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REVIEW ARTICLE

The Role of Lipopolysaccharide and Tight Junction Protein-1 (Zo-1) Levels and Symbiosis of Black Rice Extract in Obese Patients

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Abstract

Excessive fat accumulation, which is commonly known as obesity, causes health problems for the community, such as metabolic disorders. Recent studies have shown that the gut micro biota is involved in the occurrence of metabolic disorders in obesity. The gut micro biota can regulate body weight by influencing metabolic processes, regulating the expression of host genes, increasing the ability to extract and store energy. Intestinal micro biota imbalance and increased plasma lipopolysaccharide (LPS) contribute to inflammation in obesity. The latest safe approach in cases of obesity is to use active ingredients from local foods. In South Sulawesi, Indonesia and also in other Asian countries found black rice as the local product that is very good for health because the high level of bioactive compounds that are important for health such as anthocyanin, proteins, amino acids, and phenolic acids. The ingredients in black rice play a role in modulating the composition of the intestinal micro biota as indicated by the increasing composition of bifid bacterium and Lactobacillus. The increase in the composition of Bifid bacterium causes improvement in the expression of tight junction proteins in the intestinal epithelium, thereby contributing to prevent the translocation of LPS into the circulation. Apart from its role in modulating the composition of bacteria, it can also function to influence intracellular signaling.

Keywords: *Obesity, Intestinal micro biota, LPS, tight junction, Black rice.*

Introduction

The increase the prevalence of obesity that has occurred in the last few decades is related to lifestyle changes, namely the lack of physical activity and an increase in excessive consumption of foods containing high fat. Obesity is an abnormal or excessive fat accumulation that poses a risk to health. Obesity is considered to be a public health challenge whose prevalence continues to increase and underlies various metabolic and cardiovascular diseases [1]. The prevalence of obesity has spread out in most western countries over the past 30 years [2].

World Health Organization (WHO) data in 2016, more than 1.9 billion adults aged 18 years up are overweight; around 39% and 13% are from the world's population. The prevalence of obesity worldwide nearly triple between 1975 and 2016 [3].Obesity causes public health problems such as several chronic disorders, including type-2 diabetes, cardiovascular diseases (CVD), hypertension, musculoskeletal disorders (especially osteoarthritis), poor mental health, cancer, and causes negative effects on quality of life, work productivity, and health care costs [4].

New research shows that the gut micro biota is involved in obesity and metabolic disorders, with the decrease type of gut micro biota, the Bactericides / Firmicute ratio [5, 6]. The gut micro biota can regulate body weight by affecting the metabolic, neuroendocrine and immune functions of the host. The gut micro biota, as a whole, provides additional metabolic functions and regulates host gene expression, increases the ability to extract and store energy while on a diet and contributes to weight gain. Imbalances in the gut micro biota and increase plasma lipopolysaccharides in obesity may also act as inflammatory factors associated with the development of atherosclerosis, insulin resistance and weight gain [7].

Given the impact of obesity due to excessive consumption of high calorie foods, various approaches to treating obesity have been widely researched so that being overweight or obese can increase the risk of death. Aerobic training is the optimal mode of exercise for reducing fat mass. Resistance training is required to increase lean muscle mass in middle-aged and overweight / obese individuals. In addition, there is also cognitive behavioral therapy that directly deals with behaviors that require change in order to lose weight and maintain weight loss.

Pharmacological therapy can help patients to improve their risk of obesity-related diseases. The Food and Drug Administration (FDA) has approved certain drugs that can be used in the treatment of obesity for lifestyle changes. The drugs are Orlistat, Phentermine / Topiramate, Lorcaserin, Naltrexone / Bupropion, and Liraglutide. It should be noted that certain weight loss drugs have previously been withdrawn due to safety concerns and the drug effects of the various pharmacological agents used for the treatment of obesity [8-10].

The current approach that safe in treating the inflammatory process in obesity involves the use of active ingredients from local foods. Morais et al. finds that supplementing with anthocyanin-rich jussara powder can normalize weight gain, serum cholesterol, triglycerides, and restore gut bacteria Bifidobacterium and Lactobacillus in mice fed a trans fatty acid diet [11, 12].

