REVIEW

Functional Profiling and Future Research Direction of Rice Bran Oil in Bangladesh

Afroza Sultana¹, Mohammad Ali Zinnah², Habibul Bai Shozib³, Zakir Hossain Howlader², and Md Alauddin^{1*}

¹ Department of Nutrition and Food Technology, Jashore University of Science and Technology, Jashore-7408, BANGLADESH

² Department of Biochemistry and Molecular Biology, University of Dhaka, Dhaka-1000, BANGLADESH

³ Bangladesh Rice Research Institute (BRRI), BANGLADESH

Abstract: Rice bran oil (RBO) has been demonstrated to affect complex malfunctioned conditions such as oxidative stress, hyperlipidemia, hyperglycemia, hypertension, inflammation, abnormal cell growth (cancer), ulceration, immune and cognitive modulation. This unique effect of RBO is due to the presence of well-balanced fatty acid composition and several bioactive compounds, γ -oryzanol (cycloartenyl ferulate, 24-methylenecycloartanyl ferulate, campesterol ferulate, and β -sitosterol ferulate), vitamin E (tocopherol and tocotrienol), phytosterols (β -sitosterol, campesterol and stigmasterol) and other nutrients. The RBO composition of bioactive compounds varied geographically, thus the clear-cut mechanisms of action on complex disease cascades are still required. This review article summarized the RBO compositional profiling and compared it with other edible oils. This article also summarized Bangladesh RBO profiling and their proposed mechanism of action as well as the first line of defense in the prevention, management, and control of complex disease conditions. This review indicates how Bangladesh RBO increase their opportunity to be functional food for 21st century's ailment.

Key words: rice bran oil (RBO), composition, Bangladesh RBO, antioxidant, anti-inflammatory, anticancer and anti-ulcerogenic

1 Introduction

A short flashback of the history of rice grown in the world, domesticated rice species were grown worldwide among them *Oryza sativa* and *Oryza glaberrima* is called Asian rice and African rice respectively. Asian cultivars extensively cultivated *Oryza sativa Japonica* and *Oryza sativa Indica* is the history of about 13000 years ago¹. The species *Oryza sativa Indica* comes from the crosses between *Oryza sativa Japonica* and local wild rice. The genetic evolution, geographical diversity, land quality, different agronomic practices, and environmental conditions may cause nutritional variation among global rice. The composition of whole rice grain has been divided into several compartments such as edible part (70%), non-edible hull (20%), bran (7%–8.5%), and rudiment (2%–3%)². Rice bran oil (RBO), extracted from rice bran, is gained popularity as a healthy cooking oil in Japan, India, Indonesia, Korea, Thailand, China, Vietnam, and Bangladesh. The

RBO is obtained from rice bran through different extraction processes, among them, solvent extraction (using hexane) and mechanical pressing (cold pressing) is the most popular and conventional method for commercial extraction³. The percentage of yield and nutritional value of RBO may vary according to the chemical composition of bran, rice variety, treatment of the grain before milling, the technology of milling, degree of milling, and the downstream

Abbreviations: RBO; Rice bran oil, γ -oryzanol; Gamma oryzanol, CLA; Conjugated linoleic acid, SFA; saturated fatty acid, MUFA; monounsaturated fatty acid, PUFA; polyunsaturated fatty acid, α ; alpha, β ; beta, γ ; gamma, δ ; delta, FFA; free fatty acids, P-AMPK; phosphorylation of AMP-activated protein kinase, PPAR- γ ; peroxisome proliferator-activated receptor-gamma, NF- κ B; nuclear transcription factor-kappa B, TNF- α ; tumor necrosis factor-alpha, iNOS; inducible nitric oxide synthase NO; nitric oxide, COX-2; cyclooxygenase-2, mPGES-1; microsomal prostaglandin E synthase-1

*Correspondence to: Md. Alauddin, Department of Nutrition and Food Technology Jashore University of Science and Technology, Jashore-7408. BANGLADESH

E-mail: mdalauddin_nft@just.edu.bd, mdalauddin1181@gmail.com ORCID ID: <https://orcid.org/0000-0001-8850-8025>

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processing of bran^{4, 5}). This review article thoroughly discussed the functional profiling of RBO and the future research direction of RBO in Bangladesh.

