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Dietary Epigallocatechin Gallate Worsens Rat Liver Injury Induced by a High-Fat Diet and Ethanol Consumption

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Abstract

Heavy drinking and obesity, which often coexist, have been shown to promote liver injury, steatohepatitis, and fibrosis developments. The recent increase in the incidence of metabolic syndrome highlights the potential of heavy drinking and obesity to cause liver damage and consequent inflammation synergistically. Tea is consumed worldwide. Catechin, a bitter tea component, is a polyphenol. Catechins have many physiological effects, including antioxidant, bactericidal, anticancer, hypotensive, cholesterol-lowering, and blood sugar-suppressing effects. Recently, it has been suggested that they exert anti-obesity effects. This study investigated the effects of epicatechin gallate combined with a high-fat diet and chronic alcohol consumption on liver damage in rats. Twenty male Wistar rats were randomized into four groups of five: control, high-fat diet, high-fat-ethanol diet, and high-fat-ethanol-epicatechin gallate diet groups. The rats in each group were fed the experimental diets ad libitum for eight weeks. High-fat diet and ethanol consumption induced fatty liver in rats. Additionally, epicatechin gallate exacerbated liver injury. However, epicatechin gallate content in normal green tea intake is considered safe, and caution should be exercised when consuming concentrated supplements.

Key Words: epigallocatechin gallate, high-fat diet, ethanol, liver injury, rat

Introduction

Heavy drinking and obesity, which often coexist in patients, have been shown to promote liver injury, steatohepatitis, and fibrosis developments[1, 2]. The recent increase in metabolic syndrome incidence highlights the potential of heavy drinking and obesity to synergize and cause liver damage and consequent inflammation[1, 2]. Several clinical studies have demonstrated the additive effects of high alcohol consumption and obesity on steatohepatitis and liver-related mortality[3-5]. In contrast, some early observational studies have suggested that low-to-moderate alcohol consumption does not increase or decrease the risk of fatty liver disease[6-8]. A survey of Japanese men showed that those who consumed approximately 20 g of pure alcohol daily had the lowest mortality rate[9]. The graph of the relationship between the total mortality rate and the amount of alcohol consumed per day shows a J-shaped curve (J-curve effect). However, a meta-analysis later questioned this conclusion[10, 11].

Tea is a beverage that is widely consumed worldwide, and catechin, a bitter component of tea, is a polyphenol[12]. Tea catechins are classified into catechin (C), gallocatechin (GC), epigallocatechin (EGC), epicatechin (EC), epigallocatechin gallate (EGCg), epicatechin gallate (ECg), catechin gallate (Cg), and gallocatechin gallate (GCg)[12]. Catechins have many physiological effects, including antioxidant, bactericidal, anticancer, hypotensive, cholesterol-lowering, and blood sugar-suppressing effects[13]. Recently, it has been suggested that these have anti-obesity effects[14]. Previous studies reported that the antioxidant activity of catechins effectively prevents liver damage[15].

There is also information that views the harmful effects of tea as problematic. The Australian Government's Department of Health and Aged Care has cautioned that tea leaf extract can cause liver damage in rare cases[16]. They reported that tea leaf extract is used as an ingredient in many pharmaceuticals, and is often concentrated. The Government of Canada does not recommend products containing tea extracts for children

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because of the risk of liver damage from tea extracts[17]. According to the Food Compliance European Union, Belgium, France, and Italy have established upper limits for the amount of tea leaf extract supplements that can be consumed[18].

This study investigated the effects of catechin intake along with a high-fat diet and chronic alcohol consumption, which induces fatty liver, on liver damage in rats.

Materials and Methods

All animal procedures were approved by the Animal Care and Use Committee for Kagawa University.

