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Curdlan intake changes gut microbial composition, short-chain fatty acid production, and bile acid transformation in mice

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ABSTRACT

Indigestible polysaccharides, such as dietary fibers, benefit the host by improving the intestinal environment. Short-chain fatty acids (SCFAs) produced by gut microbial fermentation from dietary fibers exert various physiological effects. The bacterial polysaccharide curdlan benefits the host intestinal environment, although its effect on energy metabolism and SCFA production remains unclear. Hence, this study aimed to elucidate the effect of curdlan intake on gut microbial profiles, SCFA production, and energy metabolism in a high-fat diet (HFD)-induced obese mouse model. Gut microbial composition of fecal samples from curdlan-supplemented HFD-fed mice indicated an elevated abundance of Bacteroidetes, whereas a reduced abundance of Firmicutes was noted at the phylum level compared with that in cellulose-supplemented HFD-fed mice. Moreover, curdlan supplementation resulted in an abundance of the family Bacteroidales S24-7 and Erysipelotrichaceae, and a reduction in Deferribacteres in the feces. Furthermore, curdlan supplementation elevated fecal SCFA levels, particularly butyrate. Although body weight and fat mass were not affected by curdlan supplementation in HFD-induced obese mice, HFD-induced hyperglycemia was significantly suppressed with an increase in plasma insulin and incretin GLP-1 levels. Curdlan supplementation elevated fecal bile acid and SCFA production, improved host metabolic functions by altering the gut microbial composition in mice.

1. Introduction

Although food is an important energy source, excess and unbalanced dietary intake causes metabolic diseases such as obesity and diabetes [1]. Dietary interventions with dietary fiber have shown beneficial metabolic effects [2,3]. Dietary fibers are indigestible polysaccharides utilized as an energy source by gut microbiota in the colon as they escape digestion by host enzymes and are absorbed in the small intestine. Consequently, they improve host gut homeostasis by altering the microbial composition. Gut microbiota influence various physiological functions such as energy regulation and diseases, including diabetes and obesity, via gut microbial metabolites such as short-chain fatty acids (SCFAs) and secondary bile acids (BAs) [4,5]. Dietary fibers are finally metabolized to SCFAs (mainly acetate, propionate, and butyrate) by gut microbes, which are involved in the *de novo* synthesis of lipids and a source of energy [6]. Additionally, SCFAs affect host energy homeostasis by modulating physiological functions, such as gut hormone and insulin secretion via the G protein-coupled receptors GPR41 or GPR43 as signal molecules [7–12]. BAs also influence host energy regulation as mediators of lipid absorption and secretion of glucagon-like peptide-1 (GLP-1) via the Takeda G protein-coupled receptor 5 and farnesoid X receptor, as signal molecules [13–16].

β-glucan belongs to a group of β-D-glucose polysaccharides and is present in the cell walls of bacteria, yeast, fungi, algae, edible mushrooms, and cereal grains [17–19]. The common forms of most β-glucans consist of D-glucose units with β-(1 → 3) glycosidic bonds. Yeast and

Abbreviations: SCFA, short-chain fatty acid; HFD, high-fat diet; GLP-1, glucagon-like peptide-1; PCA, principal component analysis; NEFAs, non-esterified fatty acids; TG, triglyceride; WAT, white adipose tissue; BA, bile acid; BSH, bile salt hydrolase.

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fungal β-glucans are branched and contain β-(1 → 6) glycosidic bonds, whereas cereal β-glucans, including barley β-glucans, form β-(1 → 3) and β-(1 → 4) glycosidic bonds. Other β-glucans have a linear structure with only β-(1 → 3) glycosidic bonds. Since host amylase cannot cleave these β-glycosidic bonds, β-glucan is regarded as an indigestible polysaccharide; hence, consumption of some β-glucans has been reported to have several beneficial effects [19,20].

Curdlan, synthesized by bacteria, is a linear β-glucan with β-(1 → 3) glycosidic bonds and is used as a food additive in gelatinizers, stabilizers, and thickeners in processed foods [21]. Curdlan intake has been reported to increase intestinal SCFA levels and improve the host immune system and bone metabolism [22,23]. However, the precise effects of curdlan intake on host energy homeostasis remain unclear. In this study, we aimed to investigate the effects of curdlan intake on host energy metabolism in a high-fat diet (HFD)-induced obese mouse model.

2. Materials and methods

2.1. Animals and diet

Male C57BL/6J mice were purchased from Japan SLC (Shizuoka, Japan), housed in a conventional animal room at 24 °C, and maintained under a 12 h light/dark cycle. Mice were acclimated to the CLEA Rodent Diet (CE-2, CLEA Japan, Inc., Tokyo, Japan) for 1 week prior to treatment. 4-week-old mice were placed on a modified D12492 diet (60% kcal fat, Research Diets Inc., New Brunswick, NJ, USA) for 12 weeks. The diets were formulated based on the D12492 diet (Research Diets Inc.) and supplemented with either 10% (w/w) 38 μm (400 mesh) cellulose powder (FUJIFILM Wako Pure Chemical Corporation, Osaka, Japan) or Curdlan (FUJIFILM Wako Pure Chemical Corporation). The composition of the diets is provided in Supplementary Table S1. Body weight was measured once per week for the duration of the experiment. All mice were sacrificed under deep isoflurane induced anesthesia. All experimental procedures involving mice were performed according to protocols approved by the Committee on the Ethics of Animal Experiments of the Kyoto University Animal Experimentation Committee (Lif-K21020) and the Tokyo University of Agriculture and Technology (permit number: 28–87). All efforts were made to minimize suffering.