Black rice (Oryza sativa L.) is a local food originating from South Sulawesi, Indonesia, and is also commonly found in Asia and exported to other countries. Consumption of black rice is in great demand because of the high level of bioactive compounds that are important for health [13].

The main bioactive compounds found in black rice include gallic, protocatechuic, hydroxybenzoic, vanilic acid, cyanidin 3-O-glucoside, peonidin-3-O-glucoside, proanthocyanidin (C3G), flavanols, catechins, epicatechins, carotenoids, and γ -oryzanol [2]. Black rice, an anthocyanin-rich pigment rice, is widely consumed worldwide and is considered the most nutritious of all rice genotypes [13].Many studies have shown that diets with black rice anthocyanin extract

weaken the development of obesity, hypercholesterolemia, liver steatosis, and atherosclerosis [14, 15].Many studies have shown that these compounds can improve lipid profiles, anti-inflammatory, anti-cancer and reduce oxidative stress, can also treat heart disease, and prevent diabetes [16, 17]. Therefore, several studies have been interested in black rice in people with obesity and metabolic disorders.

Bioactive of Black Rice

Black rice is one type of rice plant with a distinctive color, black, more than 60% of the world's black rice is cultivated in Asian countries such as Indonesia, China, Thailand [18].Black rice is characterized by its high anthocyanin content. The main anthocyanin is found in black rice include cyanidin 3-O-glucoside (6.3 mg / g) and peonidin-3-O-glucoside (3.6 mg / g).

Anthocyanidine, the basic structure of the anthocyanine, consists of an aromatic ring that is bound to a heterocyclic ring containing oxygen. This oxygen forms bonds with carbon bonds in the third aromatic ring. The structural characteristics of anthocyanins make it highly reactive with reactive oxygen species (ROS). The concentration of flavones and flavonos are also found higher in black rice compared to other rice variants.

Another study reported that the mean anthocyanin content is 35 times higher in black rice compared to other rice. In addition to the content of bioactive compounds,[19]. Black rice contains protein and essential amino acids that are higher than white rice. Amino acids play a major role in individual dietary factors to modify the risk of developing pre-diabetes conditions. In addition, the anthocyanin content in black rice is reported to inhibit the levels of α-glycosidase and α-amylase enzymes, which are the main enzymes that are closely related to postprandial glucose levels.

Therefore black rice can be used in diabetes management. Anthocyanin from natural substances can also reach the colon and perform as candidates for nutritional therapy in gastrointestinal tract disorders. Anthocyanin in the intestine can be distorted as phenolic acids by ring cutting, dehydroxylation, and methylation reactions by the intestinal micro biota.

These phenolic compounds are proven to increase the growth of beneficial bacteria and inhibit the growth of bacteria that are bad for the body. Cyanidine-3-O-glucoside and ß-glycoside provide energy for bacteria and increase prebiotic activity[20, 21].Black rice is also rich in phenolic acids which are generally categorized into free phenolic acids and bound phenolic acids.

Free phenolic acids can be in the form of cinnamic, protocatechuic and gallic acids, while bound phenolic acids can be in the form of ferulic, coumaric and caffeic acids. Among free phenolic acids, protocatechuic acid is the most dominant (81-90% of the total free phenolic acid), while ferulic acid is the type of bound phenolic acid that is mostly found (about 60%) in black rice. Consumption of white rice has been associated with an increased risk of developing type 2 diabetes mellitus and an increased risk of impaired glucose homeostasis. However[22. 23].

Black Rice-Gut Micro-Biota

Black rice has high anthocyanin content. Anthocyanin is considered as substances with good health effects, such as antioxidants, anti-inflammatory, anti-cancer, anti-proliferative, and as substances that have the potential to affect the growth of susceptible microorganisms. Several in vitro studies revealed that the number of potentially beneficial bacteria (Bifid bacteria and Lactobacilli) increased after ingestion of purple sweet potato anthocyanin and grape seed extracts [18].

