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Consumption of Some Polyphenols Reduces Fecal Deoxycholic Acid and Lithocholic Acid, the Secondary Bile Acids of Risk Factors of Colon Cancer

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This study was performed to examine the effect of dietary polyphenols on fecal secondary bile acids, such as deoxycholic acid and lithocholic acid, the risk factors of colon cancer, in rats fed a high-fat diet. In experiment 1, rats were fed a 30% beef tallow diet containing 0.5% polyphenols for 3 weeks. Dietary curcumin and caffeic acid significantly reduced the fecal concentration of deoxycholic acid. Dietary caffeic acid, catechin, rutin, and ellagic acid significantly reduced fecal lithocholic acid. Fecal hyodeoxycholic acid, a metabolite of lithocholic acid, was markedly lowered by dietary curcumin, caffeic acid, catechin, and rutin. In experiment 2, rats were fed a 30 or 5% beef tallow diet with or without the addition of 0.5% curcumin. In the rats without receiving curcumin, the fecal level of deoxycholic acid was significantly higher in the high-fat diet group than in the low-fat diet group. Fecal deoxycholic acid was significantly reduced by dietary curcumin in the high-fat diets but not in the low-fat diets. The results suggest novel effects of some polyphenols favorable for colon health by reducing secondary bile acids in animals fed a high-fat diet.

KEYWORDS: Secondary bile acids; colon cancer; polyphenols; high-fat diet; rat

INTRODUCTION

A variety of plant polyphenols are well-known to have antioxidant, antiatherogenic, antidiabetic, anticancer, antiviral, and anti-inflammation properties (*1*, *2*). During a preliminary study on the effect of dietary curcumin, a polyphenol derived from turmeric, on lipid metabolisms in rats fed high-fat diet, we have unexpectedly found a marked reduction of fecal deoxycholic acid, the toxic secondary bile acid, in rats fed curcumin. Primary bile acids are synthesized from cholesterol in liver, and the primary bile acids secreted into intestinal lumen are metabolized to secondary bile acids by intestinal microflora. The secondary bile acids, such as deoxycholic acid and lithocholic acid, have been considered to be cytotoxic for normal colonic crypt cells, resulting in an increased compensatory proliferation of colonic epithelium cells, which is associated with an increased risk of colon cancer (*3*, *4*). A high-fat diet stimulates the secretion of bile acids to intestinal lumen, leading to a higher risk of colon cancer (*5*, *6*). Recent studies further suggest an association of the bile acids to the development of colitis (*7*). The secondary bile acids cause DNA damage, oxidative stress, and proinflammatory property by activating nuclear factor κB (NF-κB) (*8*). This study was conducted to examine the effect of dietary polyphenols, including curcumin, caffeic acid, catechin, rutin, ellagic acid, and quercetin, on fecal secondary bile acids in rats fed a high-fat diet. Here, we provide the first evidence for the suppressive effects of some polyphenols on fecal concentrations of secondary bile acids in rats fed a high-fat diet.

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MATERIALS AND METHODS

Animal and Diets. Male Sprague−Dawley rats, 4 weeks old, were obtained from Hiroshima Laboratory Animal Center and maintained according to the "Guide for the Care and Use of Laboratory Animals" established by Hiroshima University and approved by the ethic committee of the same university. Composition of a basal diet was 30 or 5% beef tallow, 20% casein, 0.2% L-cystine, 5% cellulose, 20% sucrose, 1% vitamin mixture (*9*), and 3.5% salt mixture (made up to 100% by corn starch) (*9*). In experiment 1, the polyphenols, including curcumin, caffeic acid, catechin, rutin, ellagic acid, and quercetin were added to a high-fat diet at the level of 0.5%. In experiment 2, 0.5% curcumin was added to either a high-fat diet (30% beef tallow) or a low-fat diet (5% beef tallow). Curcumin, caffeic acid, D(+)-catechin, rutin, and quercetin were obtained from Nacalai Tesque (Kyoto, Japan). Ellagic acid was obtained from Wako Pure Chemical Industry Co. Ltd. (Osaka, Japan). The same amount of the experimental diets was daily incorporated into the food cups at 7:00 p.m. (9 g for day 1, 10 g for days 2−4, 12 g for days 5−7, 14 g for days 8−13, and 15 g for days 14−21) to prevent changes of food intake and polyphenol intake. All of the diets were consumed everyday until the next