Materials

EGCg was purchased from FUJIFILM Wako Pure Chemical Industries（Osaka, Japan）. Soybean oil and beef tallow were purchased from Yamakei Industry Co. Ltd.（Osaka, Japan）, with a composition: soybean oil: 10.3% palmitic acid, 3.8% stearic acid, 24.3% oleic acid, 52.7% linoleic acid, and 7.9% α-linolenic acid; beef tallow: 24.0% palmitic acid, 16.6% stearic acid, 46.5% oleic acid, 2.8% linoleic acid, and 0.3% α-linolenic acid. Mineral and vitamin mixtures（AIN-76A）were obtained from Oriental Yeast Co. Ltd.（Tokyo, Japan）. The other ingredients in the diet were food-grade and obtained from Fonterra（Auckland, New Zealand）, Mitsui DM Sugar Holdings（Tokyo）, Nippon Paper Industries（Tokyo, Japan）, and Oji Cornstarch（Tokyo, Japan）, respectively. Other reagents were obtained from FUJIFILM Wako Pure Chemical Industries（Osaka, Japan）and Nacalai Tesque（Kyoto, Japan）.

Animals, diets, and experimental design

Twenty male Wistar rats（3-week-old）were obtained from Japan SLC（Shizuoka, Japan）and were individually caged at 22 ± 1°C, with light from 08:00 to 20:00. For 3 days as an acclimatization period, they were fed MF, a commercial rodent diet（Oriental Yeast Co., Ltd., Tokyo, Japan）, and had access to water *ad libitum*. The rats were randomized into four groups as follows: the control（CO）, high-fat diet（HF）, high-fat-ethanol diet（HFE）, and high-fat-ethanol-catechin（HFEC）diet groups. The rats in each group were fed the experimental diets shown in Table 1 for 8 weeks *ad libitum*. The CO diet was a low-fat diet containing 5% fat, whereas the other diets were high-fat and high-cholesterol diets containing 20% fat and 12.5% cholesterol. The HFEC diet contains 2.0% EGCg, accounting for approximately half of the tea catechins and has the highest antioxidant potential among the tea catechins[19]. The HFE and HEFC groups were administered a 5% ethanolic solution *ad libitum*, while the CO and HF groups were administered an isoenergetic dextrin solution *ad libitum*. Bodyweight and food intake were recorded daily. After the experimental period, all rats were euthanized by decapitation at 09:00 after 4 h of fasting. Blood was collected to obtain the serum. The heart, liver, kidneys, spleen, and abdominal adipose tissues（epididymal, perirenal, and mesenteric）were quickly removed and stored at −80°C until analysis. Carcass samples were obtained by removing the head and remaining the intra-abdominal and intra-thoracic tissues. They were stored at −20°C until carcass fat analysis.

Table 1. Composition of experimental diets.

Groups	CO	HF	HFE	HFEC
Ingredients（g/kg）				
Casein	200.0	200.0	200.0	200.0
DL-Methionine	3.0	3.0	3.0	3.0
Dextrin	649.9	482.4	482.4	480.4
Soybean oil	50.0	50.0	50.0	50.0
Beef tallow	0.0	150.0	150.0	150.0
Cholesterol	0.0	12.5	12.5	12.5
Sodium cholate	0.0	5.0	5.0	5.0
Mineral mixture[1]	35.0	35.0	35.0	35.0
Vitamin mixture[1]	10.0	10.0	10.0	10.0
Cellulose	50.0	50.0	50.0	50.0
EGCg	0.0	0.0	0.0	2.0
Chorine chloride	2.0	2.0	2.0	2.0
Butylhydroxytoluene	0.1	0.1	0.1	0.1
Total	1000.0	1000.0	1000.0	1000.0
Energy（kcal/g）	3.80	4.48	4.48	4.48

[1]Based on the AIN-76 mixture.
CO, HF, HFE, and HFEC are abbreviations for the control, high-fat, high-fat-ethanol, and high-fat-ethanol-catechin groups. EGCg, epigallocatechin gallate.

Serum and liver biochemical analyses

Serum glucose, triglycerides, free fatty acids, total cholesterol, high-density lipoprotein（HDL）-cholesterol, low-density lipoprotein（LDL）-cholesterol, aspartate aminotransferase（AST）, alanine transaminase（ALP）, γ-glutamyltransferase（GTP）, uric acid, urea nitrogen, and creatinine were obtained from Fukuyama Clinical Laboratory Co., Ltd.（Hiroshima, Japan）. Liver lipids were extracted using the method described by Folch, et al.[20], and liver triglyceride and cholesterol contents were determined using respective kits［Triglyceride

E-Test, Cholesterol E-Test, (FUJIFILM Wako Chemicals, Osaka, Japan)]. Carcass fat content was analyzed using the method described by Mickelsen and Anderson[21]. Total body fat was calculated as described by the method of Paik and Yearick[22].

