Review article

Therapeutic potential of rice-derived polyphenols on obesity-related oxidative stress and inflammation

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A B S T R A C T

Global obesity rates are of epidemic proportion. With limited treatments available there is a large demand for therapeutic alternatives. Polyphenols derived from coloured rice varieties may serve as a potential functional food alternative in combating obesity and obesity-related diseases. The antioxidant and anti-inflammatory properties of polyphenols found in coloured rice varieties could have the ability to neutralize oxidative stress and modulate inflammatory responses in obese populations. This review discusses polyphenols derived from rice, the oxidative stress and inflammatory pathways involved in obesity pathogenesis, bioavailability of polyphenols and the therapeutic potential of polyphenols on transcriptional and molecular pathways related to obesity and obesity-related diseases.

Introduction

Metabolic Syndrome is a multifactorial disorder that develops through the interaction of several risk factors such as hyperglycemia, dyslipidemia, and hypertension (Huang, 2009). In conjunction to the aforementioned risk factors, obesity is the central and fundamental component to the development of this syndrome (Visioli, 2016). Obesity is the accumulation of abdominal adipose tissue resulting in an increase in the waist-hip ratio (Emdin et al., 2017). The WHO (2015), characterizes individuals who have a Body Mass Index (BMI) equal to or greater than 25 as overweight and a BMI equal to or greater than 30 as obese. Due to the exponential increase in obesity rates at epidemic proportions in developed countries, the process of adipogenesis and its transcriptional and physiological mechanisms have become a focal point in medical science (Salvado et al., 2015). Obesity manifests through multiple factors including genetics, environment, nutrition and level of physical activity (Rippe et al., 1998). In particular, studies have demonstrated obese individuals to have higher baseline profiles of inflammation and oxidative stress (OS) (Huang et al., 2015; Keaney et al., 2003).

Obesity has been significantly correlated with the development of other diseases including Type II diabetes mellitus (T2DM), cardiovascular disease, hypertension, a majority of cancers, asthma, chronic back pain, osteoarthritis and gall bladder disease (Guh et al., 2009). Healthier lifestyle choices are not always effective in combating obesity. Therefore, to overcome the obesity epidemic, therapeutic treatments are required, however, there are limited pharmaceutical treatments for obesity. A majority of drug treatments have been unsuccessful due to adverse side effects questioning safety concerns, thereby creating a high demand for alternative therapeutic options (Kakkar and Dahiya, 2015). The

incorporation of functional foods with bioactive properties into diets may serve as a potential complementary alternative for obesity treatment.

Rice (*Oryza Sativa* L.) is a staple food consumed at least once a day by more than half of the world's population and is cultivated in over 100 countries (Mohanty, 2013). Specifically, coloured rice varieties have been demonstrated to possess anti-inflammatory (Candiracci et al., 2014) and antioxidant properties (Sangkitikomol et al., 2010) thus presenting rice as a potential candidate for nutraceutical and/or functional food alternatives. In particular, red and black coloured wholegrain rice varieties have been demonstrated to have therapeutic characteristics that have been attributed to the presence of polyphenols.

Polyphenols are a subclass of phytochemicals that are predominant in grains, fruits, and vegetables (Santhakumar et al., 2014). Incorporation of polyphenols into diets through rice consumption could be a potential solution for reducing the incidence of metabolic syndrome and its associated risk factors such as obesity. Therefore, it is fundamental for rice breeding programs to develop rice cultivars that not only appeal to consumers in taste and texture attributes but are also enriched with polyphenols with potentially elevated antioxidant and anti-inflammatory capacity. It is also critical to highlight to health-conscious consumers that grains, when consumed as whole-grains, can serve as functional foods to meet their culinary and nutritional needs. This review aims to focus on the antioxidant, anti-inflammatory and anti-dyslipidaemic mechanisms of action by which rice-derived polyphenols could potentially modulate risks factors attributed to the development of obesity-related OS and inflammation.
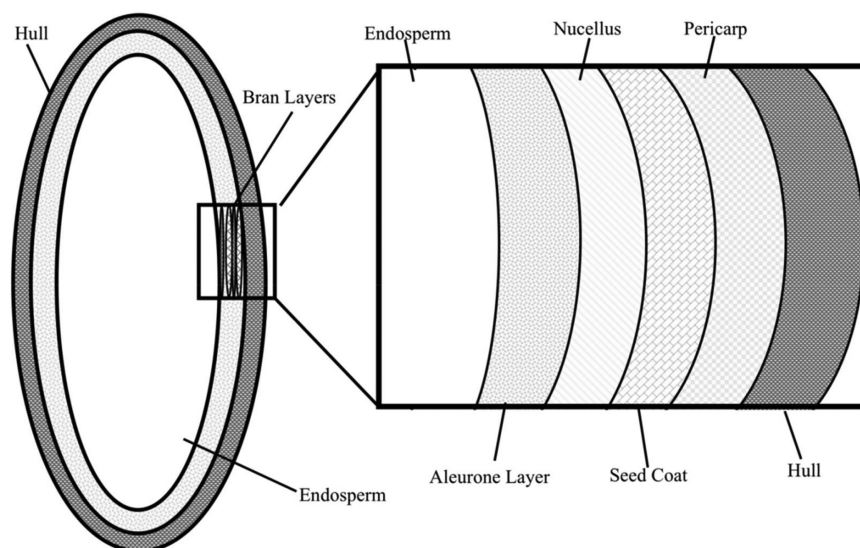
Polyphenols in rice

