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Anti-oxidant and anti-hyperlipidemic effects of cordycepin-rich *Cordyceps militaris* in a Sprague–Dawley rat model of alcohol-induced hyperlipidemia and oxidative stress

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Abstract

Hyperlipidemia is involved in serious cardiovascular disease, however, synthetic drugs to reduce lipid contents in blood stream have been found to induce serious side effects. In the current study, we compared anti-oxidant and anti-hyperlipidemic effect of *Paecilomyces japonica* (PJ), *Cordyceps militaris* (CM) and cordycepin-rich *Cordyceps militaris* (CMα) in rats induced alcoholic hyperlipidemia (AIH) and oxidative stress. The experimental groups were divided in N (water), C (30% alcohol), PJ (30% alcohol + 3% PJ powder), CM (30% alcohol + 3% CM powder), CMα (30% alcohol + 3% CMα powder) and SM [30% alcohol + 0.1% silymarin (SM)]. Compared to C group, supplementation of PJ, CM, CMα and SM slightly alleviated the increased weight ratio of liver and kidney in the alcohol-treated rats. In addition, a significant or slight reduction was identified in total lipid, total cholesterol and HDL-cholesterol levels in the rats receiving PJ, CM and CMα as compared with C group. Administration of PJ, CM and CMα also blocked alcohol-induced lipid peroxidation via a decrease of malondialdehyde (MDA), and activated anti-oxidant enzyme, glutathione (GSH), in serum and various organ tissues. Overall, cordycepin-rich CMα showed highest anti-oxidant and anti-hyperlipidemia effect under chronic alcoholic damage. Our results indicate that CMα might be useful in inhibiting the oxidation and hyperlipidemia in alcohol-induced hepatic disease possibly because of potential anti-oxidative and anti-hyperlipidemic activities of cordycepin.

Keywords: Cordycepin-rich *Cordyceps militaris*, Thiobarbituric acid-reactive substances (TBARS), Reduced glutathione (GSH), Oxidative stress, Anti-hyperlipidemic activity

Introduction

Hyperlipidemia, known as the condition of abnormally increased lipid in plasma and tissues, is a potential risk factor resulting in atherosclerosis and cardiovascular diseases (AlHajri et al. 2017). During a decade, numerous studies have focused on the importance of regulating lipid profile to prevent coronary heart disease, cerebral stroke, myocardial infarction, diabetes and renal failure. In addition, these kinds of risk factors can aggravate pathological condition to induce oxidative damage at the molecular level (Nagarthna et al. 2020). However, chemotherapeutics lowering lipid level have been found to cause serious adversary effects, such as, depression, anxiety, headache, nausea, diarrhea, vomiting, cardiac toxicity and constipation (Niharika 2017). Thus, in recent years, there has been growing interest in the development of less toxic

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anti-hyperlipidemia agent using natural product and its bioconversion process.

Cordycepin, 3-deoxyadenosine, is a derivative of the nucleoside adenosine, and it is abundantly present in *Cordyceps* species (Ju et al. 2009; Zhou et al. 2016). Since cordycepin shows chemical similarity to adenosine, it could be involved in the incorporation of RNA molecule causing a broad range of biological activities (Chen et al. 2017). Furthermore, tremendous evidences have reported its anticancer, anti-hypertension, anti-liver injury and improving immune response effects (Jing et al. 2015; Chen et al. 2017). Therefore, the consumption of *Cordyceps* species has steadily increased with the expectation of positive effect on chronic diseases.

Cordyceps militaris (*C. militaris*, CM) and *Paecilomyces japonica* (*P. japonica*, PJ) belong to the *Cordyceps* species, and they are produced by silkworm inoculated with different fungal parasites. CM is a mushroom that is widely present worldwide and has long been used as a nutraceutical and traditional medicine in the eastern Asia (Jing et al. 2015), and PJ is used as a dietary supplement that is effective in improving stamina, blood circulation and the quality of life (Shin et al. 2003; Shin et al. 2001). To date, numerous attempts have been made to identify a novel type of cordycepin-rich *Cordyceps* species (Guo et al. 2010; Sun et al. 2011). Previous studies have demonstrated that cross-bred cordycepin-rich CM (CMα) (JLM 0636) had a sevenfold larger amount of cordycepin (742 mg/100 g d.w.) as compared with normal CM (Cha et al. 2011). Moreover, it was 1.7–24.7 times larger as compared with CM (448 mg/100 g d.w.), *Cordyceps sinensis* (30 mg/100 g d.w.) and PJ (54 mg/100 g d.w.) (Oh et al. 2003). Furthermore, we have also previously demonstrated simple screening on effectiveness of CM, PM and CMα in a Sprague–Dawley (SD) model of orotic acid-induced hepatotoxicity and oxidative stress (OS) (Cha et al. 2011). Still, however, there is a paucity of data regarding the biological effects of CMα in an SD model of alcohol-induced hyperlipidemia (AIH) and OS.

