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Effect of Glutathione-Enriched *Saccharomyces cerevisiae* FF-8 on Tissues Lipid Peroxidation in Orotic Acid-Induced Fatty Liver Model Rats

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Glutathione is a well-known chemotherapeutic agent and a popular nutritional supplement for liver disease and oxidative stress. Our previous studies reported the suppressive effects of the glutathione-enriched *Saccharomyces cerevisiae* FF-8 (FF-8) strain on carbon tetrachloride- and alcohol-induced oxidative stress in rats. The purpose of the current study was to investigate the effect of the FF-8 strain on lipid peroxidation in tissues of rats with orotic acid (OA)-induced fatty liver. OA treatment showed a significant decrease in body weight gain compared to the normal diet, and simultaneous addition of FF-8 and OA had the same effect. OA treatment produced an increase in liver weight, however, this also increased with simultaneous addition of FF-8 and OA. Liver lipid peroxidation was significantly increased by OA, but was significantly decreased by FF-8 strain treatment. This same tendency was found in the kidney and heart. Concentration levels of hepatic glutathione and zinc are known to be closely associated with the antioxidant system, and OA treatment led to reductions in liver glutathione and zinc concentrations, whereas these were significantly increased by FF-8 strain treatment in OA feeding rats. These results suggest that the glutathione-enriched *S. cerevisiae* FF-8 strain may positively mediate orotic acid-induced oxidative stress by enhancing glutathione and zinc levels in rat livers.

Key words : Glutathione, zinc, yeast, orotic acid, lipid peroxidation

Introduction

Glutathione is a ubiquitous tripeptide containing L-glutamate, L-cysteine, and glycine in living organisms and oxidized glutathione play a central role in the antioxidant defense process, while reduced glutathione is decreased by oxidative tissue damage [1,17,26,27]. It is involved in the maintenance of normal cell structure and functions [16,33]. *S. cerevisiae* have been found to produce high essential bioactive components for human health [5,6]. Many studies have found that glutathione is an antioxidant and it is contained high concentration in yeast strains [6,20,25]. Previous our study reported the suppressive effect of glutathione-enriched *S. cerevisiae* FF-8 strain treatment on carbon tetrachloride-induced oxidative stress in rats [7]. A previous *in vitro* study with the intercellular glutathione-containing cell free extracts from *S. cerevisiae* FF-8 has also observed antioxidative effects [20]. As, glutathione is a well known chemotherapeutical agent and a popular nutritional supplement for liver disease and oxidative stress [14,19,34].

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In addition, zinc is an essential trace element of all organisms and zinc plays important biological roles in hepatic injury and antioxidant properties against oxidative damage in organisms [2,15,23,26,27]. Recently have been reported that highly zinc containing yeast strain isolated from the tropical fruit rambutan and this strain was protected against alcohol-induced hepatotoxicity and oxidative stress in rats [5]. However, the antioxidative effect of FF-8 strain in OA-induced fatty liver model rats has not been reported. Current study was to investigate the effect of glutathione-enriched *S. cerevisiae* FF-8 strain on the tissues lipid peroxidation of orotic acid (OA)-induced fatty liver model in rats.

Materials and Methods

S. cerevisiae FF-8 strain cultivation

S. cerevisiae FF-8 (KACC 93023) strain containing a high glutathione concentration used in this study was established in our laboratory [25]. *S. cerevisiae* FF-8 was aerobically cultured in a 100 l bioreactor containing the YM optimal medium (3.0% glucose, 3.0% yeast extract, 0.06% KH_2PO_4, and 0.06% L-cysteine) [6]. The harvested yeast cells were lyophilized to prepare experimental diet.

Animal experiments

Six-week-old male Sprague-Dawley strain rats (Hyochang Science Animals Co., Daegu, Korea) were randomly divided into three treatment dietary groups. The normal rats were fed a semisynthetic basal diet, the OA rats were fed a basal diet with 1% (w/w) OA, and the OA plus FF-8 rats were fed a basal diet with concomitant treatment OA and 5% FF-8. The amount of FF-8 supplementation to the rats was estimated from the previous reports that *S. cerevisiae* had significant effects on the liver injury and oxidative stress in the rats [5,7,29,35]. Food and water were provided *ad libitum* for 10 days.

