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- Note -

Red Yeast Rice (*Monascus purpureus*) Extract Prevents Binge Alcohol Consumption-induced Leaky Gut and Liver Injury in Mice

Gi-Seok Kwon[1], Dong-ha Kim[2], Hyun-Ju Seo[2], Young-Eun Cho[2]* and Jung-Bok Lee[3]*

[1]*Department of Horticulture & Medicinal Plant, Andong National University, Andong 36729, Korea*
[2]*Department of Food and Nutrition, Andong National University, Andong 36729, Korea*
[3]*BHNBIO CO., LTD., Jincheon-gun 27850, Korea*

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Red yeast rice, also known as Hong Qu and red Koji, has been used for a long time in Asian functional food and traditional medicine. It consists of multiple bioactive substances, which can potentially be used as nutraceuticals. Alcoholic liver disease (ALD) can range from simple steatosis or inflammation to fibrosis and cirrhosis, possibly through leaky gut and systemic endotoxemia. This study examined the liver and gut effects of red yeast rice (RYR) (*Monascus purpureus*) ethanol extract against binge ethanol-induced liver injury in mice. RYR extract was orally administered to C57BL/6N mice at a concentration of 200 mg/kg body weight per day for 10 days. Then, mice were administered binge alcohol (5 g/kg/dose) three times at 12 hr intervals. Binge alcohol exposure significantly elevated the endotoxin, aspartate aminotransferase (AST), and alanine transaminase (ALT) activity of plasma, as well as hepatic triglyceride levels; however, RYR treatments reduced these levels. In addition, RYR pretreatment significantly reduced the alcohol-induced oxidative maker protein and apoptosis maker in binge alcohol-induced gut and liver injuries. These results suggest that RYR may prevent alcohol-induced acute leaky gut and liver damage.

Key words : Binge alcohol, endotoxin, gut leaky, liver damage, red yeast rice

Introduction

Alcohol is one of the most commonly consumed beverages by humans. However, excessive consumption of alcohol affects the immune system, alters cytokine production, increases liver triglycerides and lipid peroxidation, and causes many diseases, including alcoholic liver disease (ALD) [28]. Alcoholic liver disease poses a major threat to human health worldwide. When ALD progresses, it progresses to fatty liver (steatosis), fatty hepatitis, fibrosis/cirrhosis, and eventually it is a terrible disease that can lead to liver carcinoma [1]. ALD is known to occur due to overproduction of reactive oxygen species (ROS), lipid peroxidation damage, cytokine damage and inflammation. If inflammation continues, it induces cell death due to apoptosis and necrosis and stimulates ROS production, which is an important factor in the progression of alcoholic liver disease [11]. Also, ALD is associated with increased ROS levels resulting from cytochrome P450 2E1 (CYP2E1). CYP2E1 plays an important role in the production of ROS by alcohol in the liver and other tissues. CYP2E1 expression causes alcohol-dependent metabolic changes and trigger steatosis and fatty hepatitis in early liver damage. And CYP2E1 is known to be a toxic and carcinogenic substance [18, 26]. Ethanol treatment in an *in vivo* model expresses the genes of the JNK pathways [6]. The JNK signaling pathway is activated by pro-inflammatory cytokines such as TNF-α and IL-1β [5]. This increase in inflammation continues to phosphorylate JNK, eventually leading to apoptosis, and further causing liver damage [15, 20].

In a previous study, HepG2 cells were treated with ethanol to increase inflammatory cytokines such as TNF-α, which increases ROS, CYP2E1 is expressed, and JNK is activated, eventually promoting apoptosis [3, 10, 13, 31]. From this, it seems that ethanol-induced liver damage is caused by ROS, inflammation, and CYP2E1 and phosphorylation of JNK. Thus, inhibition of CYP2E1, an inflammatory cytokine, activity or expression can interfere with ethanol metabolism and