Given the above background, this study conducted this experimental study to examine anti-oxidant and anti-hyperlipidemic effects of CMα as compared with CM and PJ in an SD model of AIH and OS.

Materials and methods

Materials

The dried fruiting bodies of PJ, CM and CMα were purchased from a commercial supplier (Chungwonnonsan Co., Ltd., Gimhae, Korea). In addition, the cordycepin standard (purity > 95%; Cat No. PHL82505) was purchased from Sigma Chemical Co. (St. Louis, MO, USA).

Experimental animals and design

A total of 36 male SD rats (Hyochang Science Animals Co., Daegu, Korea) were housed individually at room temperature (21–24 °C) under a 12-h light/12-h dark cycle. For a week before the experimental procedure, they were provided with food and water ad libitum. Then, they were randomly divided into the following 6 experimental groups (Additional file 1):

1. The Group N ($n=6$): The normal SD rats receiving water
2. The Group C ($n=6$): The SD rats receiving 30% alcohol
3. The Group PJ ($n=6$): The SD rats receiving 30% alcohol + 3% PJ powder
4. The Group CM ($n=6$): The SD rats receiving 30% alcohol + 3% CM powder
5. The Group CMα ($n=6$): The SD rats receiving 30% alcohol + 3% CMα powder
6. The Group SM ($n=6$): The SD rats receiving 30% alcohol + 0.1% silymarin (SM).

The amount of PJ, CM, CMα and SM supplemented to the diet was determined as previously described (Koh and Choi 2003; Dahiru and Obidoa 2007). The food consumption and water intake were measured every day and body weight gain was measured once a week. The current experimental study was conducted in accordance with the National Institute of Health guidelines on the care and use of laboratory animals, and it was approved by the Institutional Animal Care and Use Committee (IACUC) of our institution (IACUC approval # 160/1999/CPCSEA).

Measurement of lipid levels

After 4 weeks, the SD rats were killed by withdrawing blood from the abdominal aorta under light diethyl ether anesthesia. The serum sample was obtained by the centrifugation of the blood at 1026×*g* for 15 min at 4 °C. The concentrations of serum total lipid, triglyceride (TG), total cholesterol (TC), high-density lipoprotein- (HDL)-cholesterol and non-esterified free acid (NEFA) were measured using the Chemiclinical Chemistry Analyzer (Neodin Medicinal Institute, Seoul, Korea). Hepatic lipid was extracted, as previously described (Folch et al. 1957). Hepatic TG levels were enzymatically measured using a commercial kit (Sigma Chemical Co.), which is based on a modification of the lipase-glycerol phosphate oxidase method (McGowan et al. 1983).

Measurement of lipid peroxidation and glutathione levels

The organs such as liver, kidney, heart, spleen and testis were quickly removed, weighted and then kept in a plastic

bag at −70 °C. This was followed by the preparation of tissue homogenates and hepatic subcellular fractions as previously described (Cha et al. 2001). In addition, protein contents of the liver homogenate and cellular fractions were measured by the method of Lowry et al. (1951). The lipid peroxidation products were estimated by measuring thiobarbituric acid-reactive substances (TBARS), as previously described (Ohkawa et al. 1979). The concentration of TBARS was expressed as nmol of malondialdehyde (MDA) per g tissues or mL serum. The concentration of glutathione (GSH), nonenzymatic antioxidant, was determined as previously described (Beutler et al. 1963). It was expressed as mg/g tissue and mg/mL serum.

Statistical analysis

Statistical analysis was done using the SPSS 17.0 for Windows (SPSS Inc., Chicago, IL). All data were expressed as the mean ± SEM (SEM: standard errors of the mean). Data analysis was performed using one-way analysis of variance (ANOVA), followed by a post hoc analysis using the Duncan's new multiple-range test. A P value of < 0.05 was considered statistically significant.

