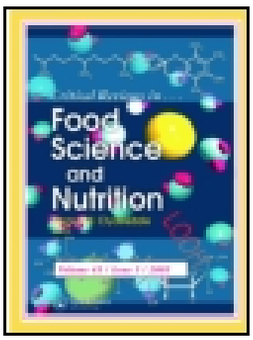

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REVIEW

The classical and potential novel healthy functions of rice bran protein and its hydrolysates

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ABSTRACT

Rice bran protein (RBP) is a plant protein obtained from rice bran, a byproduct produced during rice milling process. It has been proved to be a high quality protein due to containing all of the essential amino acids and the content closing to the FAO/WHO recommended ideal pattern. Recent studies indicated that RBP and rice bran protein hydrolysates (RBPH) served variety biological functions. In this review, we summarized the classical functions of RBP and RBPH mediating antioxidant activity, chronic diseases prevention (such as antihypertensive effect, anti-diabetic effect, cholesterol-lowering activity), and anti-cancer effect. We also proposed their potential novel functions on anti-obesity effect, attenuating sarcopenia, promoting wound healing. Furthermore, the potential benefit to coronavirus disease 2019 (COVID-19) patients was put forward, which might provide new strategy for development and utilization of RBP and RBPH.

KEYWORDS

RBP; hydrolysates; antioxidant; chronic diseases prevention; anti-cancer; novel functions

GRAPHICAL ABSTRACT

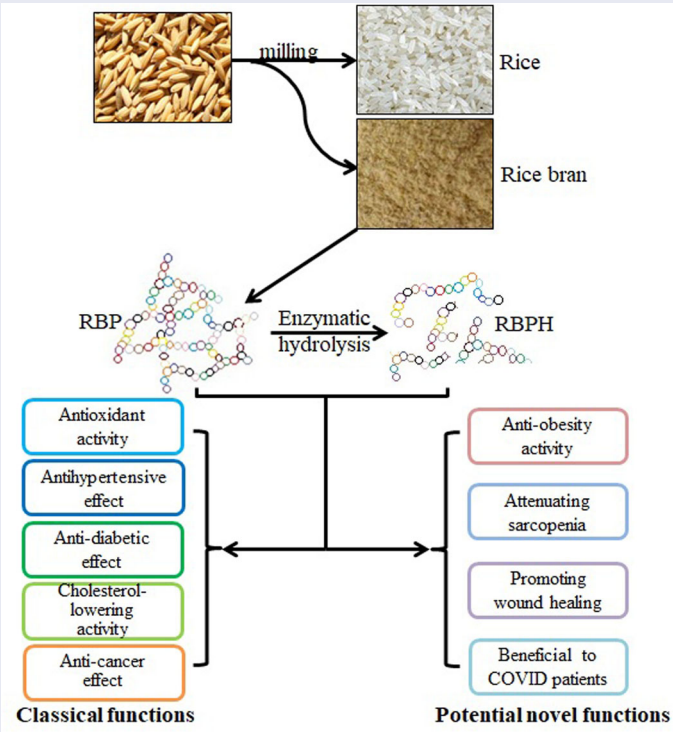

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Table 1. Amino acid composition of RBP, rice protein, whey protein, and soybean protein.

Amino acid (g/100g)	FAO/WHO recommended standard	RBP	Brown rice protein isolate	Whey protein isolate	Soybean protein isolate	Casein
Thr	4.00	6.02	2.92	7.91	3.14	3.70
Val	5.00	9.98	4.56	5.88	4.10	5.50
Met + Cys	3.50	4.81	3.97	3.78	2.18	2.00
Ile	4.00	4.54	3.47	5.60	4.25	4.20
Leu	7.00	5.87	6.41	10.24	6.78	6.30
Phe + Tyr	6.00	8.83	8.67	5.26	7.82	5.80
Lys	5.50	4.78	2.42	9.70	5.33	10.10
Try	1.00	1.12	1.17	1.89	1.16	1.10
His	–	3.37	1.82	1.31	2.30	5.40
Ala	–	5.37	4.47	4.80	3.59	3.00
Arg	–	7.84	6.32	1.78	6.67	8.40
Asp	–	8.24	6.94	10.16	10.20	4.80
Glu	–	12.85	13.91	19.31	17.45	13.60
Gly	–	4.31	3.53	1.42	3.60	3.20
Pro	–	2.23	2.88	5.74	4.96	8.80
Ser	–	2.92	3.91	4.92	4.59	5.40
TAA	–	93.06	77.37	99.73	88.12	91.30
EAA	–	39.44	29.44	45.49	30.49	38.7
Total BCAA	–	20.39	14.44	21.72	15.13	16.00
EAA/TAA (%)		42.38	38.05	45.61	34.60	42.39

The data are from previous publications (W. G. Gordon et al. 1949; D. S. Kalman 2014; C. Kalpanadevi, Singh, and Subramanian 2018; Singh and Sogi 2018)

Introduction

Rice bran, byproduct of rice milling industry, is a rich resource with about 29.3 million tons produced annually (M. Sohail et al. 2017). Rice bran consists of pericarp, seed coat, endosperm, aleurone layer and embryo, which contains various bioactive components, including protein, lipids, dietary fiber, vitamins, and minerals. And the compositions of rice bran are approximately 15-22% lipids, 34.1-52.3% carbohydrates, 7-11.4% fiber, 6.6-9.9% ash, 8-12% moisture, and 10-16% highly nutritional protein (Fabian and Ju 2011). One of the hotspots focused on rice bran is the lipids extracted from rice bran named rice bran oil. It is considered as healthy oil, which is rich in essential fatty acids, unsaturated fatty acids, and micronutrients including tocotrienol, oryzanol, and phytosterol (Pal and Pratap 2017). So there are many products of rice bran oil with different brands on the market. Another important component is rice bran protein (RBP), a plant protein derived from rice bran, with high quality and important properties for food and pharmaceutical applications. RBP has enough essential amino acids (EAAs) and the pattern of EAAs is close to the recommended standard of FAO/WHO (Table 1). Compared with proteins extracted from rice, milk, and soybean, the quality related indexes of RBP, including the content of total amino acid (TAA) and EAA, as well as the ratio of EAA/TAA, are in close proximity to those in whey protein, and much higher than those in rice protein and soybean protein. It suggests that the nutritional value of RBP is comparable with whey protein. In addition, the branch chain amino acid (BCAA), which is beneficial to muscle health (J. Zhang, Li, et al. 2020b), is much higher than that in rice protein, soybean protein, and casein (Table 1). Furthermore, RBP has high biological value due to easy absorbed and utilized by the body. In comparison with the nutritional quality of animal and vegetable protein, the protein efficiency ratio, net protein ratio, net protein utilization, biological value, and protein digestibility-corrected amino acid score (PDCASS) of RBP are 2.39, 3.77, 70.7, 72.6 and 0.90 in Sprague-Dawley rats, respectively. These indexes are all comparable with those of animal proteins. And the true digestibility of RBP was 94.8%, which is higher than that of whey protein isolate (92.8%), isolate soy protein (91.7%) and rice endosperm protein (90.8%) (S. W. Han, Chee, and Cho 2015). Subsequent study also shows that the capacities of solubility, digestibility, iron retention, transport and uptake are significantly elevated in rice bran protein hydrolysates (RBPH) than those of RBP *in vitro* (L. C. Foong, Imam, and Ismail 2015; T. P. Singh, Siddiqi, and Sogi 2021). It suggests that RBP and RBPH was a promising protein resource with high biological value and digestibility. Thus, RBP is gaining great attention of the researchers due to its nutrient-rich composition, easy availability, low cost, and promising effects against several metabolic ailments.