2 Components and Bioactivities of Rice Bran Oil (RBO)

The oil content of rice bran depends on various factors. For instance, glutinous rice contains more oil than non-glutinous rice, and parboiled rice contains higher oil content than non-parboiled rice because the oil content (lipid droplets) shifted to the bran layer from the aleurone layer during parboiling. The oil content of rice bran varies between 10% and 23% depending on extraction methods⁴). Different organizations, associations, institutes, and society have endorsed that RBO is a healthy oil because of its balanced fatty acid composition in the saponifiable compartment (0.6:1.1:1) saturated fatty acid (SFA): monounsaturated fatty acid (MUFA): polyunsaturated fatty acid (PUFA) respectively, and other bioactive components present in the unsaponifiable fraction of RBO^{6, 7}). RBO is a rich source of bioactive compounds, especially γ -oryzanol (which is rarely found in other edible oils). However, the content of bioactive compounds depends on the refining process of RBO. In previous studies, it has been observed that RBO contains 1.8%–2.2% γ -oryzanol, 0.04% α -tocopherol, and a lesser amount γ -tocopherol, 0.07% γ -tocotrienol. RBO also contains squalene and phytosterols, including β -sitosterol, campesterol, stigmasterol, and isofucosterol⁸). The fatty acid composition of RBO surprisingly is enabled to reduce body total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and apolipoprotein B (ApoB), which was observed in a previous

study⁹).

The antilipidemic effect of RBO has been observed by its PUFA because the PUFA is claimed to have anti obese, antidiabetic, and antihypertensive properties^{10, 11}). The bioactive compound γ -oryzanol have a similar antilipidemic effect but there is no significant difference between a low and high dose of γ -oryzanol for atherosclerotic condition¹²). RBO can reduce atherosclerotic conditions because it has not only γ -oryzanol but also other micronutrients like tocopherol, tocotrienol, and phytosterols like campesterol, stigmasterol, and beta-sitosterol have the synergistic effect with γ -oryzanol^{12, 13}). The macro components (various lipid compounds) and micronutrients (γ -oryzanol, vitamin E, phytosterols, squalene, policosanol) of RBO are effective against hyperlipidemia, hypertension, hyperglycemia, cancer, oxidation, inflammation, insomnia, and immunomodulation that are summarized in Fig. 1.

The fatty acid content of RBO greatly varies with their rice bran genotype and environmental factors such as temperature. Generally, RBO contains 19%–35% SFA including palmitic acid, myristic acid, stearic acid, arachidic acid, etc., and 55%–87% unsaturated fatty acids (UFA) such as oleic acid, linoleic acid, and linolenic acid, which are greatly affected by the variety and agronomic conditions. For example, glutinous rice contains more oil as well as more SFA than non-glutinous. The fat composition is also affected by downstream processing technology. For instance, a large portion of SFA than unsaturated ones are removed during the RBO dewaxing process. The triacylglycerides (TAG) of RBO vary between 3.4% and 49.9% are triunsaturated. The free fatty acids (FFA) come from TAG by the action of lipase, which can cause a bad flavor of RBO. The physical and chemical (ohmic heat and ethanol) treatment of rice bran before RBO processing limited the

Fig. 1 The major bioactive components of rice bran oil (RBO) and their therapeutic effects.

Table 1 Macromolecule and micromolecule composition of RBO (adopted from reference 2,17-20).

Name of components	Percentage (%)
Gama oryzanol	1.8-2.2
Vitamin A	0.001-0.008
Tocopherol	0.04
Tocotrinol	0.07
Phytosterols	0.8-1.3
Triacylglycerol	81-84
Diacylglycerol	2-3
Monoacylglycerol	1-2
Free fatty acid	2-6
Wax	3-4
Phospholipid	1-2
Saturated fatty acid	18.4-25.5
Mono unsaturated fatty acid	38.4-42.3
Poly saturated fatty acid	33.6-39.2

FFA between 2% and 5% without hampering the other bioactive compounds^{14, 15}. Ten components of γ -oryzanol have been isolated and identified, among them four principal components, cycloartenyl ferulate (11.40%), 24-methylenecycloartenyl ferulate (50.20%), campesteryl ferulate (24%), and beta-sitosterol ferulate (14.40%) were found in the Bangladeshi rice bran variety¹⁶. Other bioactive components (tocopherol and tocotrienol each have four major types of categories) comprise 0.1%-0.2% and phytosterols (primarily β -sitosterol, campesterol, stigmastrol) 1.5%-2.0% respectively. The most desirable RBO accounts for a thin and clear appearance, high bioactive components, and lower level of FFA¹⁷. The macro and micro molecule compositions are summarized in Table 1^{2, 17-20}.

3 Properties of Rice Bran Oils (RBO) with Other Edible Oils

Comparison of RBO in contrast to some physical and chemical aspects of other edible oils that are summarized in Table 2. This comparison has pointed out several cases, making RBO in a remarkably better position than other edible oils. RBO is healthier than soybean oil, palm oil, mustard oil, and olive oil. It is important to pay attention to the smoke points of various fats, as described fats are no longer suitable for consumption after they exceed the smoke point and begin to break down. The oils, that are listed in Table 2, are preferably used for cooking, frying, baking, salads, and seasoning. RBO is a very clean and pleasant-tasting oil with attractive color and a mild taste.