Polyphenols are the most widely occurring groups of compounds and assist plants with essential functions such as growth and reproduction, disease resistance and pigmentation (Balasundram et al., 2006). There are multiple parameters that can affect the phenolic content in different rice varieties such as climate, soil conditions, genetics and farming practices (Goufo and Trindade, 2017) hence making it extremely difficult to pinpoint the exact phenolic composition of each rice variety.

Rice consists of different layers, the outer layer, generally termed the hull constitutes between 16 and 28% of paddy rice weight (Corke, 2015). During a process called de-hulling, the hull is removed to expose the bran. The resultant product is generally known as wholegrain rice. Wholegrain rice is the endosperm (white rice) with the bran layers still intact (Kealey and Clampett, 2000). The bran is comprised of several layers (the pericarp, seed coat, nucellus and aleurone layers), which constitutes 6–7% of the total paddy rice weight (Fig. 1) (Chen et al., 1998). It is in these ectopic layers of the endosperm that a large majority of the polyphenols resides. Polyphenols exist in both soluble and insoluble forms, with the soluble form accounting for 38–66% of the phenolic compound content in light brown rice varieties to approximately 81% of the phenolic compound content in red and black rice varieties (Adom and Liu, 2002; de Mira et al., 2009). Table 1 demonstrates the soluble and insoluble polyphenol composition found in wholegrain pigmented and non-pigmented rice varieties.

Phenolic acids

At least twenty-nine different phenolic acids have been identified in rice with ferulic acid (56–77%), *p-coumaric* acid (8–24%) and sinapic acid (2–12%) being the most abundant (Goufo and Trindade, 2017). Overall, phenolic acids in rice are comprised of 61–89% hydroxycinnamic acids and 12–28% hydroxybenzoic acids (Goufo et al., 2014). Furthermore, insoluble phenolic acids comprise 51% of the total phenolic content (TPC) in bran and 61% of the total TPC in whole-grain rice. Studies have shown that brown rice varieties have higher levels of ferulic acid and *p-coumaric* acid when compared to the same varieties polished to white rice (Butsat and Siriamornpun, 2010; Zhou et al., 2004), suggesting that a large majority of phenolic acids are retained in the rice bran. In pigmented rice varieties, the global average of soluble TPC has been reported to be two to three times higher than the insoluble TPC in bran and whole-grain. However, the studies that reported these findings used extraction solutions containing methanol combined with hydrochloric acid to ascertain soluble phenolic acids (Tuncel and Yılmaz, 2011; Zhang et al., 2010). Hence, using aqueous mixtures containing alcohol and acid may facilitate in potential insoluble phenolics being released due to the acid addition, thus presenting results with higher soluble TPC compared to other studies (Goufo and Trindade, 2014; Wrolstad et al., 2005).

Fig. 1. Anatomical composition of the rice grain. The bran constitutes of several layers and it is where a large majority of the polyphenols reside in both soluble and insoluble forms.

Table 1
Average ranges of total polyphenol composition of whole-grain non-pigmented and pigmented rice varieties.