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Table 1. Effect of the Dietary Addition of Some Polyphenols on Liver Cholesterol and Serum Cholesterol and Bile Acids in Rats Fed a High-Fat Diet (Experiment 1)[a]

	liver cholesterol (μmol/g liver)	serum cholesterol (mmol/L)	serum total bile acid (μmol/L)	fecal dry weight (g/ 3 days)	fecal total neutral sterols (μmol/g dry weight)	fecal total bile acids (μmol/g dry weight)
control	14.9 ± 0.6	2.11 ± 0.07	21.6 ± 5.6	3.51 ± 0.17	27.7 ± 1.5	2.17 ± 0.38
curcumin	16.7 ± 2.4	2.20 ± 0.06	22.1 ± 5.1	3.88 ± 0.17	23.1 ± 2.1	0.44 ± 0.06[b]
caffeic acid	18.4 ± 0.4	2.04 ± 0.12	22.1 ± 3.6	4.53 ± 0.62	24.3 ± 2.0	0.62 ± 0.13[b]
catechin	15.2 ± 0.5	2.03 ± 0.08	19.1 ± 4.6	3.66 ± 0.22	29.2 ± 1.5	0.82 ± 0.12[b]
rutin	14.8 ± 0.9	2.11 ± 0.13	11.2 ± 2.7	3.52 ± 0.34	26.3 ± 0.4	0.80 ± 0.22[b]
ellagic acid	17.6 ± 1.4	2.05 ± 0.07	11.6 ± 2.8	4.31 ± 0.60	22.7 ± 1.6	1.42 ± 0.09
quercetin	15.3 ± 0.8	2.06 ± 0.07	20.1 ± 5.4	3.98 ± 0.46	11.7 ± 1.3[b]	2.08 ± 0.37

[a] Mean ± SE (n = 8). [b] Significantly different by Dunnet's multiple-range test ($p < 0.05$).

Table 2. Effect of the Dietary Addition of Some Polyphenols on the Fecal Composition of Bile Acid in Rats Fed a High-Fat Diet (Experiment 1)[a]

(μmol/g dry weight)	cholic acid	deoxycholic acid (*a*)	lithocholic acid (*b*)	hyodeoxycholic acid (*c*)	(*a*) + (*b*) + (*c*)
control	0.08 ± 0.03	0.63 ± 0.08	0.29 ± 0.04	0.94 ± 0.32	2.07 ± 0.36
curcumin	0.13 ± 0.04	0.15 ± 0.05[b]	0.15 ± 0.07	ND[c]	0.31 ± 0.03[b]
caffeic acid	0.17 ± 0.06	0.28 ± 0.07[b]	0.10 ± 0.03[b]	0.06 ± 0.05[b]	0.45 ± 0.10[b]
catechin	0.22 ± 0.05	0.31 ± 0.08	0.07 ± 0.02[b]	0.07 ± 0.03[b]	0.56 ± 0.14[b]
rutin	0.24 ± 0.13	0.35 ± 0.11	0.13 ± 0.04[b]	0.07 ± 0.05[b]	0.43 ± 0.08[b]
ellagic acid	0.30 ± 0.13	0.37 ± 0.06	0.08 ± 0.02[b]	0.44 ± 0.15	1.06 ± 0.15[b]
quercetin	0.16 ± 0.07	0.74 ± 0.14	0.17 ± 0.01	0.99 ± 0.23	1.91 ± 0.37

[a] Mean ± SE (n = 8). [b] Significantly different by Dunnet's multiple-range test ($p < 0.05$). [c] ND = not detectable.