Data analysis

All data were analyzed using one-way analysis of variance (ANOVA) and the Tukey-Kramer test (Bell Curve for Excel, SSRI, Tokyo, Japan). Statistical significance was set at $p < 0.05$.

Results and Discussion

Body and tissue weights, energy intake, and body fat (Table 2)

The final body weight and weight gain did not differ among the four groups, whereas energy intake was significantly higher in the HFEC group than in the CO group. These results suggest that ethanol intake reduces dietary energy efficiency; similar results have been obtained in many previous studies[23]. Liver weight was significantly lower in the CO group than in the other groups, and kidney weight was significantly lower in the CO group than in the HFE group. Heart, kidney, perirenal adipose tissue, and mesenteric adipose tissue weights did not differ among the four groups. Epididymal adipose tissue weight was significantly higher in the CO groups than in the other groups, and the total adipose tissue weight was significantly higher in the CO groups than in the HFE group. The carcass fat percentage was significantly higher in the CO group than that in the HFE group, and the body fat percentage was significantly higher in the CO group than that in the HFE and HFEC groups. Tissue weights and percentages of carcass and body fat did not differ among the HF, HFE, and HFEC groups fed a high-fat and high-cholesterol diet. Neither ethanol nor catechin intake affected tissue weight or body fat. Many studies have reported that catechin intake reduces body fat content[24-26]. Wang et al.[24] reported that a daily intake of 500–900 mg of green tea catechins in overweight Asians may reduce body fat mass, especially abdominal fat mass. In a randomized trial, Zang et al.[25] suggested that consuming a catechin-rich green tea beverage for 12 weeks significantly reduced visceral fat area in Chinese adults with high visceral fat areas. Nagao et al.[26] reported that daily tea consumption containing 690 mg of catechins for 12 weeks reduced body fat. The results of the present study do not support those of previous studies. The difference between the results of previous studies and those of this study may have been influenced by the type and amount of catechins administered.

Table 2. Body and tissue weights, energy intake, and body fat in each group of rats.

	Groups	CO	HF	HFE	HFEC
Body weights					
Initial	(g)	63.6 ± 3.4	63.2 ± 6.0	63.6 ± 10.7	63.6 ± 8.1
Final	(g)	262.8 ± 24.4	264.6 ± 24.8	278.8 ± 27.6	278.0 ± 18.6
Gain	(g)	199.2 ± 25.1	201.4 ± 25.2	215.8 ± 17.2	215.2 ± 17.7
Energy intake	(kcal/day)	45.3 ± 6.0^{c}	48.8 ± 5.6^{bc}	54.6 ± 4.7^{ab}	56.1 ± 3.1^{a}
Tissue weights					
Heart	(g)	0.71 ± 0.04	0.69 ± 0.06	0.75 ± 0.04	0.75 ± 0.03
Liver	(g)	9.39 ± 0.95^{b}	17.09 ± 2.29^{a}	18.02 ± 2.37^{a}	18.77 ± 2.55^{a}
Kidneys	(g)	1.60 ± 0.15^{c}	1.66 ± 0.21^{bc}	1.91 ± 0.22^{a}	1.85 ± 0.13^{ab}
Spleen	(g)	0.67 ± 0.07	0.92 ± 0.13	0.84 ± 0.07	1.14 ± 0.70
Intra-abdominal adipose tissue weights					
Epididymal	(g)	6.10 ± 0.30^{a}	4.84 ± 0.29^{b}	4.62 ± 1.42^{b}	4.76 ± 0.35^{b}
Perirenal	(g)	5.68 ± 0.76	4.97 ± 0.48	4.94 ± 1.50	5.35 ± 0.51
Mesenteric	(g)	5.27 ± 0.45	4.70 ± 0.85	4.36 ± 1.09	4.73 ± 0.73
Total	(g)	17.05 ± 1.13^{a}	14.50 ± 1.51^{ab}	13.92 ± 3.83^{b}	14.85 ± 0.89^{ab}
Carcass fat	(%)	14.4 ± 2.0^{a}	13.6 ± 2.2^{ab}	11.8 ± 1.7^{a}	13.0 ± 1.2^{ab}
Total body fat	(%)	13.2 ± 1.3^{a}	11.7 ± 1.3^{ab}	10.3 ± 1.8^{b}	11.3 ± 0.9^{b}

Data are the means ± SD for 5 rats.
CO, HF, HFE, and HFEC are abbreviations for the control, high-fat, high-fat-ethanol, and high-fat-ethanol-catechin groups.