Compound	Rice variety	Soluble	Insoluble	References
Total phenolic acids (mg/100 g DW)	Non-pigmented	0.1–254	1.64–484	(Aguilar-Garcia et al., 2007; Deng et al., 2012; Irakli et al., 2012; Vichapong et al., 2010; Zhu et al., 2010)
	Pigmented	38.1–2470	2.53–401.6	(Chung and Lee, 2003; Seo et al., 2013; Vichapong et al., 2010; Zhu et al., 2010)
Total flavonoids (mg catechin/100 g DW)	Non-pigmented	31–317	0.6–24	(Basu et al., 2012; Chung and Lee, 2003; Min et al., 2012; Vichapong et al., 2010)
	Pigmented	1.15–4680	1.66–337.0	(Kong and Lee, 2010; Min et al., 2011; Mohanlal et al., 2013; Vichapong et al., 2010)
Total anthocyanins (mg C-3-G/100 g DW)	Non-pigmented	2.0–3.26	ND	(Saikia et al., 2012; Sutharut and Sudarat, 2012)
	Pigmented	0.33–245.36	ND	(Sompong et al., 2011; Yodmanee et al., 2011)
Total proanthocyanidins (mg catechin/100 g DW)	Non-pigmented	5.02	ND	(Mohanlal et al., 2013)
	Pigmented	5.04–202	ND	(Chen et al., 2016; Finocchiaro et al., 2010; Min et al., 2012)

Non-pigmented = Brown rice varieties; Pigmented = coloured (black + purple + red) varieties. C-3-G, Cyanidin-3-Glucoside; DW, dry weight; ND, Not detected.

Flavonoids

There are limited studies that focus on the flavonoid content in rice (Sriseadka et al., 2012). Excluding anthocyanidins, seven flavonoids in rice have been quantified and confirmed. Tricin accounts for 77% of the total flavonoid content followed by luteolin (14%), apigenin (6%), quercetin (3%), isorhamnetin (1%), kaempferol (<1%) and myricetin (<1%) (Deng et al., 2013; Goufo and Trindade, 2014; Irakli et al., 2012). Other flavonoids have been identified in rice, however, confirmation of their existence and quantification in other rice varieties remains to be explored.

Anthocyanins and proanthocyanidins

Anthocyanins are glycosylated aglycones and are the primary pigments in coloured rice. About eighteen anthocyanins have been identified in rice, of which only four have been quantified (Goufo and Trindade, 2014). Among rice cultivars, the different forms of anthocyanins vary depending on bran colour and the fraction of the rice variety being analyzed. However, a large majority of studies report cyanidin-3-*O*-β-glucoside (C3G) (51–84%) and peonidin-3-*O*-β-glucoside (P3G) (6–16%) to be the major anthocyanin constituents of black/purple rice (Ichikawa et al., 2001; Shahidi and Ambigaipalan, 2015; Zhang et al., 2010). Proanthocyanidins like anthocyanidins are highly reactive to reactive oxygen species (ROS) and may have health promoting effects against diseases. In rice, catechin and epicatechin are the most abundant proanthocyanidins in the bran (21–47 mg/100 g) and husk (2.0–2.74 mg/100 g) of pigmented rice varieties (Goufo and Trindade, 2014). Furthermore, Chen et al. (2016), found a 4.3-fold variation in total proanthocyanidin content in the bran of thirty-two red and purple rice varieties. The study found no significant differences in proanthocyanidin content between the red (18.64 $\pm$ 7.06 mg/g^{-1} bran) and purple (22.58 $\pm$ 1.55 mg/g^{-1} bran) brans. However, the study did find the purple varieties to have significantly higher total phenolic and total flavonoid contents compared to the red varieties. The study attributed the higher phenolic and flavonoid contents in the purple rice to potential anthocyanins residing in the bran.

Bioavailability of rice-derived polyphenols

The bioavailability of polyphenols is a new area of interest in polyphenol research. However, there are limited studies in humans demonstrating polyphenol metabolism, absolute bioavailability and the mechanisms contributing to potential therapeutic effects. The absorption and metabolism of polyphenols is largely dependent on their chemical structure, degree of glycosylation/ acylation, conjugation with other polyphenols, molecular size, degree of polymerization and solubility (Bravo, 1998). Polyphenol profiles generated from *in vitro* gastrointestinal digestion assays on rice have found digested cooked rice to have higher TPC compared to undigested cooked and raw rice. Ti et al. (2015), found digested cooked brown rice to have 54.1% more TPC compared to raw brown rice. Of particular interest, the study found bound ferulic acid was 112.5% higher in digested cooked brown rice compared to raw brown rice. However, only one brown rice variety was used, limiting the ability to compare cooking and *in vitro* digestive processes between different rice varieties.

