

# Potential Effects of Pigmented rice on Immunity: A Review Focusing on Anthocyanins, Gamma-oryzanol, and Arabinoxylan

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**Abstract** Functional food ingredients from natural sources are gaining popularity for treating chronic inflammation associated with metabolic diseases (e.g., diabetes, hypertension, and obesity) due to their lower toxicity and no severe side effects. Pigmented rice is a natural food source in Korea commonly consumed in the whole grain form to improve the immune system. In particular, pigmented rice bran contains various nutritional components involved in the immune benefits. Of many nutrients in pigmented rice bran, anthocyanins, gamma-oryzanol, and arabinoxylan have notably shown to enhance natural killer cell activity and reduce pro-inflammatory cytokines. Especially, pigmented rice has higher amounts of anthocyanins and gamma-oryzanol than white rice. In this review, to provide further insight into the immune effects of the pigmented rice, we have focused on the immune benefits of bioactive substances (e.g., anthocyanins, gamma-oryzanol, and arabinoxylan) from pigmented rice compared to white rice. The pigmented rice has potential effects on immunity, and it can be used as a functional food.

**Keywords:** pigmented rice, immunity, anthocyanins, gamma-oryzanol, arabinoxylan

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## 1. Introduction

Aging is associated with an increase in oxidative stress that declines an immune system. Progress of aging and chronic inflammation with increased oxidative stress has negatively influenced cell function [1]. Inflammation is highly associated with immune reactions, which act as a body defense against infection [2]. Chronic inflammation is prolonged inflammation contributing to the pathogenesis of metabolic diseases such as diabetes, hypertension, and obesity [3]. Thus, it is important to treat chronic inflammation to reduce the incidence of metabolic disorders. Meanwhile, functional food has gained attention that they play a crucial role in providing health benefits and reducing health risks. Consumers are also interested in the immunomodulatory properties of functional food ingredients, having a relatively low toxicity.

Pigmented rice mainly shows three colors, such as black, purple, and red [4]. They are accumulated in the pericarp and bran layer of the rice [4]. Pigmented rice has been widely consumed in Korea, China, and Japan for a long time due to its unique color, flavor, and health

benefits [5]. Asian countries account for more than 60 % of the global production of black rice [6]. Interestingly, the demand for pigmented rice intake has also increased in European countries and the U. S. Pigmented rice is a great food source for health-improving properties such as anti-oxidant and anticancer activities enhancing immune function [7]. It contains a high level of several bioactive components, e.g., anthocyanins, gamma-oryzanol, phenolic acid, phytic acid, tocopherols, amino acids, and essential oils [5,8]. Previous studies reported that pigmented rice has two to three times higher content of anthocyanins and gamma-oryzanol than non-pigmented rice [9,10]. Of several bioactive components in the pigmented rice, anthocyanins act as the most powerful anti-oxidants that directly scavenge free radicals, repair DNA and damaged cells, and augment immunocompetent cells [2]. Gamma-oryzanol also exhibits a higher level of anti-oxidant activity compared to vitamin E components such as tocopherols and tocotrienols [11]. In the animal study, gamma-oryzanol isolated from black rice has stimulated the innate response [12] and induced natural killer (NK) cell activity [13]. Moreover, arabinoxylan processed by hemicellulose from rice bran has been shown to induce NK cell activity associated with enhancing innate

immunity [14,15]. Arabinoxylan isolated from black-pigmented rice bran reduced levels of tumor necrosis factor (TNF)-alpha and interleukin (IL)-6, which are associated with lowering inflammation [16,17]. The soluble fiber in the pigmented rice bran showed to inhibit inflammatory cytokine expression [18].

Compared with non-pigmented rice, the effects of bioactive substances (e.g., anthocyanins, gamma-oryzanol, and arabinoxylan) from pigmented rice on immunity have summarized poorly. In this current study, we investigated the potential effects of pigmented rice on immunity.

