bone mass (A), and worsening of bone architecture (B). Osteoporosis increases with population aging. It can result in disability.
Women gain their peak bone mineralization density (BMD) during the period surrounding menarche, the hallmark of puberty. It is due to higher circulating estrogens both during and after menarche. Menopause declines the levels of estrogens, and the prevalence of osteoporosis increases concomitantly. In men, the BMD still is comparatively higher than women. Osteocytes keep connections with osteoblasts, osteoclasts, and other osteocytes through an extensive canalicular network within the bone matrix. However, osteoporosis causes an excessive bone resorption, which ultimately leads to a loss of bone strength, a decrease in bone mass, and a worsening in bone quality, leading to an increased risk of fracture Osteoporosis causes a micro-architectural deterioration of bone matrix.

However, the effect of consuming phytic acid is still controversial. Addison and McKee (2010) reported that phytic acid obstructs mineralization during osteoblastogenesis, demonstrating the detrimental effect of phytic acid. Arriero et al. (2012), however, reported that phytic acid inhibits osteoclastogenesis. Lopez-Gonzalez et al. (2013) also showed that phytate consumption prevents the development of osteoporosis in women, suggesting the beneficial effect on bone formation.

Interestingly, BMD-independent mechanisms of osteoporosis might also be involved in UHHPBR-induced protection of bones. The molecules of the bone-matrix, including collagen-cross linking, are very important for the strength and mineralization of the bone. With aging, the collagen content in human bone reaches to a maximum during adolescence and gradually decreases thereafter (Saito 1999). Thus, age-induced weakening in collagen cross-links may be correlated to an increase in the bone fragility with aging (Brennan 1989). Moreover, vitamin B6 deficiencies and a decrease in the BMD are highly correlated (Fujii, Kajiwara, and Kurosu 1979). The B6 content in the bone was approximately 5 to 9-folds higher in UHHPBR or BR (Table 2) as compared to that in WR. Several in vitro studies or animal models have also demonstrated that oxidative stress has an important impact on the functioning of osteoclasts (Zhang et al. 2006; Ha, Lee, and Kim 2006)' suggesting that anti-oxidant therapy may play potential roles in inhibiting the oxidative stress-based mechanisms of this disorder. The speculation is further supported by the report that ferulic acid increased the BMD in an ovariectomized rat, concurrent with increases in the levels of estradiol in the blood and activation of the alkaline phosphatase activity (Sassa et al. 2003). Besides, an increased level of antioxidant phenolics, UHHPBR or BR individually also had higher levels of ferulic acid with the ability to increase blood estradiol and activate the alkaline phosphatase in an ovariectomized rat (Nakajima 2004; Perluigi et al. 2006). Consequently, BR may attenuate the decrease in the BMD (Sassa et al. 2003)[7]. Finally, UHHPBR used in our human intervention study (Hashimoto et al. 2017) did not have any adverse side effects on the participants. Long-term oral consumption of UHHPBR may have beneficial effects in mitigating the decline of the BMD and may attenuate osteoporosis in the elderly. Further clinical studies will be required to define the exact role of UHHPBR in the mechanism of bone metabolism and evaluate its estrogen-like behavior in postmenopausal women.

4.5. Effects of UHHPBR on cognitive functions

AD is the most common cause of dementia among the elderly population (Wilson et al. 2012). It is pathologically characterized by the presence of amyloid beta (Aβ) peptides in the neuritic plaques and neurofibrillary tangles. The majority of Aβ peptides seen in the brains of individuals with AD are in the form of tiny fragments like A$\beta_{25\text{-}35}$, A$\beta_{1\text{-}40}$ and A$\beta_{1\text{-}42}$, and they are associated with neurotoxicity and impairments in learning and memory in the AD model rats (Hashimoto et al. 2002, 2005a; Mamun et al. 2014), mice (Chen, Wright, and Barnes 1996) and human patients (Wang et al. 2017).