Table 3. Effect of the Dietary Addition of Curcumin on Liver Cholesterol and Serum Cholesterol and Bile Acids in Rats Fed Either a Low- or High-Fat Diet (Experiment 2)[a]

	final body weight (g)	liver weight (g)	liver cholesterol (μmol/g liver)	serum cholesterol (mmol/L)
LF	206 ± 2 a	9.01 ± 0.15 a	3.41 ± 0.24 a	2.03 ± 0.18
LF + curcumin	200 ± 2 a	8.59 ± 0.18 a	3.20 ± 0.25 a	2.01 ± 0.10
HF	247 ± 2 b	10.82 ± 0.14 b	4.99 ± 0.38 b	2.29 ± 0.07
HF + curcumin	245 ± 2 b	11.04 ± 0.29 b	5.92 ± 0.43 b	2.47 ± 0.10

[a] LF, low-fat diet; HF, high-fat diet. Mean ± SE (n = 8). Means with different letters were significantly different by Scheffe's multiple-range test ($p < 0.05$).

day at 12:00 a.m. Feces were collected for the final 3 days. A total of 3 weeks after feeding the diets, animals were killed by decapitation with anesthesia of diethyl ether. The liver was removed and stored at −70 °C until analysis. Blood samples were centrifuged at 3000*g* for 20 min to obtain serum samples and stored at −70 °C.

Measurement. Analysis of fecal acidic sterols was performed using a internal standard (nor-deoxycholic acid, Steraloids, Wilton, NY) according to the methods by gas chromatography described previously (*10*). The fecal bile acids were extracted with hot ethanol. Hydrolysis of bile acids was carried out in an autoclave. After acidification of the solvent to pH 1, bile acids were extracted with diethyl ether. The extracted bile acids were methylated with trimethylsilyl-diazomethane (GL Sciences, Tokyo, Japan), and trimethylsilyl derivatives of bile acids were prepared by the reaction with commercial derivatization reagents (GL Sciences). The GLC analyses were performed on a Shimadzu GC-14B (Shimadzu, Kyoto, Japan) fitted with a TC-1 column (30 m × 0.25 mm) (GL Sciences). Serum cholesterol was determined with a kit (Wako Pure Chemical Industry Co. Ltd., Osaka, Japan). Liver cholesterol and fecal neutral sterols were also determined with the same kit after extraction of liver total lipids by the method of Folch et al. (*11*).

Statistical Analysis. Statistical analysis was conducted by one-way analysis of variation (ANOVA) and Dunnet's multiple-range test in experiment 1 and by two-way ANOVA and Scheffe's multiple-range test in experiment 2 (Excel Statistics 2006 for Windows, Social Survey Research Information Co. Ltd., Tokyo, Japan). Statistical significance was estimated at $p < 0.05$.

RESULTS

Experiment 1. Dietary addition of polyphenols caused no influence on food intake, final body weight, and liver weight (data not shown). The liver and serum concentration of cholesterol was unaffected by dietary polyphenols (**Table 1**). The serum concentration of total bile acids was also unaffected by the polyphenols. Fecal dry weight was not affected by dietary polyphenols (**Table 1**). Dietary quercetin significantly reduced the fecal level of total neutral sterols, but other polyphenols did not. The fecal concentration of total bile acids was significantly lower in the curcumin, caffeic acid, catechin, and rutin groups compared to the control group.

The fecal level of cholic acid was unaffected by the polyphenols examined (**Table 2**). The fecal concentration of deoxycholic acid was significantly lower in the curcumin and caffeic acid groups ($p < 0.05$). The fecal concentration of lithocholic acid was significantly lower in the caffeic acid, catechin, rutin, and ellagic acid groups ($p < 0.05$). Fecal hyodeoxycholic acid was markedly lower in the polyphenol groups ($p < 0.05$), except for the ellagic acid and quercetin groups. Dietary polyphenols, except for quercetin, lowered the total concentrations of these bile acids, such as deoxycholic acid, lithocholic acid, and hyodeoxycholic acid ($p < 0.05$). Fecal total lipids were unaffected by dietary polyphenols (data not shown).

Experiment 2. Food intake was not different among the groups (data not shown). The final body and liver weight were significantly higher in the high-fat diet groups and unaffected by dietary addition of curcumin (**Table 3**). A high-fat diet caused a significant elevation in liver cholesterol of rats with and without receiving curcumin ($p < 0.05$). Dietary curcumin caused no influence on the concentration of liver and serum cholesterol.