However, the extraction of RBP has been proved to be difficult due to its complex nature as shown in Table 2. Although rice bran storage proteins have similarities with other cereal proteins, the proportion of these storage proteins in rice bran makes it more difficult to find a single suitable solvent for extraction. The use of enzyme and subcritical water treatment showed promising protein yields. However, the relatively expensive cost of enzyme should be addressed while the exact yield and quality of protein extracted with subcritical water treatment at relatively high temperatures needs further study. More works are needed to improve what has been accomplished and in finding a more efficient and economically viable method for RBP extraction, in order to realize its utilization as a food ingredient or nutraceutical additive (Fabian and Ju 2011). Several new extraction techniques such as solvent extraction, supercritical fluid extraction, ionic liquid extraction, microwave or ultrasonic-assisted extraction should be further explored to seek ideal extraction methods for RBP extraction (Table 2).

The compositions of RBP have been classified according to solubility and extractability, which approximately consists of water-soluble albumin (37%), salt-soluble globulin (31%), alkali-soluble glutelin (27%), and alcohol-soluble prolamin

Table 2. Extraction process of RBP and their internal mechanisms.

Extraction process	Conditions	Extraction efficiency	Potential mechanism	Cites
Alkalis method	Solid-liquid ratio: 1:4 (w/v), pH 9.5, agitating at 500 rpm for 45 min	44.4%	Breaking hydrogen and amide bonds	(C. Theerakulkait, Chaiseri, and Mongkolkanchanasiri 2006)
Alkalis method	pH 9.5, the temperature at 30 °C or 75 °C	From 21% (at 30 °C) to 48% (at 75 °C)	Breaking hydrogen and amide bonds	(G. K. Chandi 2008)
Enzymatic method	Amylase and/or protease treatment	28.1% (Amylase only), 48.4% (protease only), and 60.9% (both enzymes)	Attacking the interaction between protein and other nutrients, increasing protein liberation	(Tang, Hettiarachchy, and Shellhammer 2002)
Enzymatic method	Solid-liquid ratio: 1:7.5 (w/v), 400 PU phytase, and 240 GXU xylanase, pH 5.0 and incubation at 50 °C for 2 h	74.6%	Attacking the interaction between protein and other nutrients, increasing protein liberation	(M. Wang et al. 1999)
Physical method	Microwave-associated extraction with conditions of 100.68 W power for 100.68 s and solid-liquid ratio of 0.42 (w/v)	36.03 mg BSAE/mL	Disrupting cell wall via superheating water molecules and increasing protein release	(M. Hayta et al. 2021)
Physical method	Supercritical fluid extraction with conditions of 450 bars, 90 min of extraction, and 17.5 g/min flow rate	17.44%	Easily dissolving rice bran protein of supercritical fluid with the advantages of high solubility to solute, easy diffusion and high mass transfer efficiency	(S. Iqbal, Ismail, and Chee 2013)
Physical method	Ultrasonic-associated extraction with conditions of 76% sonication amplitude for 18 min and solid-liquid ratio of 0.99 g/10 mL	4.73%	Increasing protein solubility with the cavitation effect, thermal effect and mechanical effect of ultrasonic wave	(S. Phongthai, Lim, and Rawdkuen 2017)
Physical and enzymatic method	Sonication (output 100 at 750 W) combined with Amylase and/or protease treatment	13.5% (only sonication), 33.9% (sonication and Amylase), 23.9% (sonication and protease), and 57.8% (sonication and both enzymes)	Disrupting cell wall, providing suitable environment for enzymatic catalysis, increasing protein release	(Tang, Hettiarachchy, and Shellhammer 2002)
Physical and enzymatic method	High pressure at 800 MPa combined with Amylase and/or protease treatment	10.7% (only high pressure), 37% (high pressure and Amylase), 29.6% (high pressure and protease), and 66.6% (high pressure and both enzymes)	Disrupting cell wall, providing suitable environment for enzymatic catalysis, increasing protein release	(Tang, Hettiarachchy, and Shellhammer 2002)

(2%) (Fabian and Ju 2011). Albumin contains sufficient net charge and deficiency of disulfide cross-linking or aggregation, which contributes to its property of water solubility (J. S. Hamada 1999). And rice bran albumin has high tyrosinase-inhibitory activity (S. Kubglomsong et al. 2018). Recent studies also indicate that albumin can be used as delivery system to stabilize and delivery epigallocatechin gallate (S. Kubglomsong et al. 2018; Z. Zhou et al. 2017). Globulin carries net electronic charge which makes it easy soluble in saline solution, and is sulfur-rich. The interchain disulfide bonds are responsible for stabilizing the structure of globulin, and rice bran rancidity results in the decrease of sulfhydryl content, further leading to the change in secondary structure of globulin (Fabian and Ju 2011; W. Wu, Li, and Wu 2021). Glutelin from rice bran is hard to be dissolved because of aggregation, glycosylation, and disulfide bonds rich, but phosphorylation decreases surface hydrophobicity which may increase its solubility to some extent (Fabian and Ju 2011; Y. Ma et al. 2017). Prolamin is insoluble in dilute salt solutions and easily soluble in 60 ~ 70% aqueous ethanol. Although the content of prolamin in rice bran is quiet low, it is a prominent member with allergenic properties (S. Kumar et al. 2012). So each component of RBP has their own physical and chemical characteristics, and potential new functions are also being discovered.

Recent studies also indicate RBP and RBPH exert essential biological functions. In this review, the biological function of RBP and RBPH on antioxidant, antihypertensive effect, anti-diabetic effect, cholesterol-lowering activity, and cancer prevention were summarized, and potential novel roles in anti-obesity, attenuating sarcopenia, promoting wound healing, and benefit to COVID-19 patients were evoked.