***Corresponding authors**
Tel : +82-54-820-5484, Fax : +82-54-820-6281
E-mail : yecho@anu.ac.kr (Young-Eun Cho)
Tel : +82-2-2135-9790, Fax : +82-2-2135-9794
E-mail : bio91@hanmail.net (Jung-Bok Lee)

improve alcoholic liver disease. RYR (Red Yeast Rice) is a dark pink rice made by fermenting ordinary rice together in a fungus named *Monascus purpureus* for 15 to 30 days, and has long been used as a medicine in China [7, 17]. RYR contains monacolin K as a potent inhibitor of HMG-CoA reductase and its consumption is known to decreases cholesterol and triglyceride levels [8, 19]. RYR is produced many functional secondary metabolites and main 6 type pigments [19]. It is known that monacolin K, γ-aminobutyric acid (GABA), various pigments (yellow pigments, ankaflavin and monascin; orange pigments, monascorubrin and rubropunctanin; red pigments, monascorubramine and rubropuctamine) etc. are active substances of *Monascus purpureus* [21]. In previous studies have shown that *Monascus purpureus* extract has protective activity against alcoholic liver disease in animal models [14]. But it has not been proven through what mechanism the RYR extract is effective against alcoholic liver disease and gut leakiness. The present study aims to investigate the protective effects mechanism of RYR extract against ethanol-induced gut leakiness and liver injury.

Material and Methods

Materials

In this study, RYR was purchased from Han's Bio (Andong, Republic of Korea). The RYR extract was prepared by extracting RYR powder and 70% ethanol at a ratio of 1:10 (w/w) for 24 hr at room temperature. Then the extraction was filtered through glass funnel and filter paper. Each filtrate was concentrated to dryness under reduced pressure using a rotary flash evaporator. The concentrated sample was freeze-dried for 72 hr.

Experimental animals

Male C57BL/6N mice (5-week-old, 23.9±1.0 g body weight) were purchased from Orient Bio (Seongnam, Korea) and housed in cages under automatically controlled conditions of temperature (22±2℃), humidity (30~70%), and lighting (12: 12 hr light–dark cycle). With food and water provided ad libitum. Andong National University's Institutional Animal Care and Use Committee approved the protocol for the animal study (The animal protocol number is 2019-2-0510-02-01), and the animals were cared for in accordance with the "Guidelines for Animal Experiments" established by the university.

Animal treatments

The 5-weeks old male C57BL/6 mice kept in their cages for 7 days prior to dosing to allow for acclimatization to the laboratory conditions. For the *in vivo* hepatoprotective test against ethanol-induced oxidative stress, 40 mice were divided into four groups (n=10 per group). Age matched 6-weeks old male C57BL/6 mice were orally administered test materials i) CON; mice received distilled water, ii) EtOH; After distilled water pretreatment for 10 days, mice was exposed to 3 oral doses of binge alcohol (5 g/kg/dose) at 12 hr intervals. iii) RYR+EtOH; After 200 mg/kg RYR pretreatment for 10 days, mice were exposed to 3 oral doses of binge alcohol (5 g/kg/dose) at 12 hr intervals. iv) SM+EtOH; After 800 mg/kg Silymarin pretreatment for 10 days, mice were exposed to 3 oral doses of binge alcohol (5 g/kg/dose) at 12 hr intervals. Each group was administered 10% volume (10 ml/kg) of distilled water or silymarin and RYR daily through gastric intubation for 10 days, and alcohol was administered three times at 12 hr intervals. At the end of the experiment, the mice were sacrificed to collect serum and liver 1 hr after final administration of alcohol.

Histological analysis

Mice was briefly sedated to carbon dioxide gas followed by decapitation and immediate collection of liver from each mice. In this study, part of the largest liver lobe from each mice exposed to RYR pretreatment or control with or without binge ethanol exposure was fixed in neutral formalin. Paraffin embedded blocks of formalin-fixed individual liver or small intestine sections were cut at 4 μm, stained with hematoxylin/eosin (H/E) by American Histolabs, Inc. (Gaithersburg, MD). To further support fat accumulation, frozen liver samples embedded in optimal cutting temperature compound were cut (10 μm) and stained with Oil Red O.

Endotoxin assay

Plasma endotoxin levels were determined using the commercially available endpoint LAL Chromogenic Endotoxin Quantitation Kit with a concentration range of 0.015~1.2 EU/ml (Thermo Fisher Scientific, Waltham, MA as described [12].

Triglyceride determination in liver and plasma AST/ALT measurement

The amounts of hepatic triglyceride (TG) were assessed by using a commercially available kit (Asan Co., Ltd, Gimpo, South Korea).