Fecal dry weight was unaffected by dietary treatment (data not shown). Fecal concentrations of cholic acid and lithocholic acid were unaffected by dietary manipulation (**Table 4**). In rats without receiving curcumin, the fecal concentration of deoxycholic acid was significantly higher in the high-fat diet than in the low-fat

Table 4. Effect of the Dietary Addition of Curcumin on Fecal Composition of Bile Acid in Rats Fed Either a Low- or High-Fat Diet (Experiment 2)[a]

(μmol/g dry weight)	cholic acid	deoxycholic acid (*a*)	lithocholic acid (*b*)	hyodeoxy-cholic acid (*c*)	(*a*) + (*b*) + (*c*)	total bile acids (cholic acid +(*a*) + (*b*) + (*c*))
LF	0.34 ± 0.08	0.35 ± 0.10 a	0.36 ± 0.07	0.65 ± 0.22 a	1.36 ± 0.26 ab	1.60 ± 0.25
LF + curcumin	0.22 ± 0.08	0.20 ± 0.05 a	0.51 ± 0.23	0.03 ± 0.02 b	0.74 ± 0.20 b	0.96 ± 0.20
HF	0.50 ± 0.25	0.60 ± 0.08 b	0.24 ± 0.01	0.98 ± 0.28 a	1.83 ± 0.31 a	2.33 ± 0.33
HF + curcumin	0.47 ± 0.16	0.29 ± 0.07 a	0.20 ± 0.04	0.06 ± 0.03 b	0.55 ± 0.08 b	1.02 ± 0.19

[a] Mean ± SE (n = 7). Means with different letters were significantly different by Scheffe's multiple-range test ($p < 0.05$).

diet ($p < 0.05$). The fecal concentration of deoxycholic acid was significantly reduced by curcumin ($p < 0.05$) in the high-fat diet groups but unaffected in the low-fat diet groups. As a result, the elevation in fecal deoxycholic acid by a high-fat diet was suppressed by curcumin intake. Regardless of the dietary level of fat, the fecal concentration of hyodeoxycholic acid was markedly reduced by curcumin ($p < 0.05$). The dietary level of fat caused no influence on fecal hyodeoxycholic acid. In the groups fed low-fat diets, fecal total bile acids, including cholic acid, deoxycholic acid, lithocholic acid, and hyodeoxycholic acid, were unaffected by curcumin intake. In the groups fed high-fat diets, fecal total bile acids in rats with curcumin intake were significantly lower than those in rats without curcumin intake. As a result, the reduction in fecal total bile acids by curcumin was remarkable in the high-fat diet compared to the low-fat diet.

DISCUSSION

This study demonstrated the suppressing effect of some polyphenols, including curcumin, caffeic acid, catechin, rutin, and ellagic acid, on fecal levels of deoxycholic acid and/or lithocholic acid, the harmful secondary bile acids in rats fed a high-fat diet. To our knowledge, this is the first evidence for the reduction of fecal secondary bile acids by dietary polyphenols. This finding may imply the protective effect of dietary polyphenols against secondary bile acids. However, Longpre and Loo have recently reported that phenolic phytochemicals, such as rottlerin, quercetin, and resveratrol, were effective in protecting human colon epithelial cells against deoxycholate but epigallocatechin gallate and curcumin were ineffective (*12*). These different effects of curcumin on secondary bile acids may possibly be explained by different experimental systems between *in vivo* and *in vitro*.

Our results indicated that dietary polyphenols, such as curcumin, caffeic acid, catechin, and rutin, significantly lowered fecal total bile acids without affecting serum and liver cholesterol. These results raise the possibility that the biosynthesis of bile acids from cholesterol together with cholesterol biosynthesis is suppressed by these polyphenols. However, recently, curcumin has been reported to activate pregnan X-receptor (PXR) (*13*). PXR is known to mediate gene expression of CYP7A1 of cholesterol 7α-hydroxylase, responsible for the rate-limiting enzyme of biosynthesis of bile acids from cholesterol (*14*). Thus, further study is in progress in our laboratory to examine the influence of the polyphenols on the biosynthesis of bile acids.