Similar findings were seen by Salawu et al. (2016), where cooked digested rice had higher TPC compared to raw digested rice. In particular, the digested cooked *Ofada* brown rice variety contained 14% more total phenolics compared to digested raw *Ofada* rice. This study also included another brown rice variety called *Gboko*. The *Gboko* variety did not have a higher cooked digested TPC compared to the digest raw *Gboko* sample. Furthermore, this study did not specify the pericarp colour of the rice varieties. The study stated the rice varieties used were phenolic-rich. These studies indicate that cooking and digestive processes may increase the bioavailability of rice-derived polyphenols. In particular, these studies suggest that the thermal cooking process weakens the cell wall of the rice grain, enabling a higher extractability of polyphenols in particular of bound polyphenols.

The bound fraction has been attributed to be the major contributor of polyphenols, whereby the bound phenolics may survive the upper gastrointestinal digestive conditions and be subjected to colonic gut microflora where the bulk of the bound polyphenols are released (Adom and Liu, 2002). Some studies highlight that depending on the sugar moiety, anthocyanins are significantly hydrolyzed by gut microflora by cleavage of the 3-glycosidic linkage where the aglycones rapidly degrade into phenolic acids and aldehydes (Kay et al., 2004; Keppler and Humpf, 2005). Furthermore, methoxyl derivatives such as syringic and vanillic acid undergo O-demethylation in the presence of intestinal microflora (Faria et al., 2014). Hence, microbiota cleavage may modify the antioxidant properties and intestinal absorption capabilities of the ingested parent polyphenol.

In contrast, studies have shown that polyphenols, particularly glucuronidated and methylated conjugate metabolites of anthocyanins retain their basic anthocyanin molecular structure in urine and plasma of adult men indicating that antioxidant activity may be retained (Kay et al., 2005). de Ferrars et al. (2014) found that

anthocyanins were metabolized into an extensive range of metabolites with varying levels of kinetics in eight healthy males. The study found C3G degraded into protocatechuic acid and phloroglucinaldehyde. Interestingly, protocatechuic acid further degraded into 13 other metabolites including vanillic acid, ferulic acid and hippuric acid. The maximum serum concentration (C_{max}) of C3G post consumption was 141 nM at around 1.8 h post consumption. Protocatechuic acid had a C_{max} of 146 nM occurring 2–3 h later than C3G. Whilst the mechanism is not entirely clear, results of the study suggest that the anthocyanin C3G primarily undergoes spontaneous degradation to protocatechuic acid and phloroglucinaldehyde in the small intestine. The study reported that many metabolites did not return to baseline after the 48 h sampling period. Therefore, sampling time can be seen as a limitation to this study as it did not extend to an appropriate time to determine complete recovery of the metabolites. In conjunction, the study was also limited by the small sample size ($n = 8$). Other bioavailability studies have suggested the liver to be the site of post-absorbed anthocyanin metabolism, resulting in anthocyanin monoglucuronides (Kuntz et al., 2015).

The mechanisms behind polyphenols metabolism and absorption are still very much debated. Further detailed studies need to be conducted to determine the extent to which polyphenols are metabolized and the mechanisms surrounding direct absorption of ingested parent polyphenols and their metabolites with particular focus on coloured rice consumption.

Mechanisms in obesity pathogenesis

The mechanisms behind the pathogenesis of obesity have been extensively studied. Increased weight gain for a large majority of people is the result of high-fat diets (HFD) and high-sugar diets (HSD) in conjunction with physical inactivity. In adipocytes, excessive accumulation of intracellular triglycerides initiates lipotoxicity on mitochondria. Mitochondrial dysfunction has been associated in the pathogenesis of obesity and obesity-related diseases. In functional mitochondria, glucose is metabolized via the tricarboxylic acid cycle where electron donors are generated and enter the mitochondrial electron transport chain. However, with increased adiposity resultant of an unhealthy diet, the increased glucose load contributes to larger amounts of glucose being oxidized by the tricarboxylic acid cycle, resulting in the accrual of adenosine triphosphate (ATP) in the mitochondria. ATP accrual reduces adenosine diphosphate (ADP) levels, the efficiency of oxidative phosphorylation and mitochondrial uncoupling promoting the release of ROS and electron leakage (Savini et al., 2013).