RBP hydrolysis

The utilization of RBP is limited because of its strong aggregation and poor solubility. Peptides, hydrolyzed from protein, have variety effects on regulating somatic function with high solubility. Reports also show that peptides from hydrolyzed RBP exert critical roles in health care (A. Jarunrattanasri, Theerakulkait, and Cadwallader 2007; Y. Q. Liu et al. 2019). Although acid hydrolysis and alkali hydrolysis are commonly used to obtain amino acids and peptides from protein, RBP is usually hydrolyzed using enzymes (A.

Table 3. Enzymes for RBP hydrolysis and biological functions of hydrolyzed peptides.

Composition of enzymes	Reaction times	MW/sequence of functional peptides	Biological functions	Cites
Protease from *Bacillus licheniformis*	0.25, 0.5, 0.75 or 1 h	Peptides from RBP with degree of hydrolysis of 6.7 and 7.6%	Antioxidant ability	(N. Cheetangdee 2014)
Papain and trypsin	3 h	90 peptides with 6 to 21 amino acid residues hydrolyzed by trypsin	Antioxidant activity	(L. Wattanasiritham et al. 2016)
Umamizyme G	$\geq$ 12 h (overnight)	–	Antioxidant activity	(C. Moritani et al. 2017)
Pepsin and trypsin	Pepsin for 2 h then trypsin for another 2 h	MW $<$ 3 kDa fractions especially octapeptides with m/z at 1088	Antioxidant activity	(S. Phongthai et al. 2018)
Alcalase or flavorzyme	10 h	MW $<$ 3 kDa fractions	Antioxidant, angiotensin-converting enzyme inhibitory and blood pressure lowering effect	(I. B. B. Piotrowicz et al. 2020)
Alcalase, neutrase, flavourzyme andprotamax	4 h	MW$<$ 3 KDa fraction contains 13 peptides with 6 to 32 amino acid residues	Antidiabetic function via inhibiting β-glucosidase activity	(Uraipong and Zhao 2016)
α-amylase, pepsin, pancreatin, and bile extract	α-amylase for 5 min, pepsin for 2 h, and pancreatin and bile extract for 1 h	MW $<$ 3 kDa fractions	Inhibitory effect on α-glucosidase and angiotensin I converting enzyme	(Uraipong and Zhao 2018)
Protease G6	4 h	–	Mitigating IL-6 or high glucose-induced insulin resistant, attenuating diabetic nephrophathy and protecting renal function	(K. Boonloh et al. 2015a; K. Boonloh et al. 2018)
Protease G6	4 h	–	Antioxidant, reducing arterial stiffening, inflammatory reaction and insulin resistant of rats fed high fat diet	(K. Boonloh et al. 2015b; K. Senaphan et al. 2018)
Alcalase, neutrase, papaya latex papain and porcine pancreas trypsin	1, 2, 3 or 4 h	Fractions eluted by 75% aqueous ethanol	High micellar cholesterol inhibition ability	(Zhang, Yokoyama, and Zhang 2012)
Alcalase	0.5 h	MW $<$ 5 and 5-10 kDa fractions	Inhibiting human colon and liver cancer cell proliferation	(A. Kannan et al. 2008)
Chymotrypsin and trypsin	6 h	Peptides with a C-terminal tyrosine residue especially peptide CT-2 (Leu – Gln – Pro – Ser – His – Tyr)	Tyrosinase inhibition and preventing melanogenesis in mouse B16 melanoma cells	(A. Ochiai et al. 2016)
Bromelain	3 h	Peptide named Alpep7 with sequence of KVDHFPL(Lys-Val-Asp-His-Phe-Pro-Leu)	Antimicrobial and antibiofilm formation	(Pu and Tang 2017)
Pepsin	3 $\sim$ 6 h	Three peptides with sequences of LRRHASEGGHGPHW, EKLLGKQDKGVIIRA, and SSFSKGVQRAAF	Antimicrobial, lipopolysaccharide-neutralizing and promoting wound healing	(M. Taniguchi et al. 2017; M. Taniguchi et al. 2019)

MW: Molecular weight; -: not mentioned.

Jarunrattanasri, Theerakulkait, and Cadwallader 2007; L. Wattanasiritham et al. 2016). As shown in Table 3, different combinations of proteases such as alcalase, neutrase, flavourzyme (extracted from *Aspergillus oryzae* and purchased from Novozymes A/S), protamax, papain, trypsin and bromelain, are frequently used (L. Niu, Wu, and Xiao 2017; I. B. B. Piotrowicz et al. 2020; Uraipong and Zhao 2016; Wattanasiritham et al. 2016; Zhang, Yokoyama, and Zhang 2012). Pepsin-trypsin system is also usually employed to simulate gastrointestinal digestion *in vitro* (S. Phongthai et al. 2018; L. Wattanasiritham et al. 2016). In addition, umamizyme G (an enzyme from *Aspergillus oryzae* which contributed to removing the bitter taste) is less commonly used but also can be used for catalyzing RBP hydrolysis (C. Moritani et al. 2017). The enzymatic hydrolysates of RBP serve important roles such as antioxidant, mitigating insulin resistant, reducing inflammatory reaction, modulating cholesterol metabolism, and cancer prevention (K. Boonloh et al. 2015b; A. Kannan et al. 2008; I. B. B. Piotrowicz et al. 2020; H. Zhang et al. 2016). In summary, multiple enzymes have been employed to hydrolyze RBP and enzymatic hydrolysates are excellent resources with various bioactive activities.

Biological functions of RBP and RBPH

Antioxidant activity

Oxidative stress refers to an imbalance state of oxidation and anti-oxidation *in vivo*, which tends to oxidation and results in production and accumulation of reactive oxygen species (ROS) and reactive nitrogen species (RNS). ROS includes superoxide anion (O_2^-), hydroxyl radical (·OH), and hydrogen peroxide (H_2O_2), while the key components