Serum alanine aminotransferase (ALT) and asparate ami-

notransferase (AST) activities in each mice was determined by using the standard end-point colorimetric assay kit (Asan Co., Ltd, Gimpo, South Korea) as described [12]

Western blot analyses

Liver tissue was homogenized in buffer containing 0.5% Triton X-100 and protease inhibitor cocktail (1:1,000, Sigma-Aldrich Chemical Co.). Then, the lysates were centrifuged at 12,000 rpm for 30 min at 4℃. The SMART BCA Protein Assay Kit (iNtRON Biotechnology, Seongnam-si, Republic of Korea) was used to measure protein concentration. This homogenate was further mixed with buffer (60 mM Tris–HCl, 2% SDS and 2% β-mercaptoethanol, pH 7.2), and boiled for 5 min. The 60 μg of the protein was electrophoresed by SDS-PAGE, transferred to a nitrocellulose membrane, and blocked with 5% non-fat dry milk in 1×Tris buffered saline containing 0.05% Tween-20 (TBST) at room temperature for 1 hr. After that, the membranes were incubated with the appropriate mouse anti-CYP2E1 (1:1,000), anti-iNOS, anti-P-JNK, anti-P-BAX (1:1,000) primary antibody on a rocker at 4℃ overnight. After overnight incubation, membranes were washed with TBST and probed with horseradish peroxidase-conjugated secondary antibody at room temperature for 2 hr. For visualization, the membranes were incubated with Enhanced Chemiluminescence reagents (Dogen, Seoul, South Korea) and analyzed by using Chemi-Doc (Vilver, France).

Statistical analysis and other methods

The effect of each treatment was analyzed from 10 mice (n=10) in each group. All data were expressed as mean ± standard deviation (SD). Statistical significance was determined using one-way ANOVA and Dunnet's multiple comparison post-tests were used to compare the means of different groups. All the experiments were repeated at least twice unless otherwise stated. Data were presented as mean ± SD. Different letters in actual figures stand for significant difference between various treatments at $p<0.05$ by one-way ANOVA.

Results

RYR ameliorates liver injury in binge alcohol exposed mice

H&E staining showed markedly elevated fat accumulation in the liver after binge alcohol-exposure (Fig. 1A, Fig. 1B). However, RYR or SM treatment prevented the hepatic fat accumulation. Our results showed that plasma ALT and AST levels elevated in binge alcohol induced liver injury (Fig. 1C, Fig. 1D). However, pretreatment with RYR and SM significantly suppressed ethanol-induced increases in these serum ALT and AST. RYR and SM also inhibited hepatic TG elevated by binge alcohol exposure (Fig. 1E). Therefore, liver injury by binge alcohol is prevented with the pretreatment RYR.

RYR prevents the elevation of hepatic oxidative stress and apoptosis marker proteins in binge alcohol-exposed mice

Cytochrome P450 2E1 (CYP2E1) causes oxidative stress and hepatotoxicity by binge and chronic alcohol. Our data showed that hepatic oxidative stress maker proteins were significantly increased in binge alcohol-exposed mice. However, RYR and SM treatments reduced the elevation of the hepatic oxidative stress maker proteins (Fig. 2A).

RYR and SM has been shown to protect the liver injury by decreased levels of hepatic apoptosis caused by alcoholic hepatotoxicity (Fig. 2B). These results show that RYR significantly inhibited the oxidative stress and apoptosis of hepatic damage in bine alcohol exposed mice.

RYR inhibits binge alcohol induced gut leakiness

H&E stained histology revealed disorganization and detachment of many intestinal epithelial cells in binge alcohol-exposed mice (Fig. 3A). Both RYR and SM pretreatment significantly prevented the abnormal villi structure caused by ethanol exposure. Consistently, binge alcohol exposure markedly elevated the plasma endotoxin concentration compared to the control mice, whereas RYR and SM pretreatment significantly attenuated the elevation of endotoxin (Fig. 3B).

RYR prevents the elevation of intestinal oxidative stress and apoptosis marker proteins in binge alcohol-exposed mice

Oxidative stress maker iNOS was markedly elevated in binge alcohol exposed mice. However, RYR and SM pretreatment reduced the iNOS protein expression (Fig. 4A). RYR has been shown to protect the gut leakiness by decreased levels of intestinal apoptosis caused by binge alcohol induced gut leaky (Fig. 4B). These results show that RYR significantly inhibited the oxidative stress and apoptosis of gut damage in bine alcohol exposed mice.