Results

Effect of PJ, CM, CMα and SM on body and organ weight in the alcohol-treated SD rats

As shown in Table 1, although the initial body weight was not significant in normal, control, PJ, CM, CMα and SM, there was a statistically meaningful decrease of the final body weight in C, PJ, CM, CMα and SM. Compared to N group, C group showed markedly increased tissue weight by 0.51%, 0.08% and 0.05% in liver, kidney and testis, respectively, and decreased perirenal and epididymal fat weight by 0.72% and 0.42%, respectively. Compared to control group, administration of PJ, CM, CMα and SM slightly alleviated the increased weight ratio of liver and kidney in alcohol-treated rats. However, there was no specific correlation in weight of heart, spleen, testis, perirenal fat and epididymal fat between N, C, PJ, CM and CMα group.

Effect of PJ, CM, CMα and SM on serum and liver lipid profile in the alcohol-treated SD rats

In comparison with normal group, there were significant increase of liver and serum TG levels in the SD rats receiving alcohol (control group) (Fig. 1). However, administration of PJ, CM, CMα and SM markedly decreased liver and serum TG contents. It is noteworthy that there was no significant difference in serum and liver levels of TG between the SD rats receiving CMα and normal ones (Fig. 1). There was no significant difference in serum levels of total lipid, TC, HDL-cholesterol and NEFA between normal and control groups (Table 2). But there was a significant or slight decrease in total lipid, total cholesterol and HDL-cholesterol levels in the rats receiving PJ, CM and CMα as compared with those receiving alcohol only. Treatment of SM, positive control for hyperlipidemia, significantly improved lipid condition compared to control rats; it showed no significant difference from normal rats. There was a slight improvement in lipid conditions in the SD rats receiving CMα; total cholesterol and HDL-cholesterol levels showed no significant difference from the SD rats receiving the SM.

Effect of PJ, CM, CMα and SM on MDA and GSH levels in the alcohol-treated SD rats

There was a significant or slight increase in MDA levels in the serum, hepatic subcellular fractions, kidney, heart, spleen and testis in the SD rats receiving alcohol only as compared with normal ones. But a significant decrease in MDA levels was observed in the serum, hepatic subcellular fractions, kidney, heart, spleen and testis in the SD rats receiving CMα. Although PJ and

Table 1 Body weight and the relative weight of the tissue (%)[1] in the rats receiving alcohol

	N	C	PJ	CM	CMα	SM
Initial body weight (g)	167.7 ± 2.95^{a}	167.2 ± 3.25^{a}	166.1 ± 2.48^{a}	166.0 ± 2.25^{a}	164.8 ± 1.86^{a}	164.8 ± 1.86^{a}
Final body weight (g)	407.3 ± 10.9^{a}	342.7 ± 7.78^{b}	327.3 ± 11.0^{c}	349.0 ± 9.81^{bc}	326.9 ± 16.7^{bc}	356.7 ± 10.4^{bc}
Liver (%)	3.05 ± 0.20^{ac}	3.56 ± 0.20^{b}	2.86 ± 0.07^{ac}	2.67 ± 0.13^{a}	3.12 ± 0.09^{c}	2.91 ± 0.12^{ac}
Kidney (%)	0.69 ± 0.01^{a}	0.77 ± 0.03^{bc}	0.71 ± 0.02^{ac}	0.68 ± 0.01^{a}	0.81 ± 0.05^{b}	0.73 ± 0.02^{ac}
Heart (%)	0.35 ± 0.01^{a}	0.36 ± 0.01^{a}	0.37 ± 0.01^{a}	0.36 ± 0.01^{a}	0.36 ± 0.01^{a}	0.36 ± 0.01^{a}
Spleen (%)	0.21 ± 0.01^{a}	0.21 ± 0.01^{a}	0.25 ± 0.01^{bc}	0.22 ± 0.01^{ac}	0.27 ± 0.02^{b}	0.20 ± 0.01^{a}
Testis (%)	0.94 ± 0.03^{a}	0.99 ± 0.03^{ab}	1.11 ± 0.03^{b}	0.96 ± 0.05^{a}	1.12 ± 0.04^{b}	1.02 ± 0.06^{ab}
Perirenal fat (%)	2.26 ± 0.14^{a}	1.54 ± 0.15^{b}	1.53 ± 0.14^{b}	1.47 ± 0.09^{b}	1.15 ± 0.06^{b}	1.43 ± 0.16^{b}
Epididymal fat (%)	2.18 ± 0.18^{a}	1.76 ± 0.10^{bc}	1.87 ± 0.16^{ac}	1.61 ± 0.06^{bc}	1.43 ± 0.05^{b}	1.58 ± 0.14^{bc}

N, normal; C, control; PJ, *Psoroglaena japonica*; CM, *Cordyceps militaris*; CMα, cordycepin-rich *C. militaris*; SM, syrimarin

[1] The relative weight of the tissue (%) represents the ratio of the tissue weight to the body weight