Due to its very high smoke point ($\sim 234^{\circ}\text{C}$) and flashpoint ($\sim 350^{\circ}\text{C}$), it is very stable and has almost zero degradation and polymerization during cooking. The high smoke and special bioactive compound of RBO make it an ideal oil for all types of cooking, ranging from stewing to deep-frying. Considering this point, rice bran oil may be a better substitute. The attractive color of RBO ranging from yellow-green to dark brown depends on certain pigmented substances such as carotenoid, lutein, and gum. The refining process of RBO removes the unexpected substance and can produce the color of RBO lighter, even though the refining process cannot completely remove the pigmented substance like other vegetable oils. On the other hand, freshly prepared soybean oil is lighter. However, the color of the oil sometimes darkens during storage due to its oxidation. Olive oil naturally has a variety of colors, ranging from light yellow to dark gold due to its pigmented substance content. Lower peroxide value (PV) describes the freshness of the lipid matrix during the storage of soybean oil and RBO. A high peroxide value (PV) is an indicator of an oxidation state. The more oxidized oil produces higher PV, which indicates the lower freshness of the oil matrix during storage²¹. Density is an important factor that influences oil absorption as it affects the drainage rate after frying and also the mass transfer rate during the cooling stage of frying²². The oil density ranging from 0.91 to 0.93 (g/L) depends on the nature of the oil at a temperature of 15°C to 25°C comparing it with a water density of 1.00 g/mL. The RBO is said to be better for cooking due to its density smaller than other vegetable oils. The iodine value describes the unsaturation of oil, and the average amount of double bonds present in the oil. A decrease in the number of double bonds indicates oil is oxidized during storage time. Oxidative stability is another parameter for oil quality. A study of vegetable oil after frying food showed that soybean oil significantly reduced the iodine value after frying and storage of the oil. This indicates that the fat oxidation was relatively high for soybean oil compared to other vegetable oils such as palm oil and peanut oil. The frying and storage conditions have a significant impact on oil quality²³. The RBO has a higher induction time due to its antioxidant properties. The phenolic compounds are very important to protect PUFA present in RBO. Thus, the high quantity of phenolic compounds (ferulic acid, erucic acid, cinnamic acid, dimethyl sterol, monomethyl sterol) is responsible for the oxidation stability of RBO. Another cause of the oxidation stability of RBO is the quantity of vitamin E which exists as a mixture of four distinct types of monophenols (such as tocopherols) contain four homologues (Alpha, Beta, Gamma, Delta) of tocopherols and four diverse types of tocotrienols (Alpha, Beta, Gamma, Delta) having three double bonds on the side chain with -tocopherol serving as the methylene group. One of the studies provides an excellent overview of the percentages of differ-

Table 2 Comparison of RBO on various properties with other edible oil (ND = not detected; NA = not applicable; Tr = trace).

Factors	Rice bran oil	Soybean oil	Palm oil	Olive oil	Mustard oil	Remarks	Reference
Appearance	Greenish yellow to dark brown	Pale light-coloured	Light yellow to orange-red	Pale yellow to green	Reddish-brown or amber	Attractive colour	(28)
Smoke point (°C)	232	234	235	199-243	254	Increase frying and flavor	(28, 29)
Melting point (°C)	24.0-28.0	-16.0	24.0-35.0	-6.00	14.4	A higher melting point decreases the vapour pressure	(28)
Specific gravity at 25°C	0.90	0.91	0.92	0.90	0.91	Increases stability and good for health	(29)
Iodine value (g/100 g)	90.0-100	120-139	49.0-55.0	75.0-94.0	8.10	Degree of unsaturation	(28, 29)
Peroxide value (meq/kg)	0.60	1.30	0.0-10.0	6.40	3.60	Indicates free fatty acids	(28)
Density (g/10 ⁶ cubic cm)	0.913-0.920	0.919 - 0.925	0.891 - 0.899	0.913 - 0.916	0.9694	Influences drainage rate after frying	(22)
Saturated fatty acid (%)	18.4 - 25.5	18.3	46.3	1.1	16.0	Increase cardiovascular disease	(30, 31)
Mono unsaturated fatty acid (%)	38.4 - 42.3	23.3	41.0	72.0	49.6	Good for health	(30, 31)
Poly unsaturated fatty acid (%)	33.6 - 39.2	58.0	11.0	12.0	36.6 - 30.0	Preventing cardiovascular disease	(30, 31)
Myristic (%)	0.40	Tr. 0.5	0.5-2.0	0.1-1.2	ND	Unhealthy	(30, 32)
Palmitic acid(%)	12.0-18.0	7.0-11.0	32.0-45.0	7.0-16	3.8-5.0	Involved crucial physiological activities	(33, 40)
Stearic (%)	1.0-3.0	2.0-6.0	2.0-7.0	1.0-3.0	2.78 ± 0.59	Heart disease accelerating factor	(33)
Linoleic acid (%)	33.1 - 37.0	55.0	10.0	3.5 - 21.0	10.0-12.0	Improves insulin sensitivity	(31)
Lignoceric acid (%)	0.2	ND	ND	1.0	0.8	Saturated, rarely found	(33)
Free fatty acid (%)	0.1	0.8	5.0	0.8	0.4	Prone to oxidation and rancidity	(34)
Oleic acid (%)	38.4 - 42.3	18.0	40.0	3.5 - 21.0	20.0-28.0	Mono Unsaturated	(31)
Omega-3 fatty acids (%)	2.2	7.3	0.3	0.7	6.0	Healthy fatty acid prevents atrophy in the brain	(35)
Omega-6 fatty acids (%)	34.4	51.5	10.1	7.5	15.0	Preventing cardiovascular disease	(35)
Erucic acid (g)	ND	NA	ND	ND	30-40	Responsible for myocardial lipodosis	(33)
Trans-fatty acid (g)	ND	0.4 - 1.5	ND	ND	0.2 - 1.0 (only refined)	Harmful for human health	(36)
γ-Oryzanol (ppm)	13,324	ND	ND	ND	ND	Only present in rice bran oil, prevent disease	(28)
Phytosterols(mg/100 g)	1891.8	355.6	150.0	288.0	Tr	Anti-lipidemic effect.	(37)
Tocotrienol (alpha) (mg/100 g)	0.8 - 13.9	ND	5.7 - 26.0	ND	2.0 - 7.5 (µg/g)	Prevent diseases	(24)
Tocopherol (beta) (mg/100 g)	0.2 - 2.5	1.0 - 1.3	ND - 0.4	ND	Tr	Antioxidant	(24, 38)
Total Phenolic compounds (mg/g)	0.9	1.5	1.8-5.1	0.0 - 0.2 (mg/mL)	0.6	Antioxidant	(39, 40)