Bile acids play an important role in the digestion of dietary triacylglycerol by activating lipases. Thus, we postulated that a lower intestinal bile acid pool by the polyphenols might reduce digestion and use of dietary fat. To test this possibility, we analyzed the fecal amount of total lipids. The results indicated no influence of dietary curcumin and caffeic acid at a dietary 0.5% level on fecal lipids and apparent digestibility of dietary fat. Accordingly, the possibility that the reduction in intestinal bile acids by the polyphenols leads to lower digestibility and use of dietary fat appears to be negated.

Of interest is the finding that the reduction in fecal hyodeoxycholic acid by the polyphenols, except for ellagic acid and quercetin, was especially remarkable. Hyodeoxycholic acid is a 6-hydroxylated metabolite of lithocholic acid, which is primarily excreted as a glucuronide derivative in urine (*15*). Hyodeoxycholic acid can be effectively glucuronidated by two human UDP-glucuronosyltransferase (UGT) 2B isoforms, UGT2B4 and UGT2B7 (*15*, *16*). It is necessary to examine the effect of polyphenols on glucuronidation of hyodeoxycholic to elucidate the mechanism of the marked reduction in fecal hyodeoxycholic acid.

Primary bile acids can be metabolized to secondary bile acids by intestinal microflora. It has been reported that consumption of catechin affects the profile of intestinal microflora (*17*). Therefore, we postulated that dietary polyphenols might suppress the conversion of primary bile acids into secondary bile acids by affecting the profile of the microflora. In our results, dietary polyphenols caused no significant influence on the fecal concentration of cholic acid (a primary bile acid) and the ratio of the concentration of cholic acid to that of deoxycholic acid (a metabolite of cholic acid) (data not shown). In our results, dietary polyphenols caused no significant influence on the fecal concentration of cholic acid (a primary bile acid) and the ratio of the concentration of cholic acid to that of deoxycholic acid (a metabolite of cholic acid) (data not shown, $p > 0.2$). The results did not support the above hypothesis. However, the results should not be taken as definitive evidence and are not enough to role out the hypothesis. Further studies are necessary to obtain a clear conclusion.

Some studies have already indicated the chemopreventive effects of dietary curcumin, ellagic acid, and epigallate catechin (analogue of catechin) on the development of carcinogen-induced colon tumors in rodents (*18*−*21*). Studies with curcumin, epigallate catechin, ellagic acid, and rutin have also suggested the preventive effects of these polyphenols on chemically induced colitis in rodents (*22*−*25*). Because their results were obtained with the animals exposed to exogenous cytotoxic chemicals (*22*−*25*), it seems difficult to estimate the influence of modulation of intestinal bile acids by polyphenols on the colon diseases in such animal models.

Our study further indicated that, although some polyphenols can affect fecal total bile acids and secondary bile acids, quercetin caused no influence. On the other hand, dietary quercetin caused a significant reduction in fecal total neutral sterols, but other polyphenols did not. It is interesting to note that the effects of quercetin (the aglycone of rutin) were quite different from those of rutin. The rutinose sugar moiety on the C ring of rutin may cause lower availability of rutin compared to that of quercetin and a higher concentration of rutin in the large intestine than that of quercetin, thereby leading to the differential effects of rutin and quercetin. At present, the reason why the polyphenols examined differentially affect fecal bile acids and neutral sterols is unknown. Further studies are necessary to examine the relationship between the effects of polyphenols and their chemcal structures, the metabolisms of the polyphenols, etc.

In summary, this study provided the first evidence for the suppressive effect of some polyphenols on fecal levels of deoxycholic acid and lithocholic acid, the risk factors of colon diseases.

Our findings imply a novel function of some polyphenols favorable for the health of the large intestine. This study was conducted to test the potential effects of dietary 0.5% polyphenols for a short period of 3 weeks. Although this dietary level is among the levels of polyphenols (0.1−2%) in the diets of animal studies reported (*26*−*28*), the level of 0.5% polyphenols appears to be higher than those in human diets. Thus, further studies in our laboratory are in progress to examine the effects of lower levels of dietary polyphenols for longer feeding periods on fecal bile acids.

ABBREVIATIONS USED

NF-κB, nuclear factor κB; PXR, pregnan X-receptor; UGT, UDP-glucuronosyltransferase.

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