Furthermore, the rapid increase in adipose tissue instigates recruitment and infiltration of macrophages resulting in localized low-grade inflammation (Yang et al., 2014). M1 macrophages contribute to the pro-inflamed status and are prevalent in obese individuals (Lumeng et al., 2007). Upon phagocytosis of oxidized low density lipoproteins (ox-LDL), M1 macrophages develop inflammatory foci called crown-like structures that are utilized to surround and remove dead adipocytes (Howe et al., 2013). However, the development of crown-like structures exposes M1 macrophages to saturated fatty acids (SFA's) resultant of obesity-associated lipolysis. Exposure to SFA's activates the Toll-Like 4 Receptor (TLR4) at the cell surface of the M1 macrophage and initiates the activation Nuclear Factor kappa-B (NF-κB) signalling pathway (Lee et al., 2003). Proinflammatory cytokines (such as Tumor Necrosis Factor-α (TNF-α), Interleukin-6 (IL-6), inducible Nitric Oxide Synthase (iNOS)) and chemokines (monocyte chemotactic protein-1 (MCP1)) are secreted by M1 macrophages and contribute to obesity pathogenesis at a local and systemic level (Amano et al., 2014; Weisberg et al., 2003; Xu et al., 2003). Rice-derived polyphenols have been demonstrated to have antioxidant and anti-inflammatory potential in biological systems.

*Antioxidant properties of rice-derived polyphenols*

Rice-derived polyphenols have been shown to contain antioxidant potential. In particular, the antioxidant potential of flavonoids such as anthocyanins has been particularly attributed to their chemical structure. The level of hydroxylation on the 3′ and 4′ positions of the B-ring structure are fundamental determinants of the radical scavenging activity (Wang et al., 1997). However, there are limited studies demonstrating the antioxidant mechanisms of rice-derived polyphenols in biological systems. At the molecular level, black rice polyphenol extract (BRE) has been shown to protect supercoiled DNA from scission in peroxyl and hydroxyl radical environments (Hu et al., 2003). Furthermore, the study revealed that BRE suppressed the formation of ox-LDL in an in vitro oxidation assay and reduced nitric oxide production in macrophages without inducing cytotoxicity.

Sangkitikomol et al. (2010) screened the antioxidant activity of twenty-one commercially available red, black and black sticky rice varieties. The study found that the black-sticky rice had the highest antioxidant activity and also demonstrated to have DNA-protective characteristics in human mononuclear leukocytes in hydrogen peroxide-induced environments. Unfortunately, the study only investigated one black sticky rice variety out of the twenty-one screened rice varieties in their biological assay. The study chose the particular black sticky variety based on the antioxidant chemistry screening. However, chemistry-based antioxidant screening may not be a true representation of the antioxidant potential of rice-derived polyphenols. Nam et al. (2006) found the thiocyanate method for determining in vitro lipid peroxidation was not a true representation of the antioxidant activity of pigmented rice varieties when compared to an in vitro biological peroxidation model. The study found selected pigmented rice varieties contained high antioxidant activity in the biological assay primarily displayed pro-oxidant activity in the thiocyanate assay. Nam et al. (2006) suggested that biological in vitro models may be more beneficial than in vitro chemistry assays in determining the antioxidant mechanism of action in biological systems. A comparison between pigmented varieties would be of interest to determine the biological antioxidant properties of rice-derived polyphenols to further develop therapeutic profiles.

Physiologically, BRE has been illustrated to increase plasma high density lipoprotein (HDL) cholesterol and upregulate SOD and catalase (CAT) activity in treated mice liver tissue (Chiang et al., 2006). In the same study, SOD and CAT activity was upregulated by 161.6% and 73.4% respectively in HepG2 cells. The study attributed their findings to the ability of anthocyanins, which are predominant in BRE, to upregulate radical scavenging enzymes (Fig. 2). Mohd Esa et al. (2013), demonstrated brown rice extract supplementation to hyperlipidaemic rabbits, increased SOD and glutathione peroxidase activity by 84.9% and 43.3% respectively. Furthermore, eight week supplementation of BRE in rats on a high-fructose diet has been shown to significantly reduce blood oxidized-glutathione/glutathione ratio compared to high fructose diet controls (Guo et al., 2007). The study reported the BRE supplemented groups to having significantly lower levels of lipid peroxidation compared to the control group suggesting, the antioxidant properties associated with BRE (in particular, anthocyanins) may contribute to the inhibition of OS.