ent tocos homologues found in the majority of popular vegetable oils, including RBO²⁴⁾. Additionally, RBO includes all of the tocotrienol categories and homologues, but the four tocotrienol forms are not detected/traced in the majority of other cooking oils, including soybean oil, olive oil, sunflower oil, sesame, and safflower (except palm oil). Even though it is commonly found in most cooking oils, but RBO contains a well amount of tocopherol and tocotrienol. Among their eight stereoisomers (alpha, beta, gamma, and delta), only two stereoisomers may be more active or more sensitive than others. They are potent antioxidants and function differently from each other due to the presence of three double bonds at the 3', 7' and 11' positions in their side chains²⁴⁾. For instance, tocotrienol has neuroprotective, antioxidant, anti-cancer, and cholesterol-lowering properties than tocopherol because tocotrienol can penetrate more effectively into tissues with saturated fat layers in the brain and liver²⁵⁾. One of the important components of RBO is phytosterol, a compound that prevents dietary cholesterol absorption, thereby reducing the body's cholesterol. The unrefined RBO contains a higher amount of phytosterol (848-1034 mg / 100 g that can lower LDL cholesterol and triacylglycerol levels but increase HDL. The RBO is a good source of linoleic and oleic fatty acids, fat-soluble vitamins, and phytosterols rather than other vegetable oils²⁶⁾. RBO contains appreciable quantities of bioactive components and has attained the status of "Heart oil" due to its cardiac-friendly chemical profile²⁷⁾. Finally, the trump card bioactive component of RBO is γ -oryzanol, a mixture of esters of ferulic acid, sterol, and triterpene. It was claimed that RBO is "The Healthiest Oil," nevertheless the nutritional profile is identical to other oils, there are just a few differences over other oils. One might be a high source of MUFA (44%), PUFA (33.6%), tocopherol, tocotrienol, and phytosterol, making it a popular cooking oil in Asia and tropical nations. The physiochemical parameters of RBO are almost similar to the widely used edible oil including soybean, palm, olive, mustard oil etc. High smoke point is an important parameter for any edible oil as it starts to break down, altering its flavor and releasing free radicals at that point. After the smoke point, a substance called acrolein makes the oil taste burnt and bitter. RBO is suitable for high-temperature frying. RBO is a unique edible oil with numerous health benefits. The presence of a very small amount of Omega-3 fatty acids (α -Linolenic acid) compared to other edible oil is the main limitation of this oil^{6, 28-39)}. However, RBO is a rich source of omega-6 (linoleic acid), which is an essential fatty acid similar to omega-3, because these are not synthesized by the human body and come from food sources. Several Countries have recommended allowances of fat consumption and set the absolute values of PUFAs including balanced intake of Omega-6 and Omega-3. RBO meets the ratio of polyunsaturated fatty acid and saturated fatty acids, linoleic acid, and α -linolenic

acid in the diet 0.8 to 1.0 and 5-10 respectively (WHO/FAO, 2003). RBO is also a source of bioactive compounds such as flavonoid, sterol, and tocopherol are shown in Table 2. These substances are antioxidants, therefore inhibit the formation of free radicals, preventing chronic diseases. The presence of a huge amount of free phytosterols including gamma oryzanol, β -Sitosterol, campesterol, stigmasterol, isofucosterol in RBO makes this oil unique for preventing cholesterol levels. Thus, the comparison of RBO with other edible oil has pointed out a remarkably advantageous position than other edible oil.

