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# Chronic high intake of quercetin reduces oxidative stress and induces expression of the antioxidant enzymes in the liver and visceral adipose tissues in mice

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ABSTRACT

To obtain knowledge regarding the safe intake of quercetin-rich functional foods, we examined the effect of chronic and high intake of quercetin. We fed mice a standard diet containing 0.05 or 1% quercetin for 20 weeks. Both quercetin diets did not significantly affect the body weight, fat accumulation, and blood components. However, 0.05% quercetin significantly increased the glutathione/oxidized glutathione ratio in the liver. The 1% quercetin diet reduced the lipid peroxidation marker malondialdehyde in the liver, epididymal adipose tissues, and small intestine. The 1% quercetin diet significantly induced the expression of the antioxidant enzymes *Gpx1*, *Cat*, and *Sod1* in the liver and *Gpx1* and *Cat* in the epididymal adipose tissues. The transcription factor nuclear factor E2-related factor 2 (Nrf2) was slightly induced in the nuclear fraction of the livers of mice fed the 1% quercetin diet. Quercetin may induce antioxidant enzymes by activating the Nrf2 pathway in the liver.

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## 1. Introduction

The flavonol quercetin is widely distributed in plant-based foods and is believed to prevent lifestyle-related diseases. Epidemiological studies have suggested that quercetin reduces the risk of cardiovascular disease, although it remains a matter of debate (Arts & Hollman, 2005; Chun, Chung, Claycombe, & Song, 2008; Hollman et al., 2011; Knekt et al., 2002; Peterson, Dwyer, Jacques, & McCullough, 2012). Quercetin mostly exists as the glycosides in foods. Onions, which contain large amounts of quercetin 3,4′-o-glucoside and 4′-o-glucoside, are major food

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*Abbreviations:* Nrf2, nuclear factor E2-related factor 2; TBARS, thiobarbituric acid-reactive substances; MDA, malondialdehyde; GSH, reduced glutathione; GSSH, oxidized glutathione; HPLC, high-performance liquid chromatography; Foxo3a, forkhead box O3a; ARE, antioxidant response element

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sources of quercetin (Arai et al., 2000; Nishimuro et al., 2015). The amount of quercetin aglycone in the diet is much lower than that of quercetin glycoside; however, the metabolites of quercetin are similar to those of the glycosides because β-glycosides are mostly hydrolyzed into aglycones in the intestine (Day et al., 2001; Graf et al., 2006; Terao, Kawai, & Murota, 2008). Quercetin is metabolized to glucuronated, sulfated, and/or methylated quercetin conjugates in human, pig and rodents (Kawai et al., 2009; Santos et al., 2008; Wiczkowski et al., 2014). Onion skins contain high concentration of quercetin aglycone. Albishi, John, Al-Khalifa, and Shahidi (2013a, 2013b) reported that the phenolics content of onion skin was higher than that of their flesh counterparts and the onion skin showed high antioxidant and anti-inflammatory activities. Wiczkowski et al. (2014) determined the profile and antioxidant capacity of pig quercetin metabolites after intake of onion dry skin and found that quercetin metabolites showed higher radical scavenging activities compared to the native quercetin derivatives.

In a previous study, a diet containing quercetin was found to alleviate the streptozotocin-induced diabetic symptoms in mice (Kobori, Masumoto, Akimoto, & Takahashi, 2009). The quercetin diet suppressed blood glucose level elevation and decreased the plasma insulin levels by enabling the recovery of cell functions in both the liver and pancreas through oxidative stress reduction and the blockade of cyclin-dependent kinase inhibitor *p21*(*WAF1/Cip1*) (*Cdkn1a*) expression. Moreover, the addition of quercetin to high-fat, high-cholesterol, and high-sucrose Western diet reduced weight gain and improved hyperglycemia, hyperinsulinemia, and dyslipidemia in mice after 20 weeks (Kobori, Masumoto, Akimoto, & Oike, 2011). Quercetin reduced liver fat accumulation by decreasing oxidative stress and reducing peroxisome proliferator-activated receptor α expression that subsequently reduced the expression of genes related to steatosis in the liver (Kobori et al., 2011). Thus, dietary quercetin is believed to prevent obesity and metabolic syndrome primarily through a reduction in oxidative stress. Some other reports have also shown that quercetin-rich diets ameliorate diet-induced symptoms that constitute metabolic syndrome in mice or rats. Shen et al. (2013) reported that quercetin supplementation protected mice fed a high-fat diet against oxidant-induced endothelial dysfunction and apolipoprotein E gene knockout mice against atherosclerosis. Quercetin supplementation improves oxidative stress markers' expression and inflammation and the genes related to ω-oxidation in the livers of rodents fed either a high-fat or a high-carbohydrate and high-fat diet (Hoek-van den Hil et al., 2013; Panchal, Poudyal, & Brown, 2012). The quercetin diet induced the expression of micro RNAs miR-125b, associated with inflammation, and miR-122, associated with liver metabolism, in mice fed a high-fat diet (Boesch-Saadatmandi, Wagner, Wolffram, & Rimbach, 2012).