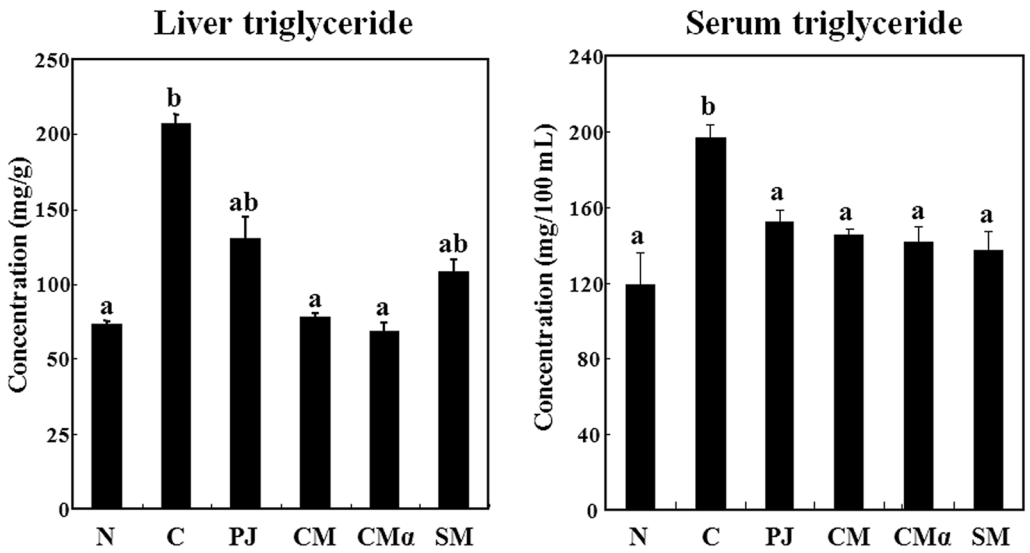

Fig. 1 Hepatic and serum levels of triglyceride

Table 2 Serum lipid levels in the rats receiving alcohol

Group	Total lipid (mg/100 mL)	Nonesterified fatty acid (mmol/L)	Total cholesterol (mg/100 mL)	HDL-cholsterol (mg/100 mL)
N	367.3 ± 24.9^{ab}	1.06 ± 0.04^{a}	65.17 ± 5.40^{a}	32.20 ± 0.65^{a}
C	398.1 ± 18.0^{a}	1.13 ± 0.15^{ab}	93.17 ± 7.39^{b}	34.40 ± 1.67^{a}
PJ	365.8 ± 25.2^{ab}	1.33 ± 0.06^{b}	70.14 ± 1.71^{a}	28.04 ± 0.42^{b}
CM	357.1 ± 12.7^{ab}	1.36 ± 0.08^{b}	70.00 ± 2.14^{a}	28.86 ± 0.46^{b}
CMα	356.0 ± 15.1^{ab}	1.34 ± 0.07^{b}	69.00 ± 6.55^{a}	29.50 ± 1.26^{b}
SM	315.0 ± 19.0^{b}	1.02 ± 0.05^{a}	71.17 ± 7.82^{a}	28.50 ± 2.31^{b}

Values are mean ± S.E. (S.E.: standard error of the mean). Different letters indicate significant differences between the groups ($P < 0.05$)

N, normal; C, control; PJ, *Psoroglaena japonica*; CM, *Cordyceps militaris*; CMα, cordycepin-rich *C. militaris*; SM, syrimarin

CM administration indicated a reducing tendency of MDA levels, CMα showed lowest MDA contents in the serum, hepatic subcellular fractions, kidney, heart, spleen and testis (Figs. 2, 3). Treatment of SM significantly down-regulated MDA contents in lipid condition in the serum, hepatic subcellular fractions, kidney, heart, spleen and testis, compared to control rats.

Furthermore, a significant increase of GSH levels were indicated in the serum, liver, kidney, heart, spleen and testis in control rats as compared with normal ones. Similarly with MDA results, CMα-treated rats showed highest GSH levels in the serum, liver, kidney, heart, spleen and testis, compared to control ones (Fig. 4). Rats administered with SM markedly increased GSH levels in liver, serum, testis and spleen, however, kidney and heart were not affected by SM treatment.