Discussion

Excessive ethanol exposure causes various ethanol meta-

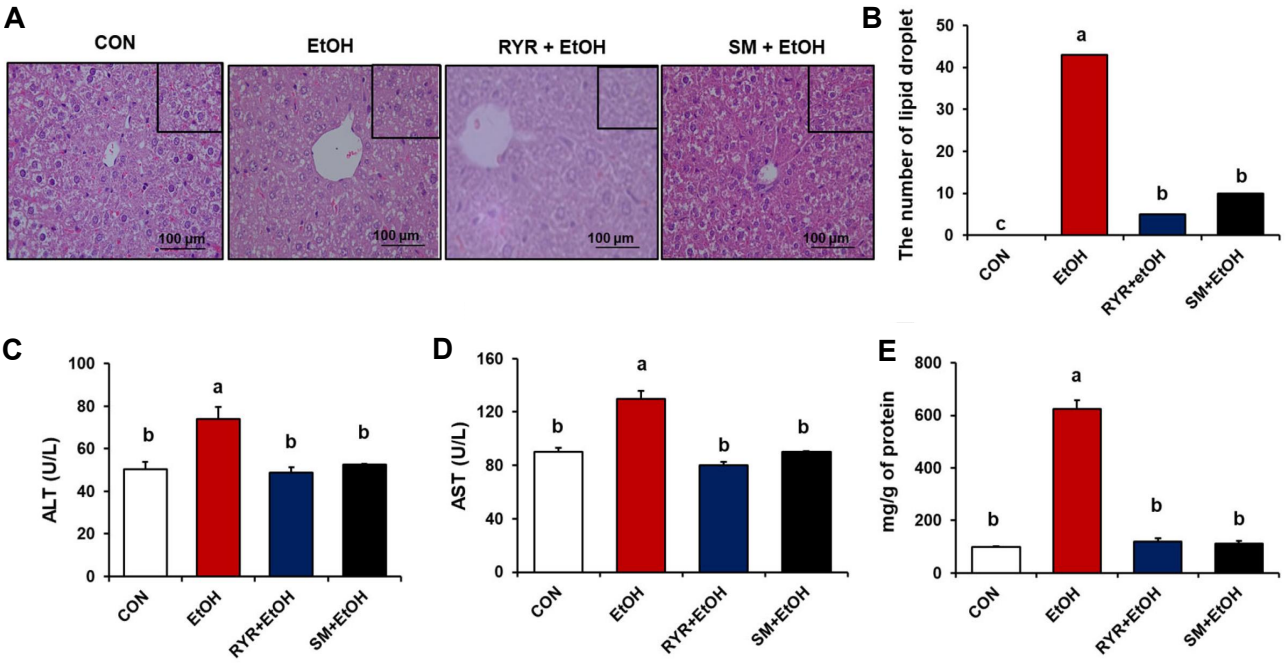

Fig. 1. RYR prevented binge alcohol-induced fatty liver injury in mice. (A) Representative H&E staining of formalin-fixed or frozen liver sections for control (CON), ethanol (EtOH), after 200 mg/kg RYR pretreatment for 10 days, mice were exposed to 3 oral doses of binge alcohol (5 g/kg/dose) at 12 hr intervals (RYR+EtOH), or after 800 mg/kg Silymarin pretreatment for 10 days, mice were exposed to 3 oral doses of binge alcohol (5 g/kg/dose) at 12 hr intervals (SM+EtOH) mouse groups. (B-E) The levels lipid droplet, plasma ALT, AST, and hepatic triglyceride (TG) are shown. Data represent means±SD. Significances between values for each group were determined using ANOVA and Tukey's HSD test. EtOH; ethanol, RYR; red yeast rice, SM; silymarin.