BRE has also been demonstrated to restore non-enzymatic antioxidant levels in rats with alcohol induced liver damage. In particular, serum glutathione levels were found to be significantly higher by 1.56 mg/l^{-1} in BRE supplemented rats compared to non-supplemented alcohol-induced controls (Hou et al., 2010). Wang et al. (2007) conducted a double-blind, randomised trial where
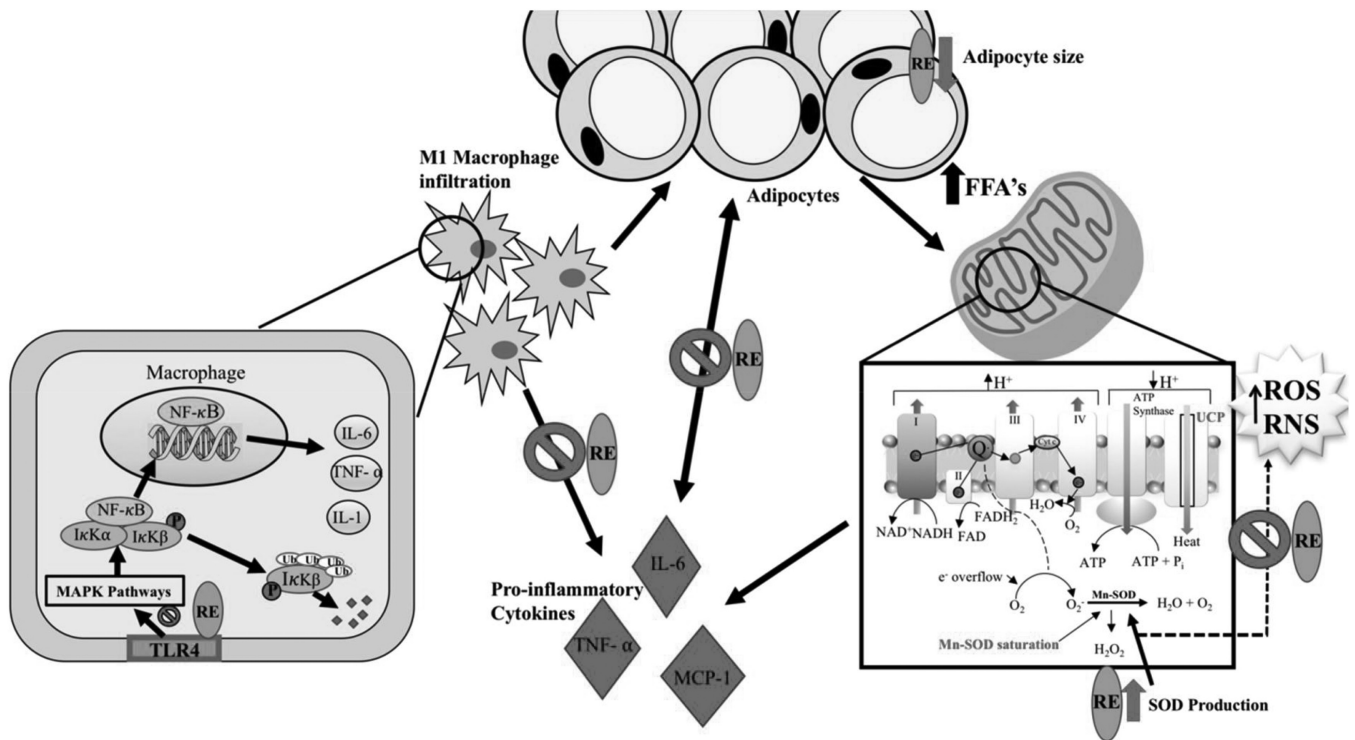
Fig. 2. The effect of rice-derived polyphenols on obesity pathways. Rice-derived polyphenol extracts (RE) have been shown to reduce adipocyte size and increase SOD production contributing to the reduction of ROS and RNS. Proinflammatory cytokines are also reduced in the presence of RE as RE have been shown to supress the secretion of proinflammatory cytokines in adipocytes and inhibit the MAPK pathways in macrophages.

10 g of BRE was administered daily over six months to participants diagnosed with coronary heart disease. The study showed that participants who ingested the BRE had an increase in plasma total antioxidant capacity by $1.3\,l^{-1}$. The study did not find a significant increase in serum SOD levels indicating that anthocyanins may not upregulate the production of *in vivo* antioxidants but rather the direct intact absorption of anthocyanins may influence the increase in total antioxidant capacity by acting as a direct scavenger of ROS.