Discussion

A number of studies have reported that periodic alcohol consumption is closely involved with fatty liver, obesity, diabetes and hepatic steatosis (Volzke 2012). In the present study, a continuous consumption of alcohol (4 weeks) inhibited the normal growth of the rats; this is well illustrated in a decreased body weight and increased liver weight in the rats receiving alcohol only as compared with normal ones. Although administration of CMα lowered body weight more than control rats, PM- and CM-served rats, CMα treatment significantly recovered fatty liver symptom which is induced by alcoholic damage. A previous study also demonstrated that the administration of water extract from *P. tenuipes* in high-fat induced obesity mice produced a significantly lower body weight gain and fatty liver (Heo et al. 2009). In addition, Guo et al. also found that cordycepin was effective in not only

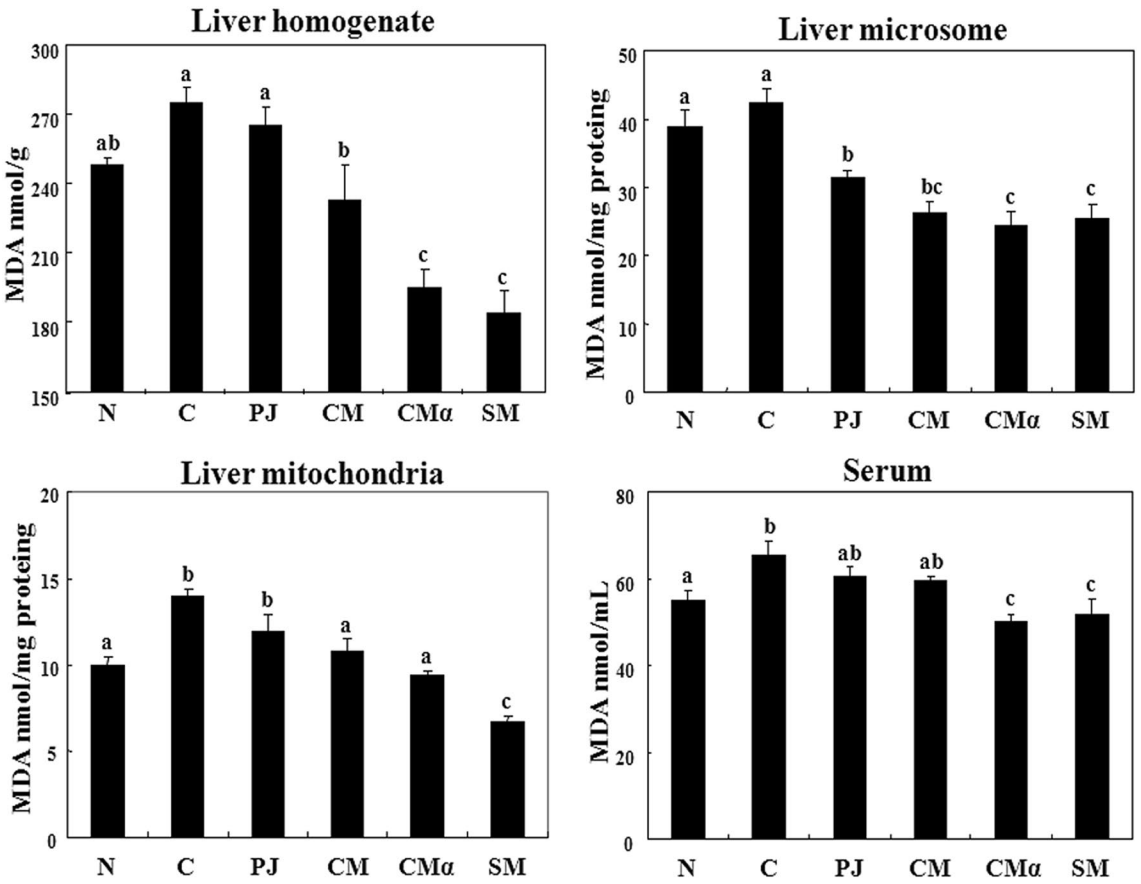

Fig. 2 Hepatic and serum levels of thiobarbituric acid-reactive substances (TBARS)

reducing the body weight gain and the relative amount of the retroperitoneal fat, but also markedly decreasing lipid droplets in liver tissue when administered to hamsters at a dose of 50 mg/kg for 2 weeks (Guo et al. 2010). These findings suggest that supplementation of cordycepin-rich *Cordyceps militaris* during alcohol consumption causes effect of weight loss and fatty liver prevention.