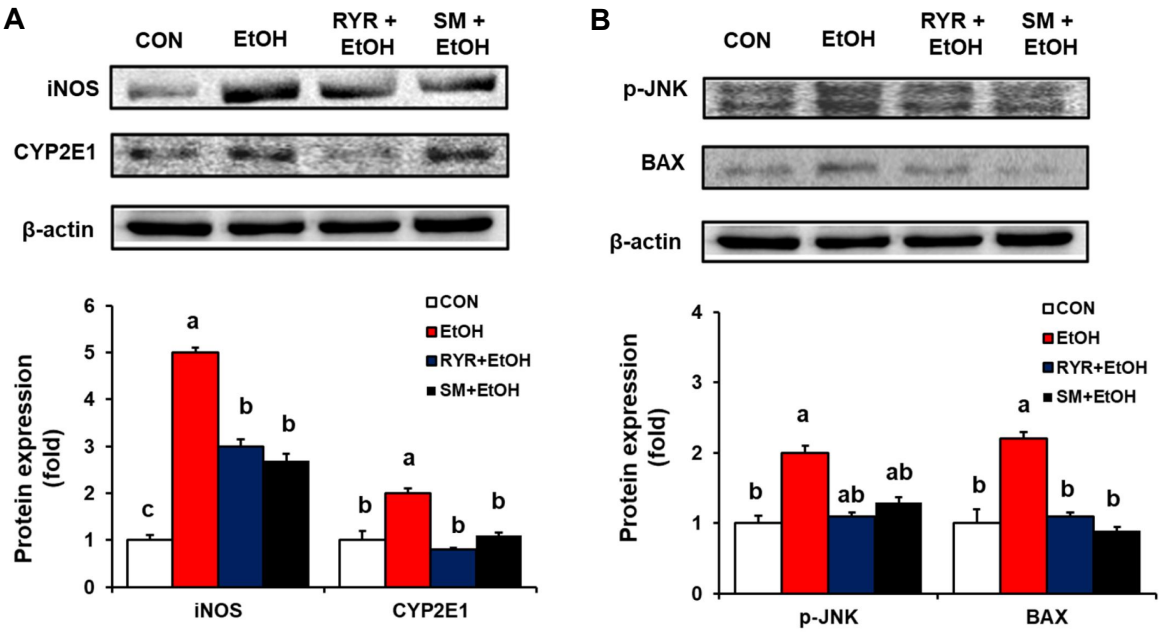

Fig. 2. RYR prevented hepatic oxidative stress and apoptosis maker proteins in binge alcohol exposed mice. (A) The levels of hepatic CYP2E1 and iNOS in the indicated groups are presented. (B) The levels of hepatic p-JNK and BAX in the indicated groups are presented. Densitometric quantitation of the immunoblots for each protein relative to β-actin is shown. Data represent means ± SD. Significances between values for each group were determined using ANOVA and Tukey's HSD test. CON; control, EtOH; ethanol, RYR; red yeast rice, SM; silymarin.

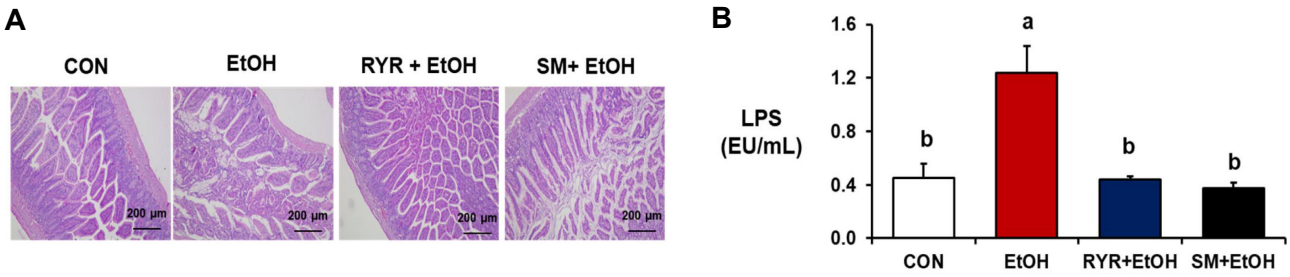

Fig 3. RYR prevented binge alcohol-induced small intestine injury and elevated the plasma endotoxin in mice. (A) Representative H&E staining of formalin-fixed or frozen small intestine sections for control (CON), ethanol (EtOH), RYR+EtOH, or SM+EtOH mouse groups. (B) The levels plasma endotoxin is shown. Data represent means ± SD. Significances between values for each group were determined using ANOVA and Tukey's HSD test. CON; control, EtOH; ethanol, RYR; red yeast rice, SM; silymarin.