Assay of tissues lipid peroxidation

The tissues were quickly removed, weighed, and eventually used for the estimation of lipid peroxidation, minerals, and glutathione. The tissues were homogenized in ice-cold 0.25 M sucrose solution containing 10 mM tris-HCl buffer (pH 7.4) and 1 mM ethylenediamine tetraacetate (EDTA) using with IKA-ULTRA-TURRAX T25 basic homogenizer (IKA-WERKE GMBH & CO., KG, Staufen, Germany) as described previously [10]. Tissues lipid peroxidations were determined according to the spectroscopic technique by measuring thiobarbituric acid reactive substances (TBARS) [12]. The reaction mixture, containing hepatic homogenate solution and thiobarbituric acid (TBA), was incubated under boiling water for 30 min. After the centrifugation at 1,000× *g* for 10 min, the light absorbance of the upper layer was measured at 532 nm. The concentrations of TBARS were expressed as nmole of malondialdehyde (MDA) per g tissue.

Assay of hepatic glutathione concentrations

The concentration of glutathione was determined by the method of Beutler *et al.* [3]. A 0.2 ml of liver homogenate was mixed well with 1.8 ml of EDTA solution then a 3.0 ml of the precipitating reagent (1.67 g of metaphosphoric acid, 0.2 g of EDTA disodium salt, 30 g sodium chloride in 1 l of distilled water) was added and mixed thoroughly then stood the mixture at 4°C for 5 min. The mixture was centrifuged at 3,000× *g* for 5 min and 2.0 ml of the supernatant was mixed with 4.0 ml of 0.3 M disodium hydrogen phosphate solution and 0.1 ml of 5,5′-dithiobis(2-nitrobenzoic acid) (DTNB) reagent then the concentration of glutathione was spectrophotometrically determined at 412 nm. Total glutathione concentrations were expressed as mg per g liver.

Assay of hepatic mineral concentrations

Mineral concentrations in hepatic were analyzed by a Perkin-Elmer (Uberlingen, Model 300) atomic absorption spectrophotometer [4]. The determination concentration was shown as ppm.

Statistical analysis

The data from animal experiments are presented as the mean±SE, and were analyzed using one way analysis of variance (ANOVA), with the differences analyzed using the Duncan's new multiple-range test [13]. A p value <0.05 was accepted as being a statistical significance of difference.

Results and Discussion

Glutathione is one of the most important protective factors against oxidative damage. Reduction in cellular concentrations of glutathione is used as the indication of oxidative stress in a organ system [26,27]. Many studies have found that glutathione is an antioxidant in organisms [2,15,19]. A highly contained glutathione from microorganisms have been found to inhibit those chemicals-induced oxidant stresses *in vitro* and *in vivo* such as ethanol, carbon tetrachloride and acetaminophen [1,2,20,29]. Previous our observation showed that glutathione-enriched FF-8 strain was effectively inhibited the alcohol-induced oxidative stress in rats [7]. A previous *in vitro* study with the intercellular glutathione-containing cell free extracts from FF-8 have also observed highly antioxidative effects [7]. In addition, administration of FF-8 significantly inhibited lipid peroxidation of liver homogenate fractions in the carbon tetrachloride treatment rats [29]. In this respect, Mannaa *et al.* also reported that the powerful antioxidative components in *S. cerevisiae* effectively participated in attenuation of the oxidative stress caused by flutamide metabolites [21].

OA treatment showed a significant decrease in body weight gain compared to the normal diet, and simultaneous addition of FF-8 and OA was also decreased (Table 1). OA treatment produced an increase in the liver weight, however, this increase decreased by simultaneous addition of FF-8 and OA (Table 1).

The current study observed significant elevations of the lipid peroxidation in the liver homogenate of the OA treated rats, compared with the normal rats (Table 2). But, the administration of FF-8 strain was significantly inhibited the lipid peroxidation of liver homogenate in the OA treatment

Table 1. Effect of glutathione-enriched FF-8 strain on body weight gain and tissues weights in OA feeding rats for 10 days

Tissues	Normal	OA	OA+FF-8
Body weight gain (g/10 d)	73.92±2.51[a]	43.53±5.21[b]	39.08±4.41[b]
Tissues weights (g)			
Liver	10.57±0.38[a]	15.87±0.55[b]	13.20±0.60[c]
Kidney	2.55±0.06[a]	2.29±0.04[b]	2.42±0.05[ab]
Heart	1.16±0.91[NS]	1.15±0.03	1.05±0.03
Spleen	0.79±0.03[a]	0.60±0.04[b]	0.58±0.03[b]
Testis	2.57±0.38[NS]	3.00±0.03	3.02±0.08

Orotic acid (1.0%, w/w) and FF-8 (5.0%, w/w) were supplemented to the normal diet.
Each value is the mean±SE of six rats per experimental group. Values with different letters are significantly different at $p<0.05$.