4 Rice Bran Oil Profiling and Future Research Directions in Bangladesh

Flashback of rice bran oil history in Bangladesh, latter half of the mid-1970 century. Nobody could ever think that rice could be a source of oil for everyday consumption or would be worthwhile to use for practical purposes. At that time, people were accustomed to some of the oil crops such as mustard, sesame, and linseed grown locally, but this scenario was replaced by the cheap soybean and palm oil imported from western countries and Malaysia, respectively. The first RBO manufacturing company was established in the 1980s. Unfortunately, their production of RBO came to a halt for unknown reasons. Since then, 35 years have passed. Now 20 companies have licensed for RBO production in Bangladesh. Only 7 are in continuous production and 3 companies have completely stopped RBO production. Bangladesh produces 3.6 million tons (MT) of rice bran annually. Average RBO production in Bangladesh accounts for 250-300 tones daily based on 6.5 kg of rice bran being used to produce 1.0 liter of RBO⁴⁰⁾. The requirement for edible oil consumption is about 15 MT for the 160 million population in Bangladesh, according to 9.7 g/capita/annum. Our existing resources of edible oil such as master seeds, sesame seeds, and groundnuts provide about 2.1 MT. Therefore, the remaining requirement of 13 MT comes from abroad, western countries, and Malaysia. Soybean and palm oil is imported by drainage of our hard-earn foreign currency to meet our demand. Currently, RBO is produced by our existing auto rice mill about 0.15 MT, if we use our potential facilities for RBO production we can produce about 0.75 MT. Unless initiatives are taken to increase the domestic production of edible rice bran oil from domestic rice bran, there will be more drainage of foreign currency to meet the increased demand in our sustainable development goal 2030⁴¹⁻⁴³⁾. Rice bran oil from different varieties in Bangladesh (BR-11, BRRI dhan-28, BRRI dhan-29, BRRI-48, and BRRI dhan-49 have been examined and were found that saturated fatty acid 16-21% (mostly palmitic acid 14-18%), monounsaturated fatty acid 39-49% (mostly oleic acid 49%) and polyunsaturated

fatty acid 33-38% (mostly linoleic acid 32-37%). Constitutional variations were observed in the variety of sources of RBO. Differentiation of fatty acids composition in RBO was obtained from the bran of nine distinct types of rice commonly cultivated in Bangladesh along with four countries including Brazil, Thailand, Vietnam, and Japan. Fatty acid profiling of popular high-yielding rice varieties presented in **Table 3** indicated that the range of saturated fatty acids 16.69 to 28.30% and unsaturated fatty acids 71.06 to 83.41% whereas, monounsaturated fatty acids from 39.82 to 49.95% and polyunsaturated fatty acids from 33.24 to 38.58%. Common fatty acids including linoleic acid from 28-35%, linolenic acid variation was observed from 0.80-2.69%, and stearic acid from 1.59-4.21% indicated the variation is not drastic in case of variation of sources⁴⁴⁻⁴⁶. The bioactive compound γ -oryzanol found 1.2-1.8%, specifically 24-methylene cycloartenol ferulate 50.20%, cycloartenyl ferulate 11.40%, campesterol ferulate 24% and β -sitosterol ferulate 14.40% among the RBO varieties in Bangladesh. Bioactive component Vitamin-A was also analyzed in different rice bran oil varieties and it was found 1.2-7.5 ppm, which was lower than the standard value of (15-30ppm)^{16, 18}. The fatty acid profile of RBO and other edible oils that are marketed in Bangladesh have been analyzed. The result showed that saturated fatty acid was 16.62% in RBO, whereas it was 12% in soybean oil and 22% in butter oil. The monounsaturated fatty acid is 48.32% in RBO, whereas it is 37% in soybean oil and 35% in butter oil. The polyunsaturated fatty acid is 35.06% in RBO, whereas it is 28% in mustard oil and 25% in butter oil. Among them, balanced fatty acid composition and the highly bioactive compound γ -oryzanol found in Bangladesh rice bran oil would aid cardiovascular disease. It has been proved by an animal experiment on the long Evan rat model, this study showed that consecutive 28 days (about 4 weeks) supplementation of RBO significantly reduced body weight, plasma cholesterol, low-density lipoprotein cholesterol,

and increased high-density lipoprotein cholesterol. There was no detrimental side effect on cardiac, renal, and kidney function. Moreover, the chronic supplementation of RBO on Swiss albino mice for 60 days significantly increased the erythrocytes and hemoglobin levels and reduced lipid profiles. Even though oils are detrimental to health, RBO is effective against lifestyle-related diseases⁴⁶⁻⁴⁸. The RBO quality in Bangladesh is improving according to composition and health benefits, but the production facilities are limited. About 17 industries are available for RBO production in Bangladesh, but few are capable of refined RBO marketing. Thus, Bangladesh is trying to increase three times more RBO production capacity and its health benefits research to minimize the dependency on imported edible oil and save foreign currency. The researchers are paying attention to resolve the insight mechanism of (a) how Bangladeshi RBO itself or its bioactive compound reduces the lipid profile. (b) Whether the RBO can reduce the glucose level and how? (c) Whether and how does the RBO modulate cancer cells *in vivo* and *in vitro*? We have discussed our proposed mechanism of how RBO shows its properties in diabetics and hyperlipidemia in this review article.