Chronic heavy drinking causes serious liver problems such as fatty liver, alcoholic hepatitis and cirrhosis. They are collectively called alcohol-related liver disease that is characterized by hepatic TG accumulation (Tahara et al. 1999). It is also seen in our previous finding and present result showing that consumption of alcohol increases hepatic TG level in the SD rats (Cha et al. 2011; Additional file 2, Table 1, Fig. 1). This is in agreement with a previous report that there was a fourfold increase in hepatic TG levels after alcohol supplementation (Oliva et al. 1998). In the current study, SD rats receiving CM and CMα showed significant lower hepatic TG as compared with control ones. Our study also found that a slight decrease of hepatic TG levels indicated in the SD rats receiving PJ and SM. It is noteworthy that CMα had a higher effect on reducing lipid accumulation in the liver as compared with the SM, one of the well-known hepatoprotective agents. These findings showed similarity with previous reports demonstrating fatty liver preventative effect of vegetable worms (Koh and Choi 2003; Han et al. 2009). In addition, Guo et al. showed that cordycepin markedly decreased the proportion of lipid droplets in the liver by Oil-Red O stain, thus suggesting that it plays a role in preventing lipid accumulation in the liver (Guo et al. 2010). These results indicate that cordycepin-rich CMα can effectively block alcohol-induced lipid accumulation in liver.

Alcohol consumption is a powerful factor that induces hyperlipidemia in both animals and humans (Singh et al. 2016). It has been suggested that the most common lipid abnormalities during chronic alcohol consumption are known to produce hypercholesterolemia and hypertriglyceridemia (Bessembinders et al. 2011). In the current study, a significant decrease was observed in serum TG levels in the SD rats receiving PJ, CM, CMα and SM as compared with those receiving alcohol only. According to Koh and Choi, there was a significant decrease in serum

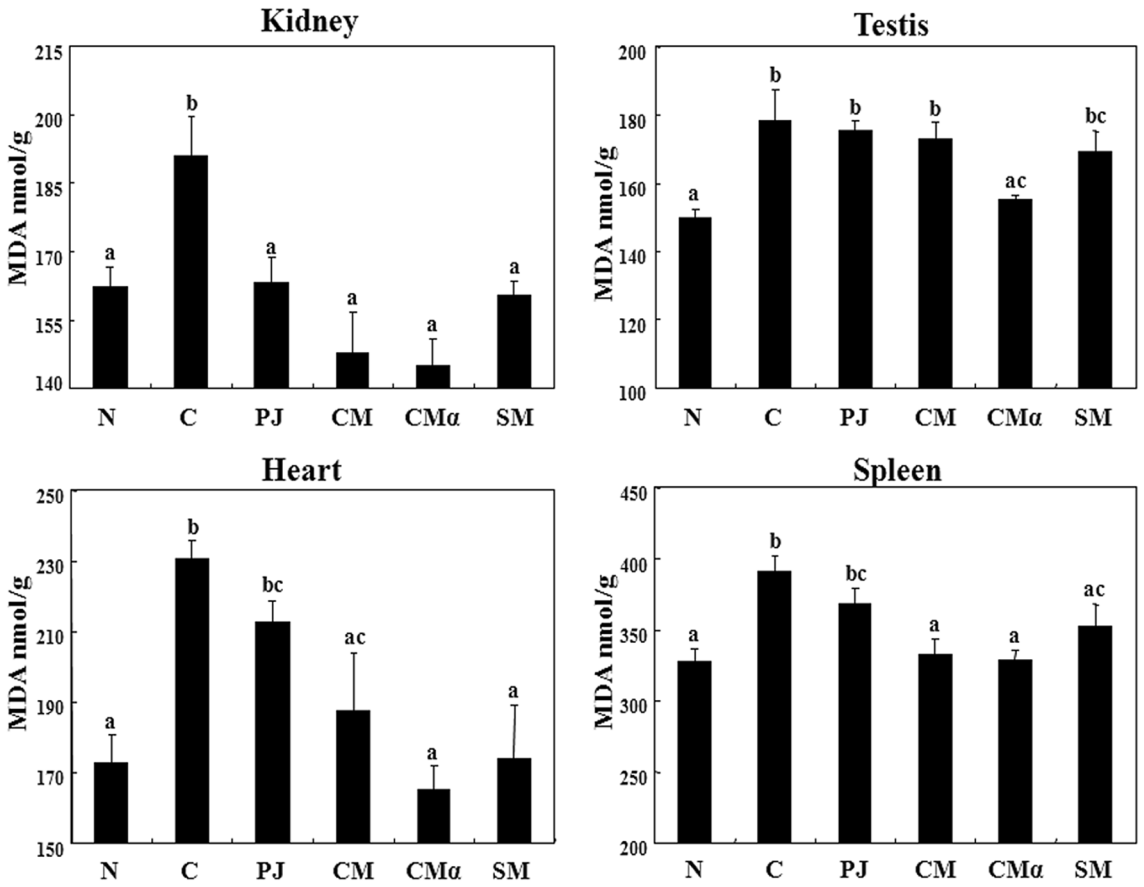

Fig. 3 Concentrations of thiobarbituric acid-reactive substances (TBARS) in kidney, heart, spleen and testis