## 2. Major Bioactive Compounds that Involve in the Immune System

### 2.1. Anthocyanins

Anthocyanins are edible and water-soluble plant pigments belonging to the flavonoid group, a subclass of the polyphenols [19,20]. Because of its anti-oxidant, anti-inflammatory, anti-tumor, anti-atherosclerosis, and anti-allergic activities, anthocyanins have been considered a key bioactive compound [21,22]. Anthocyanins also

improve immunocompetent cell activity, scavenge free radicals, repair DNA and damaged cells [2]. The high level of anti-oxidant capacity particularly has been influenced by the phenolic structure of anthocyanins resulting in a significant effect of scavenging free radicals [23,24]. Anthocyanins are mostly located within the pericarp and bran layer of rice [4]. Cyanidin 3-glucoside (95%) and peonidin 3-glucoside (5%) are dominant in pigmented rice such as black rice and red rice [25,26,27]. The major anthocyanins of pigmented rice bred in Korea (Heugjinjubyeo, Suwon 425, and Iksan 440) are cyanidin 3-glucoside (95.1-97.4%) and peonidin 3-glucoside (2.6-4.9%) [28]. Similarly, the major anthocyanins cultivars in China (Cheng-Chang, Kilimheugmi, Yongjung 4, and Hong-Shei-Lo) are cyanidin 3-glucoside (87.4-97.0%) and peonidin 3-glucoside (3.0-12.6%) [28]. The anti-oxidant activity of pigmented rice cultivars has been higher than that of non-pigmented rice cultivar [28,29]. The total anthocyanin contents of the pigmented rice extracts have been associated with the DPPH radical scavenging activity [28]. However, the various conditions such as changes in temperature, pH, light, oxygen, and metal ions have negatively impacted the activities of anthocyanins [30,31].

Table 1. Summary of immune function of anthocyanin-pigmented rice

Reference	Sample	Sample dosage (reported dosage)	<i>In vitro/In vivo</i>	Findings
[44]	Black rice	Cyanidin 3-glucoside (4.30 mg/g) Total anthocyanins (12.6 mg/g)	<i>In vitro</i>	Black rice bran extracts enhanced activity of NK cells, cytotoxic T lymphocyte, IgA, and IgG.
			<i>In vivo</i> Male Sprague Dawley rats (n=7 per group)	Black rice bran extracts elevated the number of white blood cells, lymphocyte counts, and neutrophils. This increased serum levels of Ig A and G.
[45]	Black rice	Black rice bran cultured with <i>Lentinus edodes</i> (250mg/kg body weight)	<i>In vivo</i> Male Blab/c mice (n=10 per group)	Black rice bran enhanced macrophage and splenocyte proliferation.
[2]	Black rice	Black rice extracts (50, 100, 200 µg/mL)	<i>In vitro</i>	Black rice extracts inhibited the production of TNF-alpha by cluster of differentiation (CD) 4+ T cells and NF-kB activity on CD4+ and CD8+ T cells.
[41]	Black rice	Crude extract of anthocyanins from black rice bran (20, 50, 100 mg/kg body weight)	<i>In vivo</i> Male Blab/c mice (n=10 per group)	Black rice bran increased the level of monocytes and macrophages in leukemia mice.
[42]	Black rice	Black rice anthocyanin-rich extracts (BRAE) (25, 50, 100 mg/kg body weight) Total anthocyanin content 46.25% in BRAE	<i>In vivo</i> Female C57BL/6 mice (n=8 per group)	BRAE inhibited TNF-alpha mRNA expression in a dose-dependent manner. BRAE decreased the expression of pro-inflammatory mediators, including IL-6, IL-1beta, TNF-alpha, inducible nitric oxide synthase (iNOS) and cyclooxygenase (COX)-2.
[43]	Black rice	Cyanidin 3-O-β-glucoside (1.2 mg per mouse)	<i>In vivo</i> Female BALB/c mice (n=5 per group)	Cyanidin 3-O- β-glucoside decreased the level of IL-4, IL-5, and IL-13 in a murine asthma model.
[46]	Purple rice	Total anthocyanins (2.44-10.52 mg/g)	<i>In vitro</i>	Anthocyanins (cyanidin 3-glucoside and peonidin 3-glucoside) from purple rice inhibited IL-1beta-stimulated human chondrocytes by inhibiting nuclear factor kappa B and extracellular signal-regulated kinase/mitogen-activated protein kinase (ERK/MAPK) pathway.
[47]	Purple rice	Cyanidin 3-glucoside (2.50-4.40 mg/g) Peonidin 3-glucoside (1.97-3.35 mg/g) Total anthocyanins (4.47-7.75 mg/g)	<i>In vitro</i>	Purple rice extracts had an inhibitory growth effect on human hepatocellular carcinoma HepG2 cells.