5 Properties of RBO in Diabetics and Hyperlipidemia

The positive effect of RBO on diabetics and hyperlipidemia depends on the available bioactive components γ -oryzanol and tocotrienol. Diabetes, whether it is insulin-independent or dependent (both type-I and type-II), results in glucose impairment and creates undesirable oxidative stress at the cellular and molecular levels. Studies have demonstrated that the bioactive compounds of RBO reduce oxidative stress and diabetes, suggesting that the compounds themselves or their metabolites modulate cellular or molecular biomarkers related to diabetes⁴⁸. The

Table 3 Comparison of fatty acid composition (%) of Bangladesh rice bran oil (RBO) with Reverence country's RBO (adopted from reference 45-47).

	Common Rice Varieties in Bangladesh used for RBO								RBO from Reverence country			
	BR-5	BR-10	BR-11	BRR1-28	BRR1-29	BRR1-39	BRR1-48	BRR1-49	Brazil	Thiland	Vietnam	Japan
Arachidic acid	~2.17	~2.11	~0.70	~0.54	~0.75	~1.01	~0.83	~0.97	ND	ND	ND	ND
Behenic acid	ND	ND	~0.33	ND	ND	ND	~0.38	ND	ND	ND	ND	ND
Eicosenoic acid	ND	ND	~0.44	ND	ND	ND	~0.46	~0.44	ND	ND	ND	ND
Lauric acid	ND	ND	ND	~0.66	ND	ND	ND	ND	ND	ND	ND	ND
Linoleic acid	~28.45	~30.84	~35.98	~32.13	~32.58	~31.15	~32.66	~37.26	~34.38	~33.41	~32.09	~35.04
Linolenic acid	~0.80	~1.92	~1.21	~1.11	~0.88	~1.25	~1.22	~1.32	~2.69	~2.09	~2.18	~2.05
Myristic acid	~0.45	~0.42	~0.24	~0.61	ND	~0.52	~0.44	~1.00	ND	ND	ND	ND
Oleic acid	ND	ND	~43.16	~44.7	~49.95	ND	~45.36	~39.39	~40.13	~40.47	~41.99	~42.90
Palmitic acid	~19.08	~19.86	~16.43	~18.39	~10.10	~20.86	~16.74	~17.44	~20.15	~21.04	~20.42	~17.22
Stearic acid	~4.15	~4.01	~1.52	~1.78	~1.74	~3.40	~1.91	~2.18	~1.62	~1.93	~1.86	~1.57

ND. Not determined

upstream signal of glucose metabolism is regulated by adiponectin, which is secreted by adipocytes. The level of adiponectin decreased in obesity and increased the lipogenesis and glucose levels in insulin-sensitive tissue, liver, and muscle. The adiponectin modulates the signal transduction of glucose utilization by translocation of glucose transporters (GLUT-2 and GLUT-4) to the cell surface and activation of the insulin receptor. A study showed that glucose level and lipogenesis are reduced by γ -oryzanol supplement because of its ability to increase adiponectin in obese patients. The bioactive component of RBO, γ -oryzanol induces the adipocyte to increase adiponectin secretion, which in turn increases the phosphorylation of AMP-activated protein kinase (P-AMPK) and inhibits gluconeogenesis and lipogenesis pathways in the liver⁴⁹. On the other hand, P-AMPK increased fatty acid oxidation by the activation of the transcription factor peroxisome proliferator-activated receptor- γ (PPAR- γ)^{50, 51}. RBO can reduce body weight by reducing body fat mass. The decreased fat mass can increase adiponectin secretion from adipocytes. The full length of adiponectin can bind to the adiponectin receptors (adipo-R1 and adipo-R2) and subsequently increases fatty acid oxidation and decreases gluconeogenesis gene (phosphoenolpyruvate carboxykinase and glucose-6 phosphatase) expression⁵². RBO also reduces the oxidative stress in pancreatic beta islet cells and increases insulin secretion from islet cells, subsequently increase the glucose utilization in liver and muscle cells. In this way, γ -oryzanol and tocotrienol can reduce total cholesterol, LDL-cholesterol, triglycerides, glucose level, and even bodyweight,

subsequently triggering hyperlipidemia, hyperglycemia, hypertension, insulin resistance, and hyperinsulinemia⁵³. *In vivo* experiments showed that the bioactive component of RBO, γ -oryzanol at about 26-50 ($\mu\text{mol/L}$) could be effective in reducing cholesterol uptake and lipogenesis-related gene expression in human Caco-2 cells (HBT-37) and human hepatocellular carcinoma (HepG2) cells. γ -oryzanol consumption (300mg/day) has a positive effect on serum lipids, thyroid-stimulating hormone, and menopausal abnormalities^{54, 55}. We summarized in Fig. 2, the proposed mechanism of how RBO reduces hyperglycemia and hyperlipidemia.