Concentrations of serum components and liver lipid content（Table 3）

Serum glucose, uric acid, and urea nitrogen concentrations did not differ among the four groups. Serum triglyceride and free fatty acid concentrations were significantly higher in the CO group than in the other three groups. Serum HDL-cholesterol concentration was significantly higher and LDL- and total cholesterol concentrations were significantly lower in the CO group than in the other three groups. Serum AST and ALT levels were significantly higher in the HFEC group than those in the CO and HFE groups, and GPT levels were significantly higher in the HFEC group than those in the other three groups. The serum creatinine concentration was significantly lower in the CO group than in the other groups. Liver triglyceride and cholesterol levles were significantly lower in the CO group than in the other groups. A high-fat-cholesterol diet and ethanol consumption markedly induced fatty liver disease and hypercholesterolemia in rats, whereas the effect of ethanol was minimal.

It is possible that the rats were unable to ingest sufficient ethanol to aggravate the liver damage because they were allowed to ingest ethanol *ad libitum*. Tsukada et al.[27] reported that ethanol consumption in rats on a high-fat diet was lower than that on a low-fat diet. Oral gavage may have been used to allow the rats to consume sufficient ethanol, as shown in a previous study[28]. Long-term consumption of large amounts of alcohol increases metabolism through the main pathways of alcohol dehydrogenase（ADH）and acetaldehyde dehydrogenase（ALDH）as well as by the microsomal ethanol oxidation system（MEOS）[29]. The enzyme involved in the metabolism of MEOS is the drug-metabolizing enzyme cytochrome P450（CYP）, and activation of CYP increases the rate of alcohol metabolism, producing a large amount of acetaldehyde and reactive oxygen species, and destroying hepatocytes[29]. Many studies have been conducted on the relationship between CYP and natural food ingredients, and the ingredients contained in grapefruit are known to have a strong CYP-inhibitory effect[30]. Among the polyphenols, tea catechins have a CYP-inhibitory effect, and EGCg, which has strong antioxidant activity, inhibits CYP, reduces the production of active oxygen, and suppresses liver damage[19, 31]. However, the results of this study showed that EGCg intake significantly increased the AST, ALT, and γ-GTP levels, which are indicators of liver damage. This suggests that EGCg may exacerbate liver injury; however, the cause remains unknown. Shi et al.[32] reported that EGCg caused dose-dependent hepatotoxicity in mice under dietary restriction, suggesting the potential combined effects of dietary restriction and EGCg. The combined effect of EGCg and dietary restriction may lead to the overactivation of linoleic acid and arachidonic acid oxidation pathways, signifi-

Table 3. Serum and liver biochemical test results in each group of rats.