The gastrointestinal tract contains at least 1014 bacteria, with the highest density in the large intestine. The composition of the gastrointestinal tract micro biota is influenced by many factors including genetics, gender, age, height, weight, dietary factors, immune system, stool consistency, sleep, medical history, ethnogeographic and socioeconomic conditions, sanitary conditions, smoking habits, and use of antibiotics [24].

The intestinal microbiota functions as an anti-infection, immunomodulation and in the metabolic process. One of the main metabolic activities of the gastrointestinal tract microbiota is the production of non-gas short chain fatty acids (SCFA) [25].These SCFAs can interact with the host via several pathways, thereby affecting important processes such as inflammation [26].

Like polyphenols, anthocyanin is difficult to absorb in the small intestine and can be converted into phenolic acid by the intestinal microbiota through edge ring, dehydroxylation and methylation reactions. The metabolism produced from polyphenols have proven that polyphenols can selectively motivate the growth of beneficial bacteria and inhibit the proliferation of harmful bacteria [26. 27]. Obesity is associated with phylum and specific changes in the gut micro biota, and reduce intestinal bacteria [28. 29].

The content in black rice is known to play a role in modulating the composition of the intestinal microbiota, indicated by increasing the composition of Bifidobacterium and Lactobacillus [18]. The increase in the composition of Bifidobacterium causes an improvement in the expression of tight junction proteins in the intestinal epithelium, thereby contributing to preventing translocation of lipopolysaccharides into the circulation.

Apart from playing a role in modulating the composition of bacteria, it can also work to influence intracellular signaling. works to inhibit the expression of MyD88 and NF-kB proteins, so that it can decrease the expression of proinflammatory cytokines induced by the bound between LPS and the complexes TLR4, CD14 and LBP [30, 31].Anthocyanin content also specifically increases the micro biota population of Bifid bacterium spp. and Lactobacillus-Enterococcus spp [33].

Research conducted by Flores et al. (2015) shown that the 20 mg / L anthocyanin level is not significant enough to cause changes in the microbiota profile. Proliferative and inhibitory effects on the microbiota population can be observed in the administration of anthocyanins with higher levels, namely 200 mg / L. Another possible mechanism underlying the role of anthocyanins in the microbiota profile is that anthocyanins can reduce oxygen tension in the intestinal lumen, thereby increasing the proliferation of oxygen-sensitive bacterial populations [34].

Black Rice-Lipopolysaccharide (LPS)

Obesity is caused by a high-fat diet and metabolic disorders characterized by inflammatory status associated with changes in the composition of the gut micro biota and increase plasma lipopolysaccharide (LPS) levels [35].Anthocyanin content in LPS that cause changes in the immune system. In the research of Pornngarm et al. (2016) who test the anti-inflammatory effect of high polar fraction of black rice whole grain extracts (BR-WG-P) show that BR-WG-P significantly inhibit LPS-induced proinflammatory mediators, including nitric oxide (NO) production and iNOS expression, and COX-2.

In addition, the secretion of proinflammatory cytokines including TNF-α and IL-6 was also significantly inhibit [24]. BR-WG-P and anthocyanins inhibit translocation of NF-kB and AP-1 into the nucleus. BR-WG-P also decrease phosphorylation of ERK, p38 and JNK depending on the dose used [24].

These results suggest that BR-WG-P may suppress LPS-induced inflammation through inhibition of the MAPK signaling pathway leading to decrease translocation of NF-kB and AP-1 [36]. In the research of Sung-Won Min et al (2010), black rice suppresses the production of pro-inflammatory cytokines, TNF-α and IL-1ß, and inflammatory mediators, NO and prostaglandin E2 (PGE2), as well as the expression of the nitric oxide synthase (iNOS) and cyclooxygenase genes. -2 (COX-2) in cell RAW 264.7 [37].

Black Rice-Tight Junction

Gut-derived bacterial LPS plays an important role in the intestinal, systemic inflammatory response and is involved in causing necrotizing enterocolitis and inflammatory bowel disease. Interference with tight junctions in the intestine is an important factor in intestinal inflammation. Physiologically, LPS causes an increase in the permeability of the intestinal tight junction through the TLR-4 dependent process [38]. LPS induces an increase in tight junction permeability which is mediated by an increase in enterocyte membrane expression TLR-4 and TLR-4 dependent on an increase in membrane colocalization of membrane associated protein CD14 [39].Obesity is a condition associated with increased intestinal permeability and impaired intestinal protective function due to changes in the structure of the tight junction protein observed in an obesity experimental animal model [40].