Anti-inflammatory effects of rice-derived polyphenols

Chronic inflammation has been associated in the obese and a major contributor to obesity-related diseases (Kushwaha, 2016). Rice-derived polyphenols have been demonstrated to have anti-inflammatory potential. Candiracci et al. (2014), showed that supplementation of polyphenol extract derived from rice bran exerted anti-inflammatory properties by reducing the production of pro-inflammatory cytokines TNF-α, IL-6 and iNOS in the adipose tissue of obese Zucker rats. Adipocyte analysis determined that rice-bran polyphenol supplementation reduced adipocyte size in both abdominal and epididymal adipose tissue. Nevertheless, the study did not observe any significant differences in the final body weight of the rats and did not discuss the variety of the rice bran used to obtain the extracts. Similar findings with brown rice extracts have been demonstrated to reduce IL-1α and TNF-α production cultured mouse macrophages (Okai et al., 2009).

Rice bran extracts have been shown to inhibit the release of prostaglandin E2 as well as modulate pro-inflammatory cytokine production in activated microglia (Bhatia et al., 2016). Similar findings were found by Min et al. (2010), where C3G and its metabolites, protocatechuic acid and cyanidin derived from black rice was found to attenuate the production of pro-inflammatory cytokines and their associated mediators in carrageenan-induced inflammation in BALB/c mice. Furthermore, the study found C3G and its metabolites downregulated nitric oxide synthase and cyclooxygenase-2 gene expression in the RAW 264.7 cells. Interestingly, C3G and its metabolites inhibited the phosphorylation of IκB-α, the nuclear translocation of NF-κB and the activation of mitogen-activated protein kinases (MAPK) which suggests that rice-derived polyphenols act as potent mediators of inflammation at the molecular level (Fig. 2). Shalini et al. (2015) observed similar characteristics where the flavonoid tricin isolated from red pigmented medicinal rice inhibited the signalling cascade of the MAPK pathways. Intraperitoneal injection of brown and black rice bran extract were found to reduce proinflammatory biomarkers in inflammatory mice models (Choi et al., 2010). In particular, the study found the expression of 5-LOX (5-lipooxygenase) was downregulated in mice treated with black rice bran. These findings suggest that flavonoids found in BRE may suppress the expression of 5-LOX and therefore effect downstream signalling such as intracellular adhesion molecule-1 expression reducing the infiltration of neutrophils into tissue (Choi et al., 2010).

Washing and cooking of black rice has been demonstrated to reduce the polyphenolic content and the antioxidant scavenging activity in *in vitro* antioxidant assays (Bhawamai et al., 2016). Interestingly, the study found cooked rice to have similar anti-inflammatory effects when compared to raw rice polyphenol extract, suggesting that thermal cooking did not inhibit the anti-inflammatory activity of black rice. Hence, rice-derived polyphenols may be targeting pathways of inflammation and hence may prove beneficial in overcoming the obesity epidemic.

Anti-dyslipidaemic properties of rice-derived polyphenols

Dyslipidaemia is generally termed as abnormal levels of lipids in the blood and has been significantly correlated to obesity. Biomarkers to establish blood lipid profiles include the total cholesterol, low density lipoprotein (LDL), HDL and triglycerides. Hyper-dyslipidaemia can be a consequence of increased adiposity

associated with obesity can result in elevated levels in total cholesterol, LDL and triglycerides. In *in vitro* studies, black rice extract (BRE) has been shown to reduce lipid accumulation in C3H101/2 mesenchymal stem cells (MSC's) by suppressing adipocyte differentiation via downregulating key adipogenic transcription factors peroxisome proliferator activated-receptor-γ, CCAAT-Enhancer Binding Protein-α and CCAAT-Enhancer Binding Protein-∂ (Kim et al., 2016). The same study found that BRE was able to promote osteogenesis in MSC's via the upregulation of mRNA runt-related transcription factor 2 and alkaline phosphatase elevating intracellular calcium deposition. Similar observations was demonstrated by Jang et al. (2015), however, the study identified C3G and P3G as the most abundant polyphenols in their BRE. The study proposed that the anthocyanins potentially acted as regulators of the adipocyte/osteoblast axis in precursor cells as C3G and P3G inhibited lipid accumulation and induction of adipocyte transcription factors during adipocyte differentiation. Furthermore, the study also found that BRE prevents bone density loss in ovariectomized rats, indicating that BRE could be used as potential treatments for obesity and osteoporosis.