Recently, Consumer Affairs Agency of Japan approved the beverages contained quercetin glucosides as the Food for Specified Health Uses, which are scientifically recognized as helpful for promoting health. Quercetin is attracting attention as a functional food component. However, despite the expectations of preventive effects of quercetin on lifestyle-related diseases, there have been concerns regarding the safety of excessive quercetin intake from functional food or supplements. Although quercetin has mutagenic activity *in vitro*, it has not been considered a carcinogen in humans (Harwood et al., 2007). To date, there has been no evidence of serious adverse effects of quercetin to humans (Egert & Rimbach, 2011; Harwood et al., 2007; Mennen, Walker, Bennetau-Pelissero, & Scalbert, 2005). However, *in vivo* studies have suggested that high quercetin doses may induce prooxidant toxicity or affect thyroid function (Egert & Rimbach, 2011; Mennen et al., 2005). Giuliani et al. (2014) reported that an intraperitoneal injection of 50 mg/kg quercetin for 14 days significantly inhibited thyroid function in rats. Our previous study showed that a control AIN93G diet containing high quercetin concentrations (1%, w/w) did not significantly affect the hepatic gene expression profile of mice after 2 weeks (Kobori et al., 2009). A control diet containing 0.05% quercetin significantly reduced the oxidative stress marker *thiobarbituric acid reactive substances* (TBARS) in the liver of mice after 20 weeks of the diet. In this study, to characterize the effect of chronic and high dietary intake of quercetin, we fed mice with a standard AIN93G diet containing 0.05 or 1% quercetin for 20 weeks and determined the blood components, oxidative stress markers, and related gene expression in the tissues.

## 2. Materials and methods

### 2.1. *Animals and treatments*

Four-week-old male C57BL/6J mice were obtained from the Institute for Animal Reproduction, Charles River Japan Inc. (Ibaraki, Japan). The mice were housed at 24 °C ± 1 °C and 55% ± 5% humidity; they were also under 12-h light/dark photocycles (dark period from 08:00 to 20:00) and had free access to water and an AIN93G diet (Oriental Yeast Co., Tokyo, Japan) for a week prior to the experiment. The animals were treated in accordance with the basic guidelines of the Ministry of Agriculture, Forestry, and Fisheries for laboratory animal studies, which were approved by the review board for animal ethics at our institute (permission number; H23–044).

The mice were divided into three groups of 12 mice each, housed in groups of three per cage and fed one of the following diets for 20 weeks: AIN93G (control), AIN93G containing 0.05% (w/w) quercetin (0.05% quercetin, (Funakoshi, Tokyo, Japan)), AIN93G containing 1% (w/w) quercetin (1% quercetin). Body weights and mean food consumption were monitored at 2- or 3-day intervals, and blood glucose levels were determined at 4-week intervals. Thereafter, the animals were killed under anesthesia and the blood, liver, kidney, adipose tissues, small intestines, and skeletal muscle were immediately collected.

### 2.2. *Blood analysis*

Blood glucose levels were measured using the glucose test meter Glucocard Diameter-α GT-1661 (Arkray Inc., Kyoto, Japan). Plasma insulin concentrations were measured using a Mouse Insulin Elisa Kit Akirin-011 T (Shibayagi, Gunma, Japan). Plasma total cholesterol, triglyceride, NEFA, aspartate aminotransferase (AST), and alanine aminotransferase alanine (ALT) concentrations were

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