6 Properties of RBO in Anticancer, Antioxidant, and Anti-inflammatory

The bioactive components of RBO named γ -oryzanol and tocotrienol can inhibit cancer cells, specifically cycloartenyl ferulate and γ -tocotrienol could inhibit human colon carcinoma cell line (SW480) and subsequently accelerate programmed cell death in the initial stages of colorectal cancer. It has been believed that oryzanol and tocotrienols are safe and promising anticancer compounds because of their antioxidant capacity and anti-inflammatory properties and are more effective in cancer prevention than treatment^{56, 57}. Reactive oxygen species (ROS) and new reactive species or free radicals come from mitochondrial dysfunction and can cause metabolic abnormalities by oxidation of protein, lipids, and DNA, which is the leading cause of

Fig. 2 Schematic summary of anti-lipidemic and anti-diabetic properties of RBO.

chronic disease. The RBO can help to maintain metabolic homeostasis by modulating the related pathway in the responsive arena. One of the mechanisms is by inhibiting the pathway that activates the nuclear transcription factor-kappa B (NF- κ B), responsible for a variety of inflammatory diseases, and the other is by downregulating the tumor necrosis factor-alpha (TNF- α) and can protect cell homeostasis⁵⁸. Oryzanol and tocotrienol may improve mitochondrial functions and may prevent or slow down the progression and development of disease by protecting cellular DNA, lipid and protein oxidation. In some cases, tocotrienol exhibits stronger antioxidant activity than tocopherol, which is attributed to its high capacity to donate phenolic hydrogen to ROS and free radicals. Therefore, they can neutralize more ROS than γ -oryzanol and the γ -tocotrienol (T3) component of RBO can promote tumor cell apoptosis via a chain of cascade reactions^{59–63}. The RBO has polyunsaturated essential fatty acids such as linoleic acid, which can exert an antitumor effect and ameliorate inflammation-induced colorectal cancer by activation of the PPAR- γ . Therefore, RBO bioactive compounds can exert anticancer, antioxidant, and anti-inflammatory effects through several pathways. We summarized in Fig. 3, the role of RBO in cancer and other chronic diseases that are caused by oxidation and inflammation. The γ -oryzanol and γ -tocotrienol can exert their action by trapping the oxidized molecule and neutralizing reactive oxygen species to inhibit ROS and new free radicals. On the other hand, they can activate the nuclear transcription factor NF- κ B and inhibit protein kinase C, increase IL-10 and also inhibit TNF- α and inflam-

matory cytokines and enzymes (IL-1, IL-6, IL-8, inducible nitric oxide synthase, and cyclooxygenase 2) by their anti-inflammatory action. The most important role of RBO anti-tumor can be exerted through inducing death receptors activating caspase cascade reactions^{63–65}. Abnormal cell cycle protein expression can lead to uncontrolled cell proliferation, one of the causes of carcinoma. The molecules that target the cell cycle protein to reduce cell proliferation could be effective anticancer properties. The bioactive component, γ -tocotrienol, can inhibit human gastric adenocarcinoma SGC-7901 cell proliferation by arresting the cell cycle at the G0/G1 phase, whereas the γ -oryzanol inhibits both the G0/G1 phase and the resting G2/M phase. On the other hand, cancer is developed by the deregulation of cell apoptosis. The control of cancer cell development by promotion of cell apoptosis is one of the critical approaches to cancer treatment¹⁰. The bioactive component of RBO (cycloartenyl ferulate, γ -tocotrienol) significantly induced cancer cell apoptosis via promoting the expression of proapoptotic proteins (Bax, Bcl-xl, and caspase-3, caspase-8, caspase-9). The mechanism of anticancer, antioxidant, and anti-inflammation of Bangladeshi RBO is still undetermined. Figure 3 summarized the proposed mechanism of Bangladeshi RBO for extensive research *in vitro* and *in vivo* for elucidation of anticancer properties.

Fig. 3 Schematic summary of antioxidant, anti-inflammatory and anticancer properties of RBO.