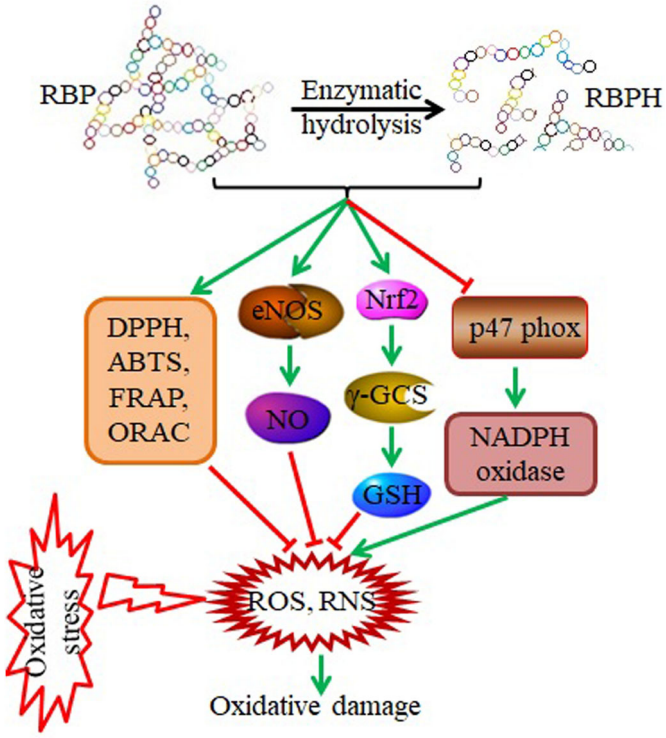

Figure 1. The function of RBP and RBPH on reducing oxidative damage. On one hand, RBP and RBPH had the radical scavenging capacity of 1,1-diphenyl-2-picryhydrazyl (DPPH) and 3-ethylbenzthiazoline-6-sulphonic acid (ABTS), Ferric Reducing Ability Power (FRAP) and Oxygen Radical Absorbance Capacity (ORAC). On the other hand, RBP and RBPH also activated eNOS and Nrf2, which subsequently resulted in promoting production of NO and GSH, respectively. Recent study also showed that rice bran hydrolysates was responsible for reducing the expression of p47 phox, the subunit of NADPH oxidase, and subsequently inactivating NADPH oxidase. These aspects finally contributed to scavenging free radicals and reducing oxidative damage.

of RNS are nitric oxide (·NO), nitrogen peroxide ($\cdot NO_2$), and nitrite peroxide ($\cdot ONOO^-$). Oxidative stress is considered to be an important factor in evoking aging and disease (C. Cabello-Verrugio et al. 2017). There are two types of antioxidant system in our body. One is enzymatic antioxidant system consisting of superoxide dismutase (SOD), catalase, glutathione peroxidase (GSH-px), etc. The other is non-enzymatic antioxidant system including glutathione, vitamin C/E, polyphenol, etc (W. Hassan et al. 2017). Thus, nutrients in food exert essential effects on antioxidant, and RBP is found to be important candidate with antioxidant activity. The RBPH are rich in hydrogen donors, which can scavenge free radicals and terminate free radical reaction chains (Y. Q. Liu et al. 2019). The antioxidant capacity was usually evaluated by measuring radical scavenging activity of 1,1-diphenyl-2-picryhydrazyl (DPPH), 3-ethylbenzthiazoline-6-sulphonic acid (ABTS), ferric reducing ability power (FRAP) and oxygen radical absorbance capacity (ORAC). Reports indicated that RBPH had strong DPPH and ABTS radical scavenging activity and high value of FRAP and ORAC *in vitro* (Cheetangdee and Benjakul 2015; S. Phongthai et al. 2018; I. B. B. Piotrowicz et al. 2020; L. Wattanasiritham et al. 2016). Further study in HepG2 cell demonstrated RBPH could activate the transcription factor of nuclear factor erythroid 2-related factor 2 (Nrf2) and promote the expression of γ-glutamylcysteine synthetase (γ-GCS) which was the rate-limit enzyme for glutathione synthesis (C. Moritani et al. 2017). An *in vivo* experiment also verified that RBPH administration increased nitric oxide (NO) production via promoting eNOS expression, and decreased $O_2^{\cdot-}$ level in vascular tissue of rats fed a high-carbohydrate and high-fat diet (K. Senaphan et al. 2018). Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is an important enzyme which is responsible for the killing of intercellular pathogens, and activation of NADPH oxidase will promote the production of ROS (L. A. Ligeon et al. 2021). And rice bran hydrolysates administration significantly reduced the expression of p47 phox (the subunit of NADPH oxidase), downregulated NAPDH oxidase activity, and therefore inhibited ROS production (G. Jan-On et al. 2020). In summary, RBPH contributed to promoting expression of GSH and eNOS, suppressing the subunit of NADPH oxidase p47 phox expression, elevating ORAC value, and down-regulating the levels of ROS and RNS, which finally exhibited antioxidant activity (Figure 1).

Antihypertensive effect

Hypertension is one of the risk factors in heart disease, stroke, and mortality (D. Ettehad et al. 2016). Studies showed that angiotensin converting enzyme (ACE) was positively correlated with hypertension occurrence and ACE inhibitors had exhibited efficacy on mitigating hypertension (G. Dell'omo et al. 2006; E. C. Li, Heran, and Wright 2014). Therefore, nutrients with the inhibiting effect on ACE might play the role on relieving high blood pressure. Rice bran extracts had exhibited effectively antihypertensive activity (Y. Q. Liu et al. 2019). *In vitro* studies showed small molecular weight fractions from RBPH with the inhibitory activity of ACE (I. B. B. Piotrowicz et al. 2020; Uraipong and Zhao 2016), which implied that these fractions had the potency of lowering blood pressure. And after RBPH administration, the lower level of plasma ACE was observed in rats fed high-carbohydrate and high-fat diet (K. Senaphan et al. 2018). Similar results were obtained in another study using two kidney-one clip (2 K-1C) rat model with renovascular hypertension that intragastrically administrated RBPH significantly reduced plasma ACE level, decreased peripheral vascular resistance, and exhibited antihypertensive effect (O. Boonla et al. 2015). Furthermore, the novel peptides with antihypertensive function from thermolysin digested rice bran were also studied, and peptides with sequences of Leu-Arg-Ala (LRA) and Tyr-Tyr (YY) exhibiting strong inhibitory activity of ACE were identified. Both two peptides possessed the function on lowering systolic blood pressure in spontaneously hypertension rat (N. Shobako et al. 2018). Further research was focused on the antihypertensive mechanism of tripeptide LRA, and the results showed that LRA treatment induced activation of endothelial nitric oxide synthesis and promoted NO production. Thus, tripeptide LRA might exert antihypertensive effect on spontaneously hypertension rats via induction of vasorelaxation mediated by NO system (N. Shobako et al. 2019). Finally, a clinical trial was designed to detect the antihypertensive effect of LRA on

individuals with high blood pressure. The results from 87 participants elucidated that systolic blood pressure was significantly reduced after orally administration of LRA (43 μg/day) for 12 weeks (Y. Ogawa et al. 2019). Taken together, publications of *in vitro*, *in vivo* or clinical trial study indicated enzymatic peptides of RBP especially LRA could inhibit ACE activity, relax systolic blood pressure, and therefore exhibit obvious antihypertensive effect.