In addition, there is increased intestinal permeability, higher plasma endotoxin levels and increased proinflammatory cytokines. A high-fat diet causes suppression of occludin, claudin-1, claudin-3, and JAM-1 levels, accompanied by an increase in plasma TNF-α levels in the intestinal mucosa [41].Research by Lei Zhao et al. (2018) mice were given 100 mg / kg of black rice via oral gavage and given 2% DSS in drinking water for five days to induce colitis in the group of mice given black rice showed a decrease in histological score, which indicates that there are less mucosal injury and edema compared to DSS treatment.

This study shows that anthocyanins can protect tight junctions by modulating the ratio of TJ-positive, negative protein and confirm the protective effect of anthocyanins from black rice in overcoming colonic inflammation. In addition, this study show a decrease in the expression levels of IL-6, IL-1ß, TNF-α and myeloperoxidase (MPO) which linearly related to neutrophil infiltration. The anthocyanin content of purple tuberous root shows down-regulated TNF-α, IFN-γ, [40. 41].

Table 1: Black rice studies

Reference	Method	Result	Conclusion
Sung-Won Min et al. 2010(37)	Cyanidin-3-O-ß-D-glycoside ((C3G) and cyanidin were isolated from Black Rice as previously reported by Han et al.(44). Indomethacin, protocatechuic acid. RPMI 1640, penicillin-streptomycin, LPS purified from Escherichia coli O111: B4, and a radio-immunoprecipitation assay	The anti-inflammatory effect of C3G, the main constituent of black rice, and its metabolites, cyaniding and protocatechuic acid (PA), were assessed in lipopolysaccharide (LPS) - RAW 264.7 cells induced and carrageenan-induced inflammation in air sacs in BALB / c mice. BR, C3G and their metabolites suppress the production of pro inflammatory cytokines, TNF-α and IL-	Based on these findings, when black rice is consumed orally, its main constituent, C3G, can be metabolized to cyaniding and / or PA, which expresses a potent anti-inflammatory effect by regulating the activation of NF-κB and MAPK.