BR has drawn huge attention to its ability to yield health benefits and prevent or protect the elderly people or AD patients from dementia by incorporating it into the daily diet as a staple food. When AD model mice infused with the A$\beta_{25\text{-}35}$ peptide were fed with germinated BR, they demonstrated a higher learning ability, as evaluated in the Morris water maze task, than the cornstarch-fed mice (Mamiya et al. 2004). This beneficial effect of BR was attributed to its high content of GABA, thus suggesting that BR can help improve the behavioral deficits of AD-like symptoms. The authors speculated that GABA inhibited the calcineurin-mediated long-term depression (LTD), and simultaneously stimulated the long-term potentiation (LTP) via N-methyl-D-aspartate-receptor (NMDAR)-mediated phosphorylation of the CaMKIIa. LTD and long-term potentiation (LTP) are two antagonistic neural attributes of memory creation where the former inhibits and the later stimulates. Yan et al. (2001) reported that an increased content of γ-oryzanol, a ferulic acid ester, in the BR ameliorates the memory deficits of the $A\beta_{1\text{-}2}$–infused AD model mice. Their speculation was consistent with other reports where a direct intraperitoneal administration of ferulic acid to rats inhibited memory deficits of rats induced by scopolamine or cycloheximide (Hiraga et al. 1993; Hsieh et al. 2002). Consistent with these animal studies, in SK-N-SH cells, the extract of germinated BR also decreased the in vitro neurotoxicity induced by $A\beta_{1\text{-}2}$ by inhibiting apoptosis and oxidative stress (Soi-Ampornkul et al. 2012) and $A\beta$ peptide-forming enzymes such as BACE1 and BACE2, as well as oxidative stress in human SH-SY5Y cells (Azmi et al. 2015).

Recently, we (Okuda et al. 2018) have reported the effects of UHHPBR consumption on cognitive dysfunction in senescence-accelerated mouse prone 8 (SAMP8) exhibiting an age-related decline in learning and memory. UHHPBR ameliorated cognitive dysfunctions of the SAMP8 mice and the ameliorative effect was attributed to UHHPBR-induced reduction in the burdens of $A\beta_{1\text{-}42}$ from their brains, whereas, the polished WR did not improve their cognitive dysfunctions. Previously, Hashimoto et al. (2002, 2005a, 2005b) reported that $A\beta$-infusion increases the levels of lipid peroxidation, ROS, and histone-associated DNA fragments in the corticohippocampal regions of the brain indicating that $A\beta$-induced oxidative stress is one of the mechanisms by which $A\beta$ confers neurotoxicity (Hashimoto et al. 2002; Hossain et al. 2009). α-tocopherol inhibits the neuronal cell death and lipid peroxidation induced by $A\beta_{1\text{-}42}$ (Schubert et al. 1995). Ferulic acid also demonstrates free radical scavenging activity and reduces peroxidative damage (Zheng and Zhang 1997). All these reports suggest that BR may have ameliorated the cognitive ability of the rats/mice by inhibiting the $A\beta$-induced oxidative stress and neurotoxicity in the brains of AD model animals or cells and hence, is likely to provide a beneficial effect to the AD patients.

Despite all these positive impacts of BR on brain cognition, reports of its effects on the cognitive ability of human elderly subjects are not available. Very recently, we (Kuroda et al. 2019) investigated the effects of dietary UHHPBR for 24 months on the cognitive functions and mental health conditions in the Japanese elderly subjects. At baseline and after 24 months, cognitive assessments were carried out using the Revised Hasegawa's Dementia Scale (HDS-R) (Imai and Hasegawa 1994), Mini-Mental State Examination (MMSE) (Folstein, Folstein, and McHugh 1975), Frontal Assessment Battery (FAB) (Dubois et al. 2000), and the Cognitive Assessment for Dementia (CADi-iPad version) (Onoda et al. 2013). Mental health conditions were tested using the Apathy Evaluation Scale (Okada et al. 1998) and the Zung Self-Rating Depression Scale (Zung 1965) and their biochemical parameters in the serum were determined. From baseline to month 24, the mean change in the FAB-subitem 1 score was found to be significantly higher in UHHPBR-intake group as compared to WR-intake group. Furthermore, apathy scores had lessened, and plasma epinephrine levels were found to be augmented in UHHPBR-intake group. These results indicate that a 2-year oral consumption of UHHPBR increased the 'conceptualization' abilities in elderly Japanese people and improved their conditions of apathy suggesting a protective effect of UHHPBR against age-related decline in the brain cognitive ability and motivation.