Anthocyanins in BRE, have been demonstrated to improve blood glucose levels (Prangthip et al., 2013), reduce serum triglyceride levels by 46% (Xia et al., 2006) and to promote weight loss of 4.6% (Yang et al., 2011) in rodents. A study by Jang et al. (2012), detailed BRE supplementation upregulated the expression of mRNA related to β and ω fatty acid oxidation. Interestingly, even though fatty acid oxidation had increased in the presence of BRE, serum triglyceride levels and total cholesterol levels significantly decreased. BRE has been shown to improve plasma triglyceride levels in mice fed high fructose diets. Over an 8 week period, BRE was supplemented to rats on a high fructose diet (Guo et al., 2007).

Twelve-week supplementation of partially-abraded brown rice has been shown to attenuate weight gain and improve lipid metabolism in pre-diabetic overweight human subjects (Araki et al., 2017). In addition, brown rice bran supplementation has been shown to significantly reduce serum cholesterol levels and improve low density lipoprotein cholesterol to high density lipoprotein cholesterol ratios by 0.6 mol/mol in moderately hyperlipidemic human subjects (Gerhardt and Gallo, 1998). Similar results were found by Qureshi et al. (2002), where human participants were supplemented with different brown rice bran fractions. The study found rice bran water solubles were effective in lowering serum glucose, total cholesterol, LDL-C and apolipoprotein B levels in both Type I and T2DM participants. The health promoting effects of the rice bran was attributed to the synergistic effect of multiple bioactive micro-components present in the rice bran (Table 2). In particular, the free-radical scavenging activities of ferulic acid, α-lipoic acid and *p*-sinapic acid were suggested in the study to improve the complications associated with diabetes such as glycation, glycoxidation, atherosclerosis and hyperlipidemia.

Conclusion and future directions

In conclusion, the use of polyphenol-rich functional foods such as coloured rice could potentially act as a complementary therapeutic alternative to obesity and obesity-related diseases such as metabolic syndrome and cardiovascular disease. Studies to-date suggest that polyphenol supplementation into a HFD/HSD can modulate microbiota environments, regulate blood glucose, insulin and triglyceride levels as well as attenuate weight gain and visceral adipose tissue deposits via targeting inflammatory and OS pathways at the transcriptional and physiological level.

Rice is a major staple in more than half of the world's population, therefore integration of polyphenol-rich coloured rice varieties into global diets may prove beneficial in combating the obesity epidemic. Future work in identifying the synergistic effects of rice-derived polyphenols is required, specifically investigating the consumption of wholegrain rice and its effect *in-vivo* may

Table 2
Anti-dyslipidaemic potential of polyphenols derived from pigmented whole-grain rice in humans.

Reference diet	Target group	Study design and intervention	Effects	Reference
Brown rice bran	Healthy normal	Participants consumed 84 g of rice bran/day for 6 weeks in a randomised double blinded trial	↑ Triglycerides ↓ Total Cholesterol ↓ LDL ↑ HDL	(Gerhardt and Gallo, 1998)
Stabilised brown rice bran	Clinically diagnosed T2DM	Participants consumed stabilised rice bran, rice bran water solubles or rice bran fibre concentrates for 60 days for each rice bran fraction with a 30-day washout period between each fraction	↓ Triglycerides ↓ Total Cholesterol ↓ LDL =HDL	(Qureshi et al., 2002)
Stabilised brown rice bran	T2DM	Participants were divided into two groups where one group consumed 20 g of rice bran daily compared to a placebo group for 12 weeks	↓ Triglycerides ↓ Total Cholesterol ↓ LDL =HDL	(Cheng et al., 2010)
Black rice pigment fraction	Clinically diagnosed coronary heart disease	Participants consumed 10 g of black rice pigment fraction daily for 6 months	↓ Triglycerides ↓ Total Cholesterol ↓ LDL =HDL	(Wang et al., 2007)
Pre-germinated brown rice	Impaired glucose tolerant females	Participants were gradually weaned onto a pre-germinated brown rice diet for 4 months as a staple food.	↓ Triglycerides ↓ Total Cholesterol ↓ LDL ↑ HDL	(Nhung et al., 2016)
Black rice bran	Overweight/obese	Participants consumed snack bars containing pigmented rice bran for 8 weeks whilst on a 25% calories restricted diet	↑ Triglycerides ↓ Total Cholesterol ↓ LDL ↓ HDL	(Hongu et al., 2014)

HDL, High density lipoprotein; LDL, Low density lipoprotein; T2DM, Type II diabetes mellitus. ↑, Increase; ↓, Decrease; =, No change.

demonstrate an alternative and possibly a more pronounced effect than the consumption of a purified polyphenol on its own.

Conflict of interests

The authors declare no conflict of interests. All authors have read and approved the final manuscript.

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