	(RIPA) lysis buffer. Antibodies to COX-2, iNOS, TNF-α, IL-1β andβ-actinwer. Antibodies for IκB-α, p-IκB-α, p65, p-p65, p38, p-p38, JNK, p-JNK, ERK, and p-ERK. The Cytokine ELISA Kit was obtained from R&D Systems. Carrageenan (Type IV). Bio-Rad Protein Assay Kit.	1β, and inflammatory mediators, NO and prostaglandin E2 (PGE2), as well as gene expression of nitric oxide synthase (iNOS) and cyclooxygenase. -2 (COX-2) in RAW 264.7 cells. This agent also inhibits phosphorylation of IκB-α, nuclear translocation of NF-κB, and activation of mitogen-activated protein kinases. In addition, this agent significantly inhibited the leucocyte count and levels of TNF-α, PGE2, and protein in air-bag exudates in carrageenan-treated mice, as well as COX-2 expression and NF-κB activation. Among the test agents,	
Hao Wang et al. 2020(5)	BRAE, fecal, and urine anthocyanins were analyzed by HPLC using column C18 (4.6 mm × 250 mm, 5 μm, SHI-MADZU, Japan), with A) water / formic acid (99: 1, v / v) and B) 100% acetonitrile as mobile phase monitored at 520 nm in the presence of a standard. Pathogen-free male C57BL6 / J mice (6 weeks old). C57BL / 6J mice were grouped into the normal chow diet (NCD) group, the high fat and cholesterol (HCD) diet group, and three treatment groups that were given HCD with various doses of black rice anthocyanin extract (BRAE) for 12 weeks.	BRAE reduces weight gain, serum triglycerides (TG), total cholesterol (TC), levels of non-high-density lipoprotein (non-HDL-C) cholesterol, and increased excretion of fecal sterols and short-chain fatty acids. (SCFAs) concentrations in HCD-induced hypercholesterolemic rats. In addition, BRAE decrease the TC content of the liver through fundamental regulation of the body's energy balance gene, adenosine 5'-monophosphate activates protein kinase (AMPK). Meanwhile, BRAE increases the expression of genes involved in cholesterol uptake and excretion, and maintains CYP7A1, mRNA expression of the 5/8 ATP-binding ATP, and the relative abundance of gut micro biota. Other than that	BRAE supplements can be a useful treatment option for preventing HCD-induced hypocholesterolemia and metabolic syndrome.
Lei Zhao et al. 2009(42)	Black rice (Oryza sativa L.) was purchased from a local market in Beijing, China. It was grounded to be fine powder by crushing and passes through a 2 sieve 60-mesh sieve. The black rice powder was then sealed in PET / Al / PE bags and stored at 4 ° C before use. The DSS (36-50 kDa, reagent class) was purchased from MP Biomedicals. RA (≥98%), cyanidin-3-O-β-glucoside (≥98%), peonidin-3-O-β-glucoside (≥98%), chlorogenic acid (≥98%) and ferulic acid (≥98 %) 8 purchased from Chengdu Must Bio-Technology Co., Ltd. .. HPLC grade acetonitrile was purchased from Mallinckrodt Baker. The real time quantitative PCR primer comes from Beijing Genomics.	The administration of black rice anthocyanin-rich extract (BRAE) and rosmarinic acid (RA), alone and in combination, significantly reduce the disease activity index (DAI) and colonic histological score in colitis-induced DSS mice. In addition, administering BRAE and RA, apart and in combination, not only reduces levels of myeloperoxidase (MPO) and nitric oxide (NO), but also inhibits the expression of pro-inflammatory mediators including interleukin (IL) -6, IL-1β, tumor necrosis. factor (TNF) -α, induced nitric oxide synthase (iNOS) and cyclooxygenase (COX) -2. Our results show that BRAE decreases histologic score and TNF-α 2 mRNA expression in a dose-dependent manner, while BRAE + RA attenuated histological score and IL-6 mRNA expression are dose-dependent 3 24. However,	The BRAE and RA diets, apart and in combination, relieve the symptoms and inflammation of colitis due to DSS in mice, and can provide a promising dietary approach for the management of inflammatory bowel disease.
Yongsheng Zhu et al. (2018)(18)	Anthocyanins from black rice were obtained by membrane filtration and column chromatographic separation. Five anthocyanin monomers in black rice extract were identified by HPLC-MS / MS, and the main anthocyanin monomer (cyanidin-3-glucoside, C3G) was purified by preparative HPLC (Pre-HPLC). The proliferative effect of anthocyanins on Bifidobacteria and Lactobacillus was investigated by determining the pH of the media, bacterial population and metabolic products. After anaerobic incubation at 37C for 48 hours,	Anthocyanins and anthocyanin monomers from black rice have prebiotic activity and are metabolized into several small molecules by Bifid bacteria and Lactobacillus.	Various phenolic acids are obtained after the metabolism of C3G bacteria. The modulating effect of C3G on the gut micro biota through in vivo fermentation provides strong evidence of the health benefits of the anthocyanin diet.

	not only was the pH of the media containing C3G lower than black rice anthocyanin extract (BRAE), but the number of Bifid bacteria and Lactobacillus also increased significantly. Furthermore, hydroxypenylpropionic acid, hydroxypenylacetic acid, and hydroxybenzoate and other metabolites were detected by GC-MS in vitro.		

Conclusion

Obesity affects almost all physiological functions of the body and it is significant on health problem. This increases the risk of several diseases such as metabolic disorders, diabetes mellitus, cardiovascular disease, cancer, a range of musculoskeletal disorders and poor mental health. Intestinal micro biota imbalance and increased plasma LPS contribute to inflammation in obesity. Black rice has a high content of bioactive compounds such as anthocyanin, proteins, amino acids, and phenolic acids. The ingredients of black rice have role in modulating the composition of the intestinal micro biota, inhibiting LPS-induced pro-inflammatory mediators, can protect the tight junction so that it can protect inflammation in the colon.

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