Although the mechanism by which the consumption of UHHPBR improves cognitive function in the elderly remains to be elucidated, we speculate that these results emerged due to improvements in their working memory, which depends on the function of the dorsolateral prefrontal cortex. Neuroimaging studies on apathy and AD suggest that the neurocircuitry that links the specified cortical regions, basal ganglia and thalamus plays an important role in decision-making, executive functions and motivation (Stella et al. 2014). Mori et al. (2014) reported that the deposition of $A\beta$ correlates positively with apathy, poor diet and general fatigue. Sleep deprivation has a positive impact on the onset and duration of apathy (Ishizaki and Mimura 2011). Therefore, a decrease in the apathy scores in UHHPBR-intake group may reflect a possible role of UHHPBR in reducing the amyloid burden in the elderly population. Moreover, the catecholaminergic systems are key modulators of motivated behaviors. It might be recalled that the hypothalamic-pituitary-adrenal (HPA) axis plays a central role in the manifestation of stress-related homeostasis and emotions such as apathy and depression (Urlich-Lai and Herman 2009; Smith and Vale 2006), suggesting that the improvement in motivated behavior may be associated with the catecholamine levels in the serum. Mamiya et al. (2007) also reported that germinated BR attenuates depression-like behavior in mice. In our study, the mean change in the apathy scores from baseline to month 24 (Kuroda et al. 2019) showed a mild to moderate inverse correlation with the mean change in the serum epinephrine levels. These results suggest that the long-term dietary intake of UHHPBR may improve apathy scores by modifying the activity of behavior-specific regions of the HPA axis which regulate apathy and related depression.

BR is enriched with nutrients crucial for the maintenance of cognitive function and potential neuroprotective benefits such as GABA, ferulic acid, tocopherols, tocotrienols, γ-oryzanol, B6, B12, and folic acid (Patil and Khan 2011). BR enriched with nutrients, particularly antioxidants, can withstand the neuronal loss caused by ageing. More fascinatingly, the concentration of GABA in UHHPBR was higher by approximately 4-5-folds compared to that in WR.

Clinical evidence also implicates the roles of GABA in the inhibition of anxiety (Krystal et al. 2002), depression (Frazer 1997) and mental relaxation (Cryan and Kaupmann 2005). Yet, the roles of GABA need to be clarified as supporting (Boonstra et al. 2015; Takanaga et al. 2001), as well as conflicting (see GABA section) findings on the penetration of GABA in the CNS have emerged. Whether the effect of GABA in modulating and decreasing the mesenteric and systemic blood pressures is direct or indirect requires investigation, as also does its role in the development of depression in elderly subjects. Humans were once adapted to the BR but switched to WR due to the grace of the modern technology of rice processing in the present day. Therefore, it is also very important to know whether BR, along with all its nutritious chemicals, turns on a genetic switch in the human body for optimum beneficial effects, and this needs to be investigated extensively. In summary, the levels of GABA were significantly higher in UHHPBR than WR. Daily intake of UHHPBR for 24 months increased the cognitive ability for conceptualization of objects and decreased the apathy scores such that the emotions of 'no-feeling' or 'hopelessness', two important parameters resulting from depression and lowered brain cognition that should be prevented during age-related decline in the elderly, were reduced. Thus, UHHPBR could prove beneficial in protecting against neurodegenerative diseases like AD.

5.0 Conclusion

Compared to WR, BR had a higher content of almost all nutrients. This enabled the BR to afford more adequate nutrition and health benefits on hyperlipidemia, diabetes and hypertension than those of the WR. However, due to nutty taste and difficulties in cooking, the consumption of BR is not noteworthy. The non-thermal ultra-high hydrostatic pressure (UHHP)-treated brown rice (UHHPBR), on the other hand, retained a better *nutritional profile and* displayed a superior quality with regards to texture, appearance and taste *as compared to that of the BR*. Furthermore, UHHPBR increased bone mineralization, cognitive ability, concurrently decreased the apathy-related anxiety and depression, typical characteristics of neurodegenerative disorders, prevalent in the elderly population and in people with AD. The more beneficial effects of UHHPBR correlated with the enhanced bio-accessibility of diverse nutrient contents of UHHPBR, like vitamins, minerals, antioxidants, γ-oryzanol, and GABA. Finally, our results indicate that the UHHP treatment could represent a promising technology to be employed for rice processing; and UHHPBR could be ideal staple food with protective benefits against the risks of hyperlipidemia, hypertension, diabetes, osteoporosis, age-related cognitive decline and apathy. However, further research is essential to find out the exact molecular mechanisms underlying the beneficial effects of UHHPBR.

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Disclosure statement

The authors have declared that there is no conflict of interest.

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