Consumption of anthocyanins in the pigmented rice has a potential for enhancing immunity (Table 1). Anthocyanins and their metabolites (e.g., syringic, *p*-coumaric, 4-hydroxybenzoic, and vanillic acids) have been associated with a favorable bacterial population that modulates inflammatory markers [3]. For example, *in vitro* and *in vivo* studies have shown an elevated growth of potentially beneficial bacteria such as *Bifidobacterium* spp. and *Lactobacillus-Enterococcus* spp. after administration of anthocyanin-rich products [32]. Wang et al. (2015) observed that two beneficial bacteria strains, *Bifidobacterium* and *Lactobacillus*, have been associated with attenuating the inflammation in rodent intestinal microbiota [33]. D'Argenio G et al. (2013) also unveiled that *Lactobacillus paracasei* alleviated the inflammation in rodents [34]. Rodes et al. (2013) reported that *Bifidobacterium* and *Lactobacillus* strains had been involved with the ability to reduce TNF-alpha [35]. Further, a 2018 study investigating the modulatory effects of anthocyanins from black-colored rice *in vitro* found that anthocyanins were metabolized into smaller molecules by *Bifidobacteria* and *Lactobacillus*, suggesting a prebiotic potential [36]. In terms of modulating inflammatory markers, anthocyanins downregulate nuclear factor-kappa B (NF-kB) signaling pathway (the initiator of the pro-inflammatory pathway [37,38,39] via decreasing plasma concentration of pro-inflammatory chemokines and cytokines [37]. According to the 8-week open-label clinical trial, the daily consumption of 215 mg anthocyanins (extracted from black rice, blueberry, and black currant) and 2.7 g prebiotic fibers modulated intestinal microbiota and inflammation positively [40]. Anthocyanins from black rice have been shown to be related to an increase in the immune response by enhancing phagocytosis of macrophages *in vivo* [41] and a decrease in activities of pro-inflammatory cytokines, including TNF-alpha, interferon (IFN)-gamma, and IL-6 [2]. Black rice, its major anthocyanin (cyanidin 3-glucoside), and metabolites of cyanidin 3-glucoside also have significantly reduced the production of pro-inflammatory cytokines such as TNF-alpha and IL-1 beta [21]. Black rice extract inhibited the expression of pro-inflammatory mediators including TNF-alpha, IL-6, and IL-1 beta in dextran sulfate sodium-induced colitis mice related to immune system [42]. Cyanidin 3-glucoside extracted from black rice suppressed type 2 helper T cell (Th2)-related cytokines (e.g., IL-4, IL-5, and IL-13) in a murine asthma model, indicating alleviating allergic inflammation [43]. A recent study investigating the immunostimulatory effect of black-colored rice found that black-colored rice bran extracts exerted activity of NK cells, cytotoxic T lymphocyte, and immunoglobulins (Ig) A and G [44].

## 2.2. Gamma-oryzanol

Gamma-oryzanol is a bioactive phytochemical compound found in rice bran oil, comprising of ferulic acid esters (campesterol, stigmaterol, and beta-cytosterol) and triterpene alcohols (cycloartenol, cycloartenol, 24-methylenecycloartanol, and cyclogranol) [12,48,49]. Gamma-oryzanol has several nutritional benefits (e.g., anti-oxidant, anti-inflammatory, and anti-tumor activities) [12,50] that are directly related to improvement in the immune system [51]. A previous study found that [11] gamma-oryzanol in rice bran oil has

shown a six-fold higher anti-oxidant activity than vitamin E. Several studies have agreed that gamma-oryzanol in rice bran oil exhibited higher anti-oxidant capacities when comparing with the other investigated vitamin E components (alpha-tocopherol, beta-tocopherol, alpha-tocotrienol, and beta-tocotrienol) [11,52,53,54,55]. Further, the pigmented rice such as black (63 µg/g) and red rice (79 µg/g) has contained a higher level of gamma-oryzanol than white rice (8.2 µg/g) [56]. The gamma-oryzanol contents in pigmented and non-pigmented Thai rice cultivars, pigmented rice showed statistically higher gamma-oryzanol contents than non-pigmented rice [8].