Anti-diabetic effect

Diabetes mellitus, a common chronic disease with high incidence, is characterized by hyperglycemia. It mainly includes type I diabetes caused by pancreatic cell damage and decrease of insulin secretion, and type II diabetes induced by insulin resistance (F. Maraschin Jde 2012). Glucosidase is one of the important enzymes for carbohydrate utilization and increasing postprandial blood sugar. So screening of glucosidase inhibitors from natural products has been considered as one of the key approaches to attenuate diabetes (Zhang, Li, et al. 2020). Recent studies indicated that extracts from rice bran had the potency to inhibit glucosidase activity. Rice bran extracts significantly suppressed activity of α-amylase and α-glucosidase and promoted glucose uptake of L6 muscle cells (K. B. Arun et al. 2020). In particular, fractions of RBPH with molecular weight less than 3 kDa possessed high inhibition activity of α-amylase, α-glucosidase, and β-gluosidase (Uraipong and Zhao 2016, 2018), indicating that RBPH was a potential candidate for prevention and mitigation of diabetes. Report also showed that inflammatory factor IL-6 treatment led to decreasing expression of IRS1 and inhibition of phosphorylated Akt, while high glucose administration reduced phosphorylation of AMPK and Akt, both of which impaired glucose utilization and caused insulin resistant in HepG2 cells (K. Boonloh et al. 2015a). However, RBPH treatment effectively prevented IL-6 or high glucose induced insulin resistance via increasing AMPK and Akt activation (K. Boonloh et al. 2015a). *In vivo* study also demonstrated that high carbohydrate and high fat diet resulted in occurrence of insulin resistance in MS rats, and orally administrated RBPH markedly attenuated blood glucose and restored insulin sensitivity (K. Boonloh et al. 2015b). Further analysis found that RBPH treatment increased *PPARγ* mRNA level and reduced pro-inflammatory factor IL-6 expression (K. Boonloh et al. 2015b). It elucidated that RBPH not only inhibited the secretion of insulin resistant inducer IL-6, but also promoted glucose metabolism via increasing PPARγ expression. These two pathways were beneficial for attenuating the occurrence of insulin resistance. In addition to glucose metabolic disorders, complications are commonly occurred in diabetic patients, such as diabetic nephropathy characterized by renal dysfunction, chronic inflammation (Van Buren and Toto 2013). Subsequent study also revealed that RBPH administration reduced urinary albumin level and ratio of albumin/creatinine, which implied the improvement of renal function. And the potential mechanism might involve reducing inflammatory cytokines expression, down-regulating proangiogenic and profibroic proteins level (K. Boonloh et al. 2018). Dipeptidylpeptidase-IV (DPP-IV) was recently identified circulating peptide hormone which involved in inactivating the insulinotropic hormone glucagon-like peptide-1 (GLP-1). And GLP-1 exerted an important role in promoting insulin secretion and reducing blood glucose level (Avogaro and Fadini 2014). Thus, inhibiting DPP-IV activation provided a new approach to control blood glucose. And the study also indicated that dipeptides Ile-Pro and Leu-Pro from rice bran contributed to inhibiting the activation of DPP-IV, which might be a potential new mechanism for anti-diabetic effect of RBPH (T. Hatanaka et al. 2012). Taken together, as shown in Figure 2, RBPH exerted essential roles in suppressing amylase and glucosidase activation, promoting insulin sensitivity, inhibiting DPP-IV activation, reducing blood glucose and finally attenuating diabetic symptoms. What's more, it also contributed to mitigating chronic inflammatory reaction, protecting and restoring renal function of diabetic patients.

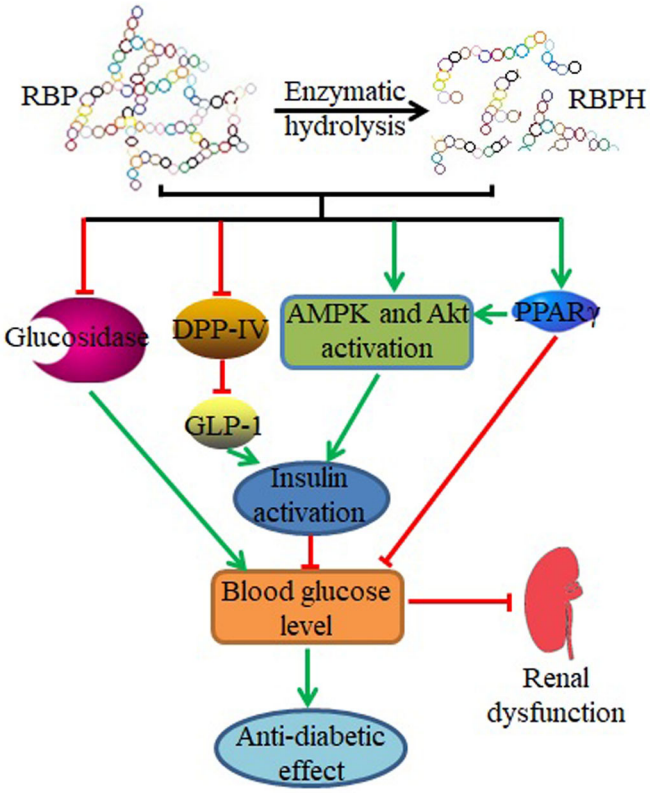

Figure 2. RBP and RBPH exerted effects on regulating glucose metabolism. RBP and RBPH had inhibitory activity of glucosidase, and suppressed carbohydrates digesting and glucose production. They could also improve activation of AMPK and Akt, and mitigate insulin resistance, accelerate blood glucose intake and promote glycogen synthesis. RBPH also contributed to inhibiting the activity of DPP-IV, elevating GLP-1 level, and promoting insulin secretion. In addition, RBP and RBPH up-regulated expression of PPARγ, and then promoted glucose metabolism in insulin-independent pathway. All the pathways were beneficial to reducing blood glucose level, attenuating diabetic symptoms, and reversing renal dysfunction.

Cholesterol-lowering activity

Hyperlipoidemia is a chronic disease charactered by excessive high blood lipid level. The values of clinical indexes of

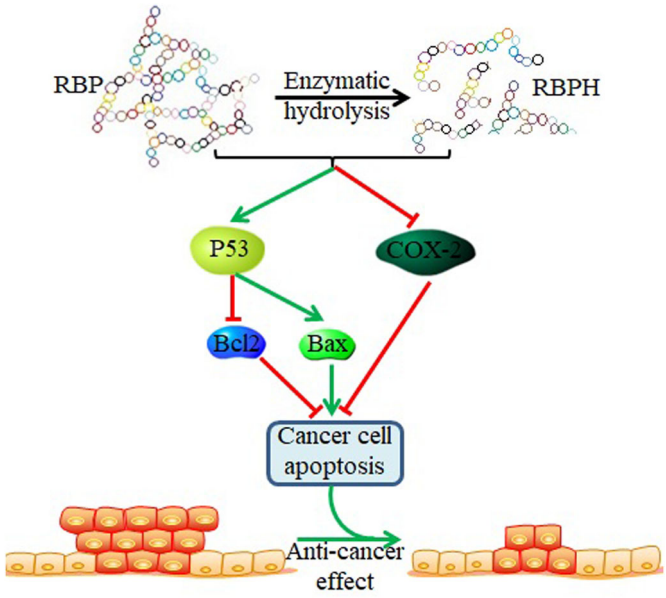

Figure 3. Effect of RBP and RBPH on cancer prevention.
RBP and RBPH promoted the expression of tumor suppressor gene P53, and subsequently inhibited anti-apoptotic gene Bcl2 expression and elevated level of pro-apoptotic gene Bax, and finally resulted in cell apoptosis. They also promoted cell apoptosis in a COX-2-dependent manner. So RBP and RBPH exerted the function of cancer prevention via up-regulating P53 and down-regulating COX-2 expression, which finally led to cancer cell apoptosis.