Table 2. Effect of glutathione-enriched FF-8 strain on the tissues lipid peroxidation in OA feeding rats for 10 days (nmol/g)

Tissues	Normal	OA	OA+FF-8
Liver	165.02±2.94[a]	178.98±4.76[b]	161.82±8.75[b]
Kidney	126.66±4.18[a]	162.86±8.46[b]	78.04±10.59[c]
Heart	106.18±6.30[a]	127.50±7.99[b]	99.42±5.43[a]
Spleen	107.32±11.78[NS]	118.50±12.55	110.44±2.28
Testis	159.90±4.28[NS]	169.00±5.76	167.18±5.15

Orotic acid (1.0%, w/w) and FF-8 (5.0%, w/w) were supplemented to the normal diet.
Each value is the mean±SE of six rats per experimental group. Values with different letters are significantly different at $p<0.05$.

rats. An increase in lipid peroxidation has been found in liver after poisoning with hepatotoxic substances and following dietary changes, i.e. choline-devoid diet and orotic acid-rich diet [9,11,18]. Treatment with 1% OA in rats did not elevate the lipid peroxidation content of fresh liver homogenate when butylated hydroxytoluene (BHT) was present in the test system, however, when the antioxidant was omitted, the increased levels of TBARS were found which correlated with the triglyceride content [28]. This has been taken as indication for a prooxidative action of OA. A minor changes in lipid peroxidation occurred in the liver microsomes of rats fed 5% OA-diet for 2 weeks, whereas after 6 weeks of treatment showed a more pronounced elevation [30]. It is also evidence that oral administration with *S. cerevisiae* fermented substance, which produced significant quantities of glutathione and its related thiol-compounds suppressed dose-dependently acetaminophen-induced hepatic damage [19,32].

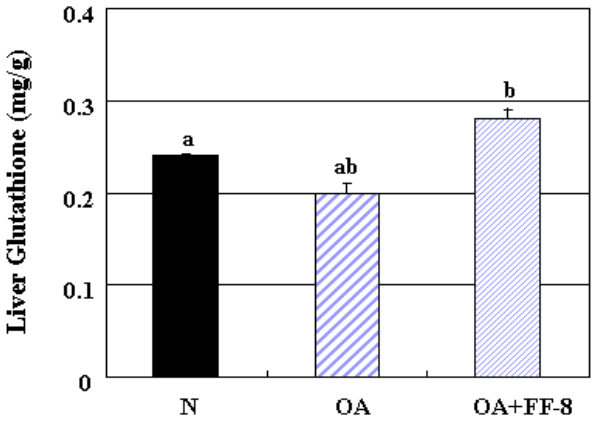

Fig. 1. Effect of glutathione-enriched FF-8 strain on the liver glutathione concentration in OA feeding rats for 10 days. Orotic acid (1.0%, w/w) and FF-8 (5.0%, w/w) were supplemented to the normal diet. Each value is the mean±SE of six rats per experimental group. Values with different letters are significantly different at $p<0.05$.

The OA treatment was slightly reduced the hepatic glutathione level in the current study without statistically significant, compared to the normal rats (Fig. 1). But, the hepatic concentration of glutathione in the FF-8 strain fed rats was significantly increased compared to the OA treated rats (Fig. 1). The result suggest that high-glutathione *S. cerevisiae* FF-8 would be useful for the treatment of hepatotoxicity and oxidative stress of which induced by OA-treatment in rat. Lipid peroxidation levels in kidney and heart were observed the same tendency as the liver. The concentrations of lipid peroxidation in the homogenates of spleen and testis from orotic administered rats were similar to those of normals and this is in agreement with the result in the previous study [8].