Gamma-oryzanol isolated from rice bran oil may exhibit the potential of improving innate immunity, the first line of defense against pathogens. Gamma-oryzanol augmented the innate response by secreting the innate cytokines and IL-8 that stimulated phagocytosis of RAW 264.7 cells [12]. Moreover, gamma-oryzanol has enhanced NK cell activity associated with innate immunity and activated macrophages [13] and modulated the immune system by enhancing B-lymphocyte proliferation [57]. TNF-alpha, IL-6, IL-8, and IL-10 are also major players in the innate defense system [58]. The activity of COX-1 and -2, the key pro-inflammatory enzymes, has been inhibited by gamma-oryzanol [59].

## 2.3. Arabinoxylan

Arabinoxylan is a non-starch polysaccharide found in various cereal brans (e.g., rice and wheat), which is indigestible in the upper gut and can supply a source of fermentable carbon in the large bowel [60,61]. Multiple carbohydrate hydrolyzing enzymes from Shiitake mushrooms modifies arabinoxylan from rice bran (processed hemicellulose) [15]. Arabinoxylan has a high concentration of ferulic acid, which is the most abundant phenolic acid constituent in pigmented rice (black, brown, and red rice) bran extracts [62]. Interestingly, arabinoxylan has immune benefits and acts as a prebiotic that feeds gut microbiota [63]. It has been proven that prebiotics can positively modulate the immune system of the intestine [64]. Arabinoxylan from black-colored rice bran inhibited inflammatory cytokines (e.g., TNF-alpha and IL-6) [16] and arabinoxylan unregulated NK cell activity [15].

Arabinoxylan, particularly water-soluble arabinoxylan, has been widely investigated for its immunostimulatory activity [65]. More specifically, the immunostimulatory activity is associated with arabinoxylan structural characteristics [60]. Arabinoxylan has the potential effect of stimulating NK cells (the major lymphocytes of the innate immune system), dendritic cells, and T-helper 2 cell immunity [65]. The concentration of arabinoxylan, derived from pigmented rice bran hydrolysates, was approximately 20 µg/mL in cultured media [66]. This concentration of the arabinoxylan was reported to show immunomodulatory effects [67,68]. Crude fermentation-polysaccharide isolated from black rice bran has modulated immune system activity via increasing IFN-gamma level by activated murine macrophage and splenocyte [45]. Arabinoxylan has increased murine NK cell activity from aged mice [14] via upregulating and influencing NK cell activity against neuroblastoma *in*

*vitro* and *in vivo* [15]. In a randomized, double-blind placebo-controlled trial, the consumption of modified arabinoxylan from rice bran significantly elevated NK cell activity in the geriatric group compared with the placebo group [69]. A study on patients with tumors has also revealed that arabinoxylan augments NK cell activity elevated the levels of T and B lymphocytes [70,71,72]. The intake of arabinoxylan from rice bran may positively affect the quality of life in patients with cancer by improving immunity [73].

### 3. Conclusions

Pigmented rice contains immune-enhancing compounds such as anthocyanins, gamma-oryzanol, and arabinoxylan. Especially, pigmented rice has higher amounts of anthocyanins and gamma-oryzanol than white rice. Anthocyanins, gamma-oryzanol, and arabinoxylan effectively decrease the expression of pro-inflammatory cytokines and enhance the activity of natural killer cells and their innate responses. This review could pave the way for the potential use of pigmented rice as a functional food in treating chronic inflammation. A future investigation needs to determine whether pigmented rice can be used as nutraceutical rice to improve the immune system.

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