7 Other Properties of RBO

7.1 Anti ulcerogenic function of RBO

The prevalence of ulceration varies geographically and in food habits around the world. The high prevalence of ulceration was found in refined grains as a staple food consuming area, whereas a low prevalence was found in unrefined rice and wheat staple food consuming areas⁶⁶. RBO can reduce ulcer formation 66.75% by modulating gastric acid levels⁶⁷. Moreover, γ -oryzanol protects the gastric mucosa from ethanol-induced gastric lesions by increasing the level of gastric mucus⁶⁷. Different animal model experiments showed that RBO has ulcer protective activity due to its high level of phospholipid, sterol, and sterol ester fractions such as phosphatidylcholine (lethicin) and phosphatidylethanolamine (cephalin) predominantly. The sterol, β -sitosterol, stigmasterol, and an unidentified isomer of β -sitosterol showed protective activity against ulceration. The protective activity of RBO may also be of clinical importance in giving protection against the ulcerogenic effect⁶⁶⁻⁶⁸. Several studies have observed that hydroxycinnamic acid derivatives, such as curcumin and caffeic acid phenethyl ester, can inhibit NF- κ B activity, one of the most important transcriptional factors in inflammation^{69, 70}. A lot of related hydroxycinnamic acids, such as phytosterol ferulic acid esters, have been found in RBO. One animal experiment reported that phytosterol ferulates significantly inhibit inducible nitric oxide synthase (iNOS) expression and nitric oxide (NO) production in activated macrophages by interfering with NF- κ B activation in dextran sulfate sodium (DSS)-induced colitis⁷¹. Another study explained the inhibitory mechanism of phytosteryl ferulates on the NF- κ B signaling pathway. RBO (Phytosteryl ferulates) can inhibit degradation of I- κ B, resulting in the inhibition of NF- κ B p65 nuclear translocation that is responsible for transcription of related genes⁷². RBO can also reduce ROS through its scavenging and antioxidative abilities. Thus, the RBO could be a remedy for ulcerogenic treatment, but further experiments need to be explored.

7.2 Neuroprotective function of RBO:

RBO is the richest source of γ -oryzanol than any other vegetable oil. The RBO showed antioxidant and effective anti-proinflammatory effects on the cerebral milieu as indicated by a significant reduction in active glial cells and was found to improve synaptic and neuronal signaling. This is caused by γ -oryzanol, a compound that can cross the blood-brain barrier with its active form and affects brain function. Studies have shown that only 100 mg/kg/day, γ -oryzanol can modulate the hippocampal protein that is involved in synaptic and neuronal signaling, thereby functioning as a neuroprotector and antioxidant. On the other hand, 0.5% γ -Oryzanol can control anxiety-like behavior by modulating the monoaminergic neuronal signaling pathway^{73, 74}. Thus, the bioactive component of RBO,

γ -oryzanol, exhibits its candidature as a therapeutic moiety to improve cognitive behavior in neurodegenerative disorders. One study has observed that rice bran extracts significantly inhibited the release of prostaglandin E2 (PGE2) and free radical formation (8-iso-PGF2 α) in LPS-activated primary microglia—a type of neuroglia (glial cell) located throughout the brain and spinal cord⁷⁵. Inhibition of PGE2 by rice bran extract (RBE) was dependent on reduced cyclooxygenase-2 (COX-2) and microsomal prostaglandin E synthase-1 (mPGES-1) immunoreactivity in microglia. It was also observed that treatment of activated microglia with RBE further enhanced the gene expression of the microglial M2 marker IL-10 and reduced the expression of pro-inflammatory M1 markers (TNF- α , IL-1 β). Specific protective properties of RBO were observed in the post-synaptic receptor (D2) antagonist haloperidol-induced Tardive dyskinesia, which has potential implications in the treatment of schizophrenia and motor disorders⁷⁶. Nevertheless, the exact mechanism of the whole RBO's activity in cognitive development remains to be discovered.

7.3 Immune system modulation by RBO:

Immune system modulation, also called immunomodulation, is the process that involves the use of therapy to modify the immune response, often to prevent tissue damage resulting from an excessive response. The immune system is controlled both by direct interaction of several types of cells (lymphoid cells: B and T lymphocytes, T helper (Th) cells, natural killer (NK) cells; myeloid cells: neutrophils, basophils, monocytes, macrophages) and secreted molecules (immunoglobulins, cytokines: interleukins, colony-stimulating factors, growth factors, interferons, etc.) by them. RBO modulates the immune system by enhancing B-lymphocyte proliferation and TH1-type cytokines such as IL-2 or TNF- α . Reduction of TH2 cytokine IL-4 and immunoglobulin E (IgE) levels suggested that anti-allergic properties of RBO⁷⁷⁻⁷⁹, it has been observed that γ -oryzanol possesses sufficient potential for augmenting immune activity by cellular mediated mechanisms.

8 Conclusion

The RBO itself or therapeutically bioactive components both are safe and effective in ameliorating lifestyle-related diseases. This review suggested some possible beneficial effects of Bangladesh RBO such as anti-hyperglycemic and antilipidemic, antioxidative, anti-inflammatory, anti-cancer, anti-ulcerogenic, immune, and neurodegenerative disease prevention. RBO seems to be a very promising oil to reduce the growing incidence of non-communicable disease for 21st century's ailment. However, more research is needed to confirm the beneficial effects of RBO. Nevertheless, the exact mechanism of RBO in Bangladesh remains to be dis-

covered.

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