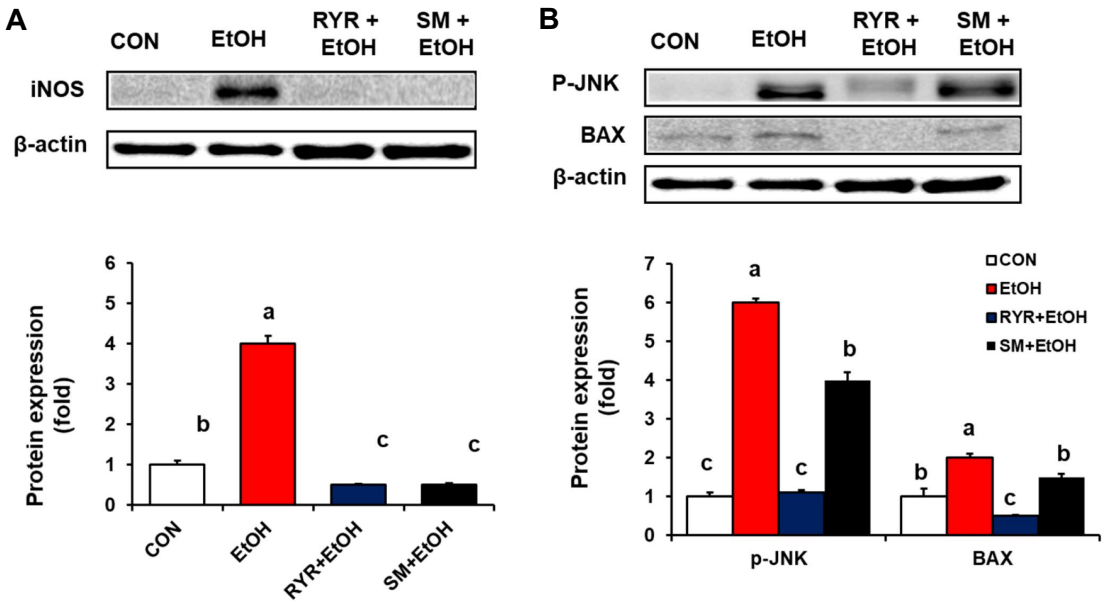

Fig. 4. RYR reduced the elevation of oxidative stress and apoptosis maker proteins in binge alcohol-mediated gut damage. (A) The levels of intestinal iNOS in the indicated groups are presented. (B) The levels of intestinal p-JNK and BAX in the indicated groups are presented. Densitometric quantitation of the immunoblots for each protein relative to β-actin is shown. Data represent means ± SD. Significances between values for each group were determined using ANOVA and Tukey's HSD test. CON; control, EtOH; ethanol, RYR; red yeast rice, SM; silymarin.

bolic reactions in the liver [29]. Binge ethanol exposure is known to have a significant impact on immunity, but it is not known exactly. Alcoholic liver disease (ALD) caused by binge ethanol is known to increase human or mouse inflammation, increasing the mortality rate from complications [23, 28]. Many studies have shown that oxidative stress and inflammation have played an important role in the development of ALD and that compounds with antioxidant or anti-inflammatory activity improve the progression of ALD in animal models [2, 9, 12]. RYR is known to be effective for liver-related diseases such as ALD and arteriosclerosis [33]. Therefore, in this study was to investigate the anti-inflammation effect of RYR on the improvement of binge alcohol induced liver and gut injury.

The clinical spectrum of alcoholic liver disease (ALD) includes an increased risk of alcoholic fatty liver (AFLD), steatohepatitis (ASH), and hepatocellular carcinoma [12]. Alcoholic fatty liver is caused by excessive fatty acid synthesis and is characterized by deposition of TG in the liver [24]. The effects of RYR treatment were confirmed by the H&E staining microscopic histological characterization in liver tissue. In addition, a significant increase in plasma ALT, AST and liver TG level was observed in the binge-alcohol model. Treatment of RYR (200 mg/kg B.W) on the alcohol induced

mice normalized liver TG concentrations as well as plasma ALT and AST, liver function marker. Our observation suggests that RYR treatment can be effective against liver damage in binge alcohol.