In addition, zinc play antioxidant properties against oxidative damage in organisms [2,15,23,26,27]. It was previous reported that the highest concentrations of zinc was found in the cell wall and membrane debris in yeast *Yarrowia lipolytica* by electrochemical methods [31]. Present study also used the yeast whole cell containing a highly concentration of zinc, and the liver zinc concentrations were slightly lowered in rats fed OA compared to the normal rats, but this reduction was significantly increased by FF-8 strain supplementation in OA feeding rats (Table 3). Recent rat studies reported an increase in serum and liver zinc due to an increase in the zinc absorption values [22,24]. Recently our study also demonstrated that the reduction of serum zinc concentration in rats fed ethanol was significantly increased by zinc-enriched yeast strain supplementation [4].

Table 3. Effect of glutathione-enriched FF-8 strain on the liver mineral concentrations in OA feeding rats for 10 days (ppm)

Liver Minerals	Normal	OA	OA+FF-8
Fe	1.20±0.00^{NS}	1.20±0.00	1.20±0.00
Zn	0.25±0.01^{a}	0.16±0.01^{b}	0.29±0.01^{c}
Cu	0.03±0.00^{ab}	0.02±0.00^{a}	0.04±0.01^{b}
Na	2.00±0.02^{NS}	1.80±0.01	2.80±0.03
Mg	2.40±0.01^{a}	1.60±0.00^{b}	1.80±0.00^{b}
Ca	8.00±0.00^{NS}	10.00±0.00	8.00±0.00
Mn	0.01±0.00^{NS}	0.02±0.01	0.01±0.00

Orotic acid (1.0%, w/w) and FF-8 (5.0%, w/w) were supplemented to the normal diet.
Each value is the mean±SE of six rats per experimental group. Values with different letters are significantly different at $p<0.05$.

The concentrations of Fe, Na, Ca, Mn in the liver were not significantly different among the experimental groups (Table 3). Zinc concentration was significantly decreased in the OA feeding rats compared with the normal rats, but this reduction was significantly elevated by concomitant with OA and FF-8 strain. This result was found to be a positive correlation between the zinc level and antioxidative action against lipid peroxidation in the liver.

In conclusion, OA treatment caused liver injury as oxidative stress by increased the liver lipid peroxidation level and administration of yeast strain containing highly glutathione and zinc concentrations provided antioxidative activity by reduced hepatic oxidative stress.

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초록 : 지방간의 과산화지질에 미치는 글루타티온 고함유 효모 *Saccharomyces cerevisiae* FF-8 균주 급여의 영향

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간 질환 개선용 영양보충제로 시판되고 있는 글루타티온 고함유 *Saccharomyces cerevisiae* FF-8 효모 균체(FF-8) 급여가 사염화탄소 및 알코올-유발 흰쥐 조직 스트레스에 대하여 억제효과가 있다는 것을 보고한 바 있다. 본 실험에서는 글루타티온 고함유 효모 FF-8 급여에 의한 오르트산-유발 지방간에서 각 조직 중 과산화지질 농도와 간 조직 내 미네랄 성분과의 관계를 검토하였다. 체중 증가량은 정상군은 두 실험군에 비해 증가하였으나, 오르트산 급여 실험군들에서는 체중 증가량이 5% 수준에서 유의적으로 감소하였다. 각 조직 중량은 오르트산 급여군에서 간 조직에서 5% 수준에서 유의적으로 증가하였고 FF-8 투여에 의해 다소 감소하는 것으로 나타났다. 한편, 신장 및 비장에서도 오르트산 급여에 의해 5% 수준에서 유의적으로 감소하였다. 간 조직 중의 과산화지질 농도는 오르트산 급여군에서 5% 수준에서 유의적으로 증가하였고, FF-8 균체 급여군에서 감소하였다. 이때 간 조직 중의 글루타티온 농도도 유사한 경향을 보였다. 천연 항산화 미네랄로 알려진 간 조직 중의 아연 농도는 정상군에 비해 오르트산 유발 지방간에서 감소하였고, FF-8 균체 급여에 의해 다소 증가되는 것으로 나타났다. 이상의 실험 결과에서 오르트산-유발 지방간에서 지질과산화 농도의 증가는 간 조직내 천연 항산화 물질인 글로타티온과 아연 농도의 현저한 감소에 기인하였고, 항산화 물질인 글루타티온을 고함유한 *S. cerevisiae* FF-8 효모 균체 동시 급여에 의해서는 글로타티온과 아연 농도의 증가에 의해 과산화지질 농도가 경감됨으로서 오르트산 유발 산화스트레스를 경감시키는 효과가 있는 것으로 확인되었다.