total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-c), and high density lipoprotein cholesterol (HDL-c) are usually used for diagnosis of hyperlipoidemia. Dietary intervention is one of the important ways to regulate hyperlipidemia, which can alleviate hyperlipidemia by limiting fat intake and promoting cholesterol excretion (D. Ristic-Medic et al. 2009). Cholesterol is a familiar term to us. There are some diseases, which are associated with this. Previous studies showed that RBP and RBPH administration contributed to lowering cholesterol level. *In vitro* assay indicated that RBP could bind to bile acids and inhibit the micellar solubility of cholesterol, and the component with bile acid-binding capacity in rice bran was further separated and named OsJ_13801 (J. Wang et al. 2015). The bile acid-binding capacity of RBPH was also analyzed, the results revealed that hydrophobic fraction of RBP hydrolyzed by alcalase, neutrase, papain, and trypsin had the high inhibitory activity on micellar cholesterol (Zhang, Yokoyama, and Zhang 2012). It suggested that both RBP and RBPH potentially possessed cholesterol-lowering activity. Subsequent publications indicated that RBP supplementation decreased serum total cholesterol levels of rats fed a high-cholesterol diet accompanied with increasing excretion of fecal steroids *in vivo* (J. Wang et al. 2015). And RBPH were also used for intervention of mice fed high fat diet. After RBPH treatment, contents of LDL-c and hepatic cholesterol significantly decreased, and levels of fetal total cholesterol as well as total bile acid were elevated (H. Zhang et al. 2016). Further study revealed that the mRNA levels of bile acid synthesis and cholesterol efflux related genes *CYP7A1*, *ABCA1* and *PPARγ* were activated, while the activation of cholesterol synthesis related genes *HMG-CoAR* and *SREBP-1* were suppressed (H. Zhang et al. 2016). Finally, the active components in RBP for inhibiting cholesterol micellar solubility were identified as lectin and nonspecific lipid-transfer protein 1, which had been verified to bind with steroid and increasing fecal cholesterol excretion (Carvalho and Gomes 2007; T. Kayashima et al. 2005; J. Wang, Shimada, and Nagaoka 2017). In summary, all the studies illustrated that inhibiting cholesterol synthesis and promoting fecal steroid excretion might be one of the potential mechanisms for lowering cholesterol of RBP and RBPH.

Anti-cancer effect

Cancer is a disease characterized by the unchecked division and survival of abnormal cells. It has become a chilling word for human being since the end of last century. By now, scientists and medical experts still could not find effective way to treat this disease. There are different kinds of cancer like breast cancer, skin cancer, lung cancer, colorectal cancer, prostate cancer, lymphoma, etc. According to statistic data, there are an estimated 18.1 million new cancer cases (17.0 million excluding nonmelanoma skin cancer) and 9.6 million cancer deaths (9.5 million excluding nonmelanoma skin cancer) in 185 countries at 2018. And lung cancer is highest incidence cancer followed by breast, prostate, and colorectal cancer in the world (F. Bray et al. 2018). In recent years, rice bran extracts including protein had been proved to exhibit anticancer activity (Y. H. Yu et al. 2019). To detect the anticancer activity of enzymatic peptides from RBP, the fractions with molecular weight of >50, 10-50, 5-10, and <5 kDa were extracted after hydrolyzed by Alcalase and/or followed by treatment with simulated gastric and intestinal juices. And the results showed that peptide <5 kDa fraction significantly reduced the proliferation of colon cancer cell HCT116, Caco-2, liver cancer cell HepG2 and breast cancer cell HTB-26 (A. Kannan et al. 2008; A. Kannan, Hettiarachchy, and Narayan 2009). It meant that specific peptide fractions from hydrolyzed RBP had a potency of anti-tumor activity. Subsequent studies focused on the anti-cancer activity of single peptide extracted from RBPH. A pentapeptide with amino acid sequence of Glu-Gln-Arg-Pro-Arg (EQRPR) derived from <5 kDa fraction had remarkable anti-proliferative effects on colon cancer, breast cancer and liver cancer cells (A. Kannan et al. 2010). It implied that the major anti-cancer activity of <5 kDa fraction might be exerted by the pentapeptide. More detailed research showed that anti-proliferative property on human breast cancer cells MCF-7 and MDA-MB-231, and significantly reduced the expression of anti-apoptotic protein Bcl-2 and elevated the expression of pro-apoptotic protein Bax (R. Li, Heran, and Wright 2014b). Further study indicated that the pentapeptide treatment dramatically promoted apoptosis of breast cancer cells MCF-7 and MDA-MB-231. And the apoptotic signal pathway were activated via up-regulating P53 expression and suppressing COX-2 level (R. Li, Heran, and Wright 2014a). In conclusion, RBPH possessed strong activities of inhibiting cancer cells proliferation and promoting cancer cells apoptosis, which were necessary for exerting anti-cancer effect (Figure 3).