TG levels after treatment of 3% PJ in high-fat feeding rats (Koh and Choi 2003). Moreover, Han et al. also reported that a significant decrease in serum TG levels was identified after treatment with 6% PJ (Han et al. 2009). Furthermore, most of the studies in this series have reported the serum TC levels is increased due to heavy alcohol consumption, and disruption of cholesterol metabolism (Saini et al. 2019; El-Tantawy and Temraz 2019). Based on our results, supplementation of PJ, CM and CMα effectively regulated accumulation of lipid in liver and serum under the chronic alcohol intake.

It is widely known that acute or chronic alcohol intake is closely associated with excessive lipid peroxidation. Lipid peroxidation, particularly reaction of reactive oxygen species (ROS) with lipids, produces oxidative stress biomarkers, such as MDA and 4-hydroxy-2-nonenal (HNE) (Tsikas 2017). In addition, its degree is considered as an indicator of early acute hepatic damage (Ho et al. 2013). This is in agreement with our results showing that there was a significant increase in MDA levels in the serum, hepatic subcellular fractions, kidney, heart, spleen and testis in the SD rats receiving alcohol as compared with normal ones. However, supplementation of CMα suppressed lipid peroxidation in various organs, specifically liver (Figs. 2, 3). Interestingly, the degree of decrease in that of lipid peroxidation was significantly higher in the SD rats receiving CMα as compared with those receiving PJ and CM. In the blood stream and organ tissues, circulation and accumulation of MDA is one of the major contributions to induce oxidative stress resulting in cancer, diabetes, asthma, atherosclerosis and Alzheimer's disease (Dalle-Donne et al. 2006). Thus, our results demonstrate that administration of CMα effectively prevents lipid peroxidation in blood and organs during alcohol intake.

Cordycepin and adenosine have been reported to show outstanding anti-oxidant and radical scavenging activities (Jiang et al. 2011). Moreover, it is presumed that bioactive compounds play an important role in preventing the oxidative damage as a dietary supplement. Several photochemical studies have identified flavonoids, phenolics and adenosine analogues as anti-oxidant ingredients isolated from CM and PJ (Yu et al. 2006). This is also accompanied by a report that CM and CS extracts had polyphenolic and flavonoid compounds at a concentration of 60.2