2.2. Analysis of gut microbiota by 16S rRNA gene sequencing

Fecal DNA was extracted from frozen samples using the FastDNA® SPIN Kit for Feces (MP Biomedicals, Santa Ana, CA, USA). The V4 region of the 16S rRNA gene was amplified using dual-indexed primers. Amplicons were sequenced using an Illumina MiSeq with a MiSeq Reagent Kit V3 (Illumina, San Diego, CA, USA). Paired-end sequencing was performed using the Illumina MiSeq platform. Processing and quality filtering of reads was performed using Quantitative Insights into Microbial Ecology (QIIME) (v1.9.1) and the chimera-free sequences were aligned with the SILVA database (http://www.arb-silva.de) at Unclassified. Other data were used for further analysis at each level, which were then re-normalized. Principal component analysis (PCA) plots were generated using the function prcomp in the R package to identify clustering within each level. The raw data were deposited in the DNA Data Bank of Japan (DDBJ) under accession no. DRA011809. To detection of *Muribaculum*, *Paramuribaculum*, *Duncaniella* and *Catenibacterium*, the 16S rRNA gene copies of each sample were evaluated by real-time PCR using specific16S forward and reverse primers. The universal 16S rRNA gene was used as the internal control, and the genus was expressed as relative levels to 16S rRNA. Quantitative real-time-PCR analysis was performed using SYBR Premix Ex Taq II (TaKaRa, Shiga, Japan) and the StepOnePlus™ Real-Time PCR System (Applied Biosystems, Foster City, CA). The bacterial primer sequences are listed in Supplementary Table S2.

2.3. SCFA measurement

Fecal SCFAs were determined following a modified protocol, as previously described [24]. The SCFA-containing ether layers were collected and pooled for gas chromatography-mass spectrometry (GC-MS) analysis using a GCMS-QP2010 Ultra (Shimadzu, Kyoto, Japan). The concentration of SCFAs in each sample was determined using an external standard calibration over a specified concentration range.

2.4. Biochemical analyses

Blood glucose levels were assessed using a portable glucometer (OneTouch® Ultra®, LifeScan, Milpitas, CA, USA). The concentrations of plasma cholesterol (LabAssay™ Cholesterol, FUJIFILM Wako Pure Chemical Corporation), non-esterified fatty acids (NEFAs) (LabAssay™ NEFA, FUJIFILM Wako Pure Chemical Corporation), and triglycerides (TG) (LabAssay™ Triglyceride, FUJIFILM Wako Pure Chemical Corporation) were measured according to the manufacturer's instructions. Plasma GLP-1 [glucagon-like peptide-1 (Active) ELISA, Merck Millipore, Darmstadt, Germany], and insulin [Insulin ELISA KIT (RTU), Shibayagi, Gunma, Japan] levels were determined using an enzyme-linked immunosorbent assay (ELISA) as described previously [24]. For plasma GLP-1 measurement, the samples were treated with a dipeptidyl peptidase IV (DPP-IV) inhibitor (Merck Millipore) to prevent the degradation of active GLP-1.

2.5. Quantification of hepatic triglyceride content

Hepatic triglyceride content was measured following a modified protocol as previously described [11]. Briefly, liver homogenates were subjected to crude lipid extraction using a mixture of chloroform/methanol/0.45 M acetic acid. The organic phases were dried, and the sample was reconstituted in 2-propanol as an assay sample. Triglyceride levels were determined in the assay samples using a LabAssay™ Triglyceride kit.

2.6. Hepatic histology

Fresh frozen liver tissues were sectioned at 10 μm. All slices were stained with hematoxylin and eosin (H&E) for microscopic examination.

2.7. Real-time PCR (RT-PCR)

The RT-PCR protocol was conducted following a modified protocol as previously described [11]. cDNA was reverse transcribed using Moloney murine leukemia virus reverse transcriptase (Invitrogen, Carlsbad, CA, USA). RT-PCR was performed using SYBR Premix Ex Taq II (TaKaRa) and the StepOne™ real-time PCR system (Applied Biosystems). Gene expression data were normalized using the comparative $2^{-\Delta\Delta Ct}$ method, using the housekeeping gene 18S. The primer sequences are listed in Supplementary Table S3.