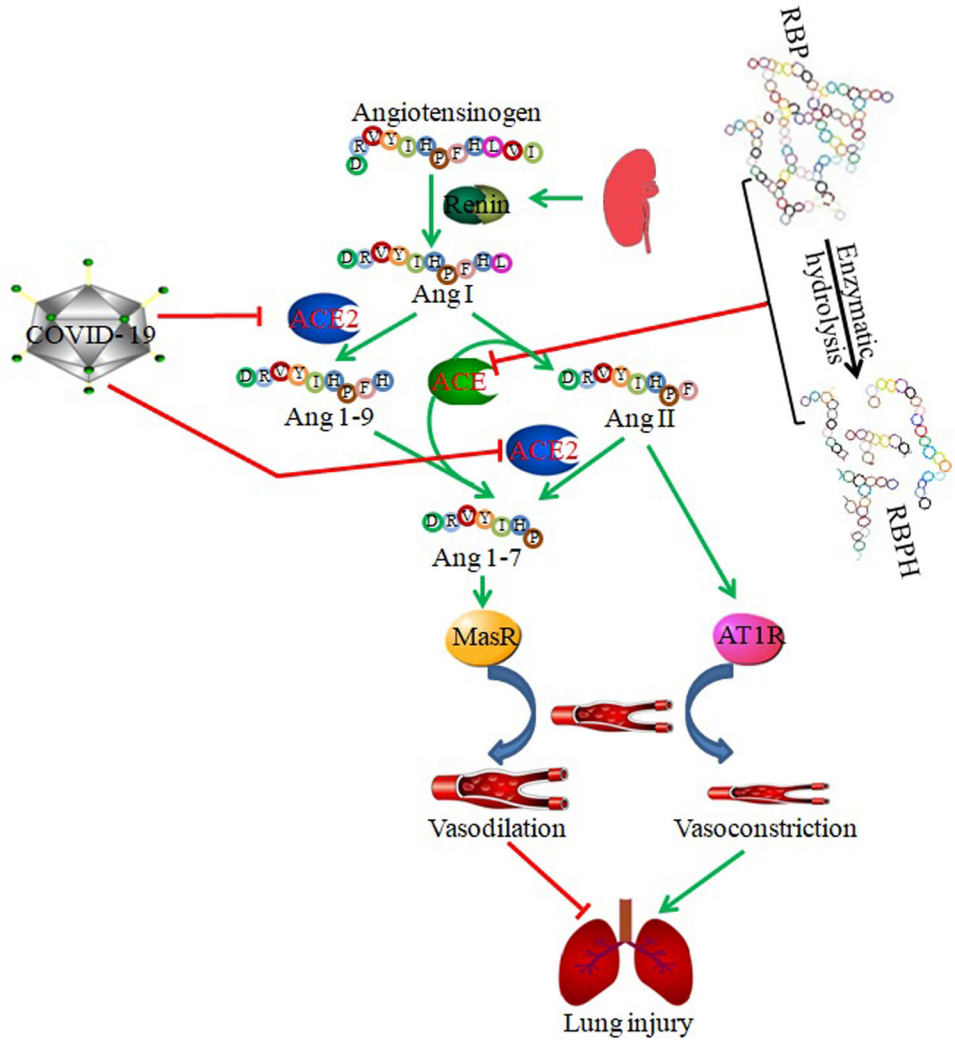

Figure 4. The potential novel function of RBP and RBPH on attenuating severe lung injury of patients with COVID-19.
ACE and ACE2 are involved in mediating angiotensinogen metabolism. Angiotensinogen is first digested into Ang I by kidney secreted renin, which is further converted to Ang II by ACE or Ang 1-9 by ACE2. And Ang 1-9 or Ang II is subsequently converted to Ang 1-7 by ACE or ACE2, respectively. Ang 1-7 serves an effect of vasodilation via combined with Mas receptor (MasR), and Ang II activates Ang II type 1 receptor (AT1R) and results in vasoconstriction. ACE2 is also cell surface receptor of COVID-19 and mediates its infection; however, after COVID-19 infection, ACE2 expression is significantly suppressed which breaks the balance of ACE/Ang II and ACE2/Ang 1-7, and finally leads to severe lung injury via Ang II mediated vasoconstriction. ACE inhibitory activity of RBP and RBPH might contribute to reducing Ang II production and preventing severe lung injury of patients with COVID-19.

Potential novel functions

Anti-obesity effect

Obesity is a worldwide pandemic partially due to the changes of global food system and energy overconsumption. Body mass index (BMI) is a general standard for obesity evaluation. By 2008, the globally estimated populations of overweight (BMI >25kg/m^2) and obese (BMI >30kg/m^2) adults had reached 1.46 billion and 502 million, respectively. In addition, there were approximately 170 million children suffered overweight and obesity (B. A. Swinburn et al. 2011). Last decade, the number kept rising, up to more than 2 billion overweight or obese individuals (B. Caballero 2019). Obesity was also one of the risk factors which can evoke cardiovascular diseases, insulin resistance, hyperlipidemia, etc. Recent publication even verified that individuals with obesity had higher risk of COVID-19 infection, hospitalization, ICU admission and mortality (B. M. Popkin et al. 2020). Up to now, physical exercise, pharmacotherapy and dietary intervention are considered as major ways to control obese (G. A. Bray et al. 2016). Rice bran, the potential food ingredient for dietary intervention, was reported to be beneficial for attenuating obese via modulating lipid metabolism and gut microbiota (S. C. Yang et al. 2019; Y. Zou, Chen, et al. 2020). And peptide fractions extracted from rice bran with molecular weight <5 kDa and 5 ~ 10 kDa significantly promoted preadipocytes differentiation. Further analysis showed the activity of pentapeptide Glu-Gln-Arg-Pro-Arg against obesity (A. Kannan, Hettiarachchy, and Mahadevan 2012). Adipokines such as adiponectin and leptin, secreted by adipocytes, serve as the main regulators of obesity. Circulating adiponectin usually decreased while leptin increased during obesity, and replenishment of adiponectin contributed to reducing body weight and improving glucose/lipid homeostasis (M. O'Driscoll et al. 2021). There was also study reported that RBPH administration significantly up-regulated expression of adiponectin and down-regulated leptin

level, which therefore improved insulin resistance and lipid metabolism of rats fed with high-carbohydrate and high-fat diet (K. Boonloh et al. 2015b). These results suggested that RBP and RBPH could be the useful and potential natural products for anti-obesity.

Attenuating sarcopenia

Sarcopenia is a common metabolic disease under both physiological and pathological conditions, which usually occurred in older people and patients with wasting diseases. Protein nutritional support have been shown the potency to attenuate sarcopenia (J. Zhang, Li, et al. 2020b). Studies showed that whey and/or soybean protein ingestion significantly reduced burn injury or cancer cachexia induced muscle protein degradation, attenuated body mass loss and improved muscle function (G. Ren et al. 2021; Zhao et al. 2018). On one hand, protein intake could suppress skeletal muscle protein degradation and attenuate sarcopenia via inactivating ubquitin-proteasome system, reducing oxidative response, and inhibiting cell autophagy (J. Zhang, et al. 2020b). It has been shown that dietary supplementation of soybean derived peptides could reduce burn-induced sarcopenia through suppression of TLR4 expression and inhibition of phosphorylation of p65 (Zhao et al. 2018). Recent publications reported that RBPH had strong radical scavenging activity via decreased levels of ROS and RNS, and thus exhibited antioxidant effect (Y. Q. Liu et al. 2019; L. Wattanasiritham et al. 2016). Further study showed that peptides derived from rice bran could bind with TLR4, suppress phosphorylation of p65 and subsequently reduce H_2O_2-induced oxidative stress (Y. Liang et al. 2018), indicating the potential effect of RBPH on protecting skeletal muscle and mitigating sarcopenia via reducing oxidative stress. On the other hand, the protein rich in BCAA had been proved to be beneficial for promoting skeletal muscle protein synthesis and attenuating sarcopenia (C. J. Fuchs et al. 2019). Whey protein with high level BCAA was reported to be ideal protein to alleviate sarcopenia (J. D. P. Soares et al. 2020), while the content of BCAA in RBP was second only to that in whey protein isolate (20.39 vs. 21.72, Table 1). Therefore, the high content of BCAA in RBP might determinate its potential of promoting skeletal muscle protein synthesis. In summary, RBP and RBPH might exert potential capacity on attenuating sarcopenia via reducing oxidative stress and promoting skeletal muscle protein synthesis.