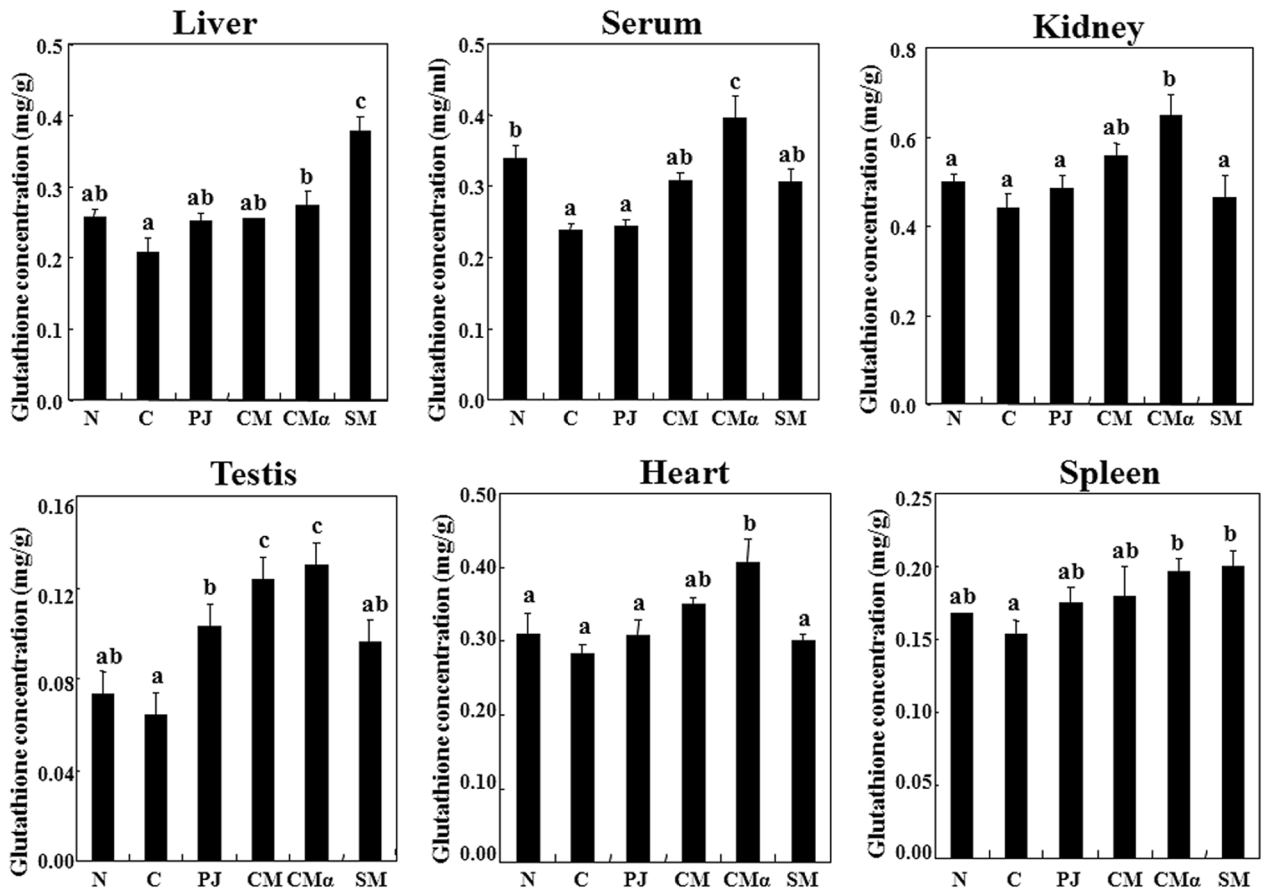

Fig. 4 Concentrations of glutathione (GSH) in the serum, hepatic homogenate, kidney, heart, spleen and testis

and 0.598 μg/mL and 31.8 and 0.616 μg/mL, respectively (Yu et al. 2006). The anti-oxidant effects of CM may also arise from an abundant presence of polyphenolic compounds and cordycepin derivatives. This is also associated with a previous report showing that the ethanolic extract from fruiting bodies of CM has an anti-oxidant effect arising from a strong free radical scavenging activity (Jing et al. 2015).

Nonenzymatic anti-oxidants, such as GSH and ascorbic acid, are considered as the cellular anti-oxidant defense system against oxidative damage due to free radicals (Kurutas 2016). GSH is a major non-protein thiol tripeptide containing L-glutamate, L-cysteine and glycine in living organisms (Aquilano et al. 2014). Decreased GSH levels were also reported to arise from GSH oxidation and lipid peroxidation during alcohol metabolism (Zakhari 2013). Thus, it is involved in an endogenous defense mechanism against the peroxidative destruction of cellular membranes. In the current study, there was no significant difference in GSH levels between CM, CMα and normal rat groups. It showed similar tendency with MDA contents, suggesting that a lower degree of lipid peroxidation is closely associated with a higher level of anti-oxidant enzyme activity. In addition, according to our previous results, the higher cordycepin contents in CMα can expect inducing activation of anti-oxidant enzyme (Cha et al. 2011). These results indicate that intake of cordycepin-rich CMα effectively blocks lipid peroxidation through regulation of the anti-oxidant enzymes.

Conclusions

Based on our results, it can be concluded that CMα might be used as a drug and functional food in inhibiting the oxidation and hyperlipidemia in an SD model of alcohol-induced hepatic disease possibly because of cordycepin and polyphenolic compound with potential anti-oxidative and anti-hyperlipidemic activities.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s40643-020-00323-9.

Additional file 1. A schematic diagram of the experiment.

Additional file 2. Histopathologic findings.

Abbreviations

AIH: Alcohol-induced hyperlipidemia; CM: *Cordyceps militaris*; CMα: Cordycepin-rich CM; GSH: Glutathione; HDL: High-density lipoprotein; OS: Oxidative stress; PJ: *Paecilomyces japonica*; SD: Sprague–Dawley; SM: Silymarin; TBARS: Thiobarbituric acid-reactive substances; TC: Total cholesterol; TG: Triglyceride.

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Non applicable.

Authors' contributions

HYA and YSC conceived and coordinated the study and performed the experiments. YSC validated the experimental design. HYA, HDC and YSC analyzed the experimental results. HYA, HDC and YSC wrote and edited the paper. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this article.

Ethics approval, consent to participate and consent for publication

Non-applicable.

Competing interests

The authors declare that they have no competing interests.

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