Until now, continuous or excessive alcohol intake is well known to break down alcohol into acetaldehyde by alcohol dehydrogenase (ADH) and cytochrome P450 2E1 (CYP2E1), which are key enzymes that break down alcohol in the liver [4]. CYP2E1 is one of the major P450 forms both in human and rat liver that has been shown to be sensitive to inflammatory stimulus and cytokines both in vivo and in primary hepatocytes [25]. In particular, CYP2E1 is known to continuously induce reactive oxygen species (ROS) in the process of decomposing alcohol into acetaldehyde. ROS damages cells and it is a cause of toxicity and carcinogenicity [25]. In addition, which is well known as a major cause of liver damage that causes hepatitis [32, 33]. The administration of RYR suggests that it can down-regulate oxidative stress markers, effectively remove apoptosis markers induced by binge alcoholic liver injury.

According to a recent study, binge alcohol intake causes gut leakiness, which causes an imbalance of the bacterial balance axis and secretes endotoxins into the blood [12]. Previous studies have shown that alcohol-induced hepatotoxicity is triggered by increased endotoxin delivery [27]. A distinctive feature of alcohol abuse is the disruption of the intestinal barrier. Animal models of ALD represent gut leaky, and impairment of intestinal barrier function were found in alcohol-dependent patients [16]. Alcohol has a direct effect on these functions of the gut and indirect effects by alcohol and/or alcohol metabolites distributed through the blood stream [22]. In addition, alcohol-induced lesion severity is positively correlated with Lipopolysaccharide (LPS) blood endotoxin [12]. Therefore, it is important to evaluate the beneficial effects of RYR on binge alcohol-induced gut intestinal leaks in animal model. In endotoxin level, the elevated plasma levels LPS were significantly reduced to control group levels due to RYR treatment. Protein expression of oxidative stress marker and apoptosis were significantly decreased in the RYR treated group compared to the EtOH group. In addition, the RYR treatment group showed a superior effect than the positive control group, silymarin treatment.

Our results show that RYR has been shown to be effective for binge alcohol by reducing oxidative stress in the liver and various apoptosis markers and protecting the gut leakiness. Therefore, it is suggested that RYR could be a potential remedy for the treatment of binge alcohol disease.

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The Conflict of Interest Statement

The authors declare that they have no conflicts of interest with the contents of this article.

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초록 : 알코올성 간 및 장 손상 마우스모델에서 홍국쌀 추출물의 항산화효과

권기석[1] · 김동하[2] · 서현주[2] · 조영은[2*] · 이중복[3*]

([1]국립안동대학교 생명과학·건강복지대학 산림과학과, [2]국립안동대학교 생명과학·건강복지대학 식품영양학과, [3]비에이치앤바이오)

Red rice Yeasts는 홍국 또는 붉은 코지로 불리며 오래전부터 아시아에서 기능성 식품 친 전통의학에서 사용되고 있다. 홍국쌀에는 여러가지 생리 활성 물질을 포함하여 기능적인 2차대사산물과 6가지 유형의 색소를 생성한다. 간 질환의 주요한 원인인 알코올로 인한 알코올성 간 질환(ALD)은 단순 지방증 또는 염증으로 섬유증 및 간경변에 이르기까지 다양할 수 있으며, 장 누수 및 전신 내독소혈증을 유발하여 장 장벽을 파괴하고 장내 미생물 변화를 증가시킨다. 본 연구는 홍국쌀(*Monascus purpureus*; RYR) 에탄올 추출물이 과량의 에탄올로 유발된 간 및 장 손상 마우스모델에서 간 및 장에 미치는 영향을 조사하였다. RYR 추출물을 10일 동안 200 mg/kg 체중/일의 농도로 C57/BL/6N 마우스에 경구 투여한 후 과량의 알코올(5g/kg/용량)을 12시간 간격으로 3회 처리하였다. 과량의 알코올 노출은 혈장의 내독소, AST 및 ALT 활성과 간 트리글리세리드 수치를 유의적으로 증가시켰지만 RYR 처리는 이들 수치를 감소시켰다. 또한, RYR 전처리는 과량의 알코올 유발 장누수 및 간 손상에서 알코올 유발 산화 인자 단백질 및 세포사멸 인자를 유의하게 감소시켰다. 이러한 결과는 RYR이 알코올로 인한 급성 장누수 및 간 손상을 예방할 수 있음을 시사한다.