2.8. Quantification of BA

BA levels in feces were determined following a previously described protocol [25,26]. Lyophilized feces (approximately 50 mg) were finely ground and mixed with 0.2 M NaOH (1 mL). The mixtures were then purified from lipids by extraction with hexane (1 mL). The extraction step was repeated three times. The samples were centrifuged (20,000×*g*, 10 min, 4 °C) and supernatants were further cleaned using Oasis PRiME HLB 1 cc cartridges (Waters, Milford, MA, USA) that were conditioned with methanol (1 mL) followed by ultrapure water (3 mL). The loaded cartridges were washed with ultrapure water (500 μL), and the analytes were eluted with methanol-acetonitrile (1:1, v/v, 1 mL) for liquid chromatograph-mass spectrometry (LC-MS/MS) analysis. BA was

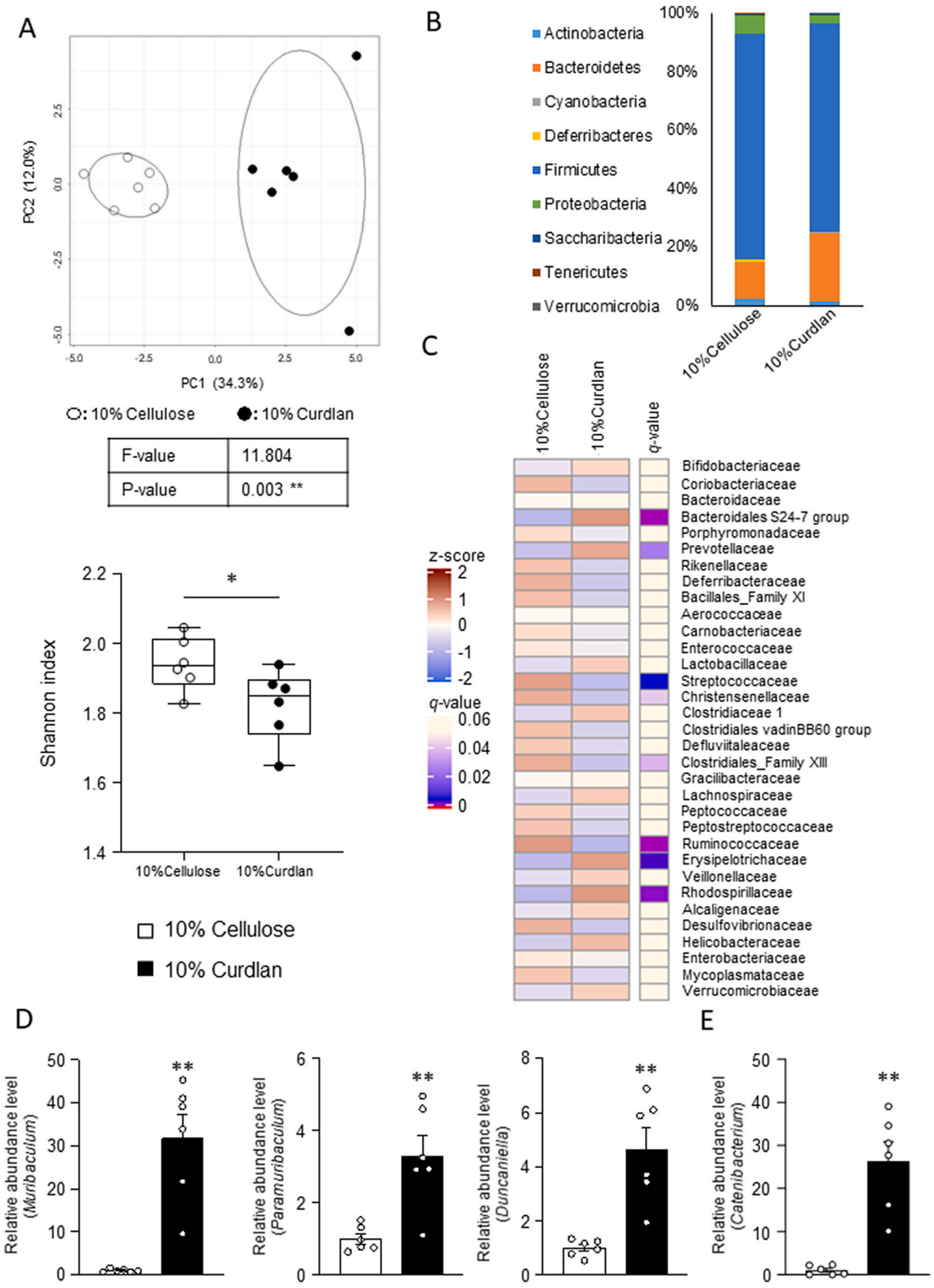

Fig. 1. Changes in fecal microbiota of mice supplemented with curdlan. (A) Principle component analysis (PCA) of taxonomic groups at the family level. Difference in α-diversity between cellulose and curdlan groups. (B) Relative abundance of major taxonomic groups at the phylum level. (C) Heat map of relative abundance of major taxonomic groups at the family level (mean relative abundance > 0.1%). (D, E) The relative abundance of the gene *Muribaculum*, *Paramuribaculum*, *Duncaniella* (D), and *Catenibacterium* (E) between cellulose or curdlan groups were detected using real-time PCR. Data are expressed as means ± SEM (Cellulose-supplementation group: n = 6, Curdlan-supplementation group: n = 6). $P < 0.05$ was considered statistically significant (*$P < 0.05$ and **$P < 0.01$).