	Groups	CO	HF	HFE	HFEC
Serum					
Glucose	(mg/dL)	140.4 ± 7.3	152.8 ± 11.5	144.2 ± 12.4	147.8 ± 9.4
Triglyceride	(mg/dL)	103.2 ± 24.1^{a}	43.2 ± 25.8^{b}	39.2 ± 25.8^{b}	56.8 ± 25.3^{b}
Free fatty acids	(mEq/L)	1.82 ± 0.14^{a}	1.55 ± 0.34^{b}	1.51 ± 0.10^{b}	1.49 ± 0.15^{b}
HDL-Cholesterol	(mg/dL)	93.6 ± 9.8^{a}	59.0 ± 11.3^{b}	61.8 ± 3.6^{b}	58.2 ± 5.7^{b}
LDL-Cholesterol	(mg/dL)	13.8 ± 2.6^{b}	253.6 ± 99.1^{a}	279.0 ± 71.9^{a}	279.4 ± 179.6^{a}
Total-Cholesterol	(mg/dL)	115.6 ± 12.3^{b}	357.6 ± 124.5^{a}	386.2 ± 89.6^{a}	393.0 ± 235.7^{a}
AST	(IU/L)	286.4 ± 27.9^{b}	311.0 ± 84.7^{ab}	280.8 ± 34.0^{b}	363.4 ± 53.7^{a}
ALT	(IU/L)	86.2 ± 10.4^{b}	140.0 ± 65.8^{ab}	130.2 ± 28.3^{ab}	172.4 ± 64.0^{a}
γ-GTP	(IU/L)	1.00 ± 0.00^{b}	1.00 ± 0.00^{b}	1.00 ± 0.00^{b}	1.40 ± 0.55^{a}
Uric acid	(mg/dL)	1.70 ± 0.23	1.64 ± 0.05	1.60 ± 0.16	1.64 ± 0.24
Urea nitrogen	(mg/dL)	15.9 ± 1.4	16.7 ± 3.2	18.6 ± 2.1	18.3 ± 2.0
Creatinine	(mg/dL)	0.21 ± 0.02^{b}	0.25 ± 0.01^{a}	0.26 ± 0.01^{a}	0.27 ± 0.03^{a}
Liver					
Triglyceride	(mg/g)	33.8 ± 17.3^{b}	104.8 ± 83.9^{a}	122.3 ± 48.7^{a}	113.3 ± 28.9^{a}
Cholesterol	(mg/g)	5.6 ± 1.6^{b}	115.9 ± 46.1^{a}	139.1 ± 29.2^{a}	136.79 ± 20.8^{a}

Data are the means ± SD for 5 rats.
CO, HF, HFE, and HFEC are abbreviations for the control, high-fat, high-fat-ethanol, and high-fat-ethanol-catechin groups.
AST, aspartate aminotransferase; ALT, Alanine transaminase; γ-GTP, γ-glutamyltransferase.

cantly increasing the accumulation of pro-inflammatory lipid metabolites, and thus mediating liver injury. These findings show that EGCg exacerbates liver injury depending on dietary conditions, and this study partially supports their findings. The European Food Safety Authority (EFSA) has assessed the safety of green tea catechins from dietary sources, with concerns regarding their possible harmful effects on the liver. The EFSA concluded that catechins from green tea infusions and similar drinks are generally safe[33]. However, when taken as a food supplement, catechin doses at or above 800 mg/day may pose health concerns.

In this study, we investigated the effects of dietary EGCg combined with a high-fat diet and chronic alcohol consumption on liver damage in rats, resulting in EGCg exacerbating liver injury. However, EGCg content in normal green tea intake is considered safe; however, caution should be exercised when consuming concentrated supplements.

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エピガロカテキンガレートは高脂肪食とエタノール摂取によるラットの肝障害を悪化させる

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要　約

多量飲酒と高脂肪食誘発性肥満は，肝損傷，脂肪肝および肝線維症の発症を促進することが明らかにされている．近年，メタボリックシンドロームの発生率の増加は，多量飲酒と肥満が相乗的に肝臓損傷とそれに伴う炎症を引き起している可能性がある．一方，茶は世界中で広く普及している飲料である．茶の苦味成分であるカテキンは，ポリフェノールの一種であり，これまでに抗酸化作用，殺菌作用，抗がん作用，血圧降下作用，コレステロール低下作用，血糖抑制作用および抗肥満作用など，多くの生理学的作用が報告されている．本研究では，長期の高脂肪食およびエタノール摂取によるラットの肝損傷に対するエピカテキンガレートの影響について検討した．20 匹のWistar系雄ラットを 5 匹ずつ4群に分け，それぞれ 対照群，高脂肪食群，高脂肪・エタノール食群，および高脂肪・エタノール・エピカテキンガレート食群とした．各グループのラットには実験食を8週間自由に与えた．その結果，高脂肪食とエタノール摂取は，ラットの脂肪肝を誘発し，エピカテキンガレートは肝障害を悪化させた．通常摂取レベルでの緑茶に含まれるエピカテキンガレートは安全であると考えられているが，濃縮サプリメントを摂取する場合には注意が必要かも知れない．

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