Promoting wound healing

With the emergency of an aging society, the proportion of older people is steadily increasing. And the incidence of chronic trauma such as pressure ulcers and diabetic foot ulcers is much higher in older long-term bedridden or diabetic patients due to most of them are either malnourished or at risk of malnutrition (J. A. Molnar, Vlad, and Gumus 2016). Thus, nutritional support was reported as an effective way to promote wound healing (J. K. Stechmiller 2010). In addition, infection and excessive inflammatory reaction is another influence factor of wound healing, since the microbiome change and biofilm formation significantly inhibited fibroblasts migration, re-epithelization and wound repair (T. R. Johnson et al. 2018). In study using all-layer skin defect rat model, wound healing was obviously accelerated in rats fed with normal protein diet than those fed with protein-free diet (K. Tsuda et al. 2010). Further study showed that soybean protein/cellulose nanofiber scaffolds which was used to mimic skin extracellular matrix could promote fibroblast proliferation, migration, infiltration *in vitro*, and accelerate re-epithelization and wound healing *in vivo* (S. Ahn et al. 2018). Moreover, soybean protein derived peptides treatment also contributed to correcting negative nitrogen balance, reducing inflammatory reaction and accelerating burn wound healing (J. Zhang, et al. 2020a; Zhao et al. 2019). Recently, peptides with sequences of LRRHASEGGHGPHW (Leu-Arg-Arg-His-Ala-Ser-Glu-Gly-Gly-His-Gly-Pro-His-Trp, LRR), EKLLGKQDKGVIIRA (Glu-Lys-Leu-Leu-Gly-Lys-Gln-Asp-Lys-Gly-Val-Ile-Ile-Arg-Ala, EKL), and SSFSKGVQRAAF (Ser-Ser-Phe-Ser-Lys-Gly-Val-Gln-Arg-Ala-Ala-Phe, SSF) were isolated and identified from enzymatic hydrolysates of RBP, and subsequently the antimicrobial activity and endotoxin-neutralizing activity of the peptides were further verified (M. Taniguchi et al. 2017). The results suggested that these peptides had the potency of reducing inflammatory reaction via their antimicrobial and endotoxin-neutralizing activities, which might be beneficial for accelerating wound healing. Chemically synthesized LRR, EKL and SSF were subsequently studied and the effects on enhancing proliferation, tube formation, and migration of HUVECs were revealed. These peptides also exerted important roles in promoting cell migration and wound healing of HUVECs using scratch migration assays (M. Taniguchi et al. 2019). Although there was still lack of evidence from *in vivo* study, existing evidence suggested RBPH had the potential of promoting wound healing.

Potential benefit to COVID-19 patients

COVID-19 is a global pandemic infectious disease, which is one of the greatest challenges facing humanity at present. An estimating model was established based on the data from 45 countries, and it was estimated that approximately 5% of populations had been infected in these 45 countries by September 1, 2020 (M. O'Driscoll et al. 2021). ACE2, as human homologue of ACE, was firstly identified and reported at 2000 (M. Donoghue et al. 2000), with high level expression in 23 human tissues including type II alveolar cells in the lung, proximal tubule cells in the nephron, myocardial cells, epithelial cells in the ileum and esophagus, and urothelial cells in the bladder (F. Chaudhry et al. 2020; X. Zou, Chen, et al. 2020). Difference with the function of ACE which contributes to producing angiotensin II (Ang II) and leads to vasoconstriction, ACE2 can convert Ang I into Ang 1-9 via digesting carboxy terminal leucine, and Ang 1-9 is subsequently hydrolyzed by ACE into Ang 1-7, which severs a role of vasodilation (M. Donoghue et al. 2000; V. B.

Patel et al. 2016). And ACE2 also can degrade Ang II to Ang 1-7 (M. Oz, Lorke, and Kabbani 2021). As shown in Figure 4, the function of ACE2 opposes to ACE. However, some prescription drugs with inhibiting activity of ACE in the treatment of hypertension, heart failure, diabetes mellitus, hyperlipidemias, coagulation disorders, and pulmonary disease may increase ACE2 expression in cellular and animal models, but this phenomenon was hardly observed in clinical trials (M. Oz, Lorke, and Kabbani 2021). Research focused on the infective mechanism of COVID-19 revealed that ACE2 was the cell surface receptor and mediated host cell entry of COVID-19 (M. Hoffmann et al. 2020; P. Zhou et al. 2020). However, after COVID-19 infection, the expression of ACE2 was significantly inhibited which might result in severe lung injury and poor prognosis. Interestingly, recent studies demonstrated that usage of ACE inhibitors was associated with shorter hospitalization and lower risk of mortality in hypertensive COVID-19 patients (N. Senkal et al. 2020; Zhang, Zhu, et al. 2020). Previous studies also revealed that RBPH treatment could inhibit ACE activity *in vitro* and reduce plasma level of ACE in animal model (O. Boonla et al. 2015; I. B. B. Piotrowicz et al. 2020; K. Senaphan et al. 2018; N. Shobako et al. 2018; Uraipong and Zhao 2016, 2018), indicating that RBHP was candidate plant based compounds to reduce the level of ACE and inhibit its activity. There still need more direct evidence from animal model and clinical trials for predicting whether RBPH's inhibitory activity of ACE is beneficial for COVID-19 patients.

Conclusion

With the in-depth study of RBP and RBPH, their functions including antioxidant activity, antihypertensive effect, antidiabetic effect, cholesterol-lowering activity, and cancer prevention were verified. And increasing functional peptides derived from RBPH were isolated and identified. They all absolutely elucidated that RBP and RBPH had better nutrition and health care effect. Although further studies also needed to confirm the potential novel functions of RBP and RBPH on anti-obesity effect, attenuating sarcopenia, promoting wound healing and benefiting to COVID-19 patients, it still provided future trends for new functional development of RBP and RBPH. In summary, RBP and RBPH are very promising functional ingredients which are worthy of further study, development and utilization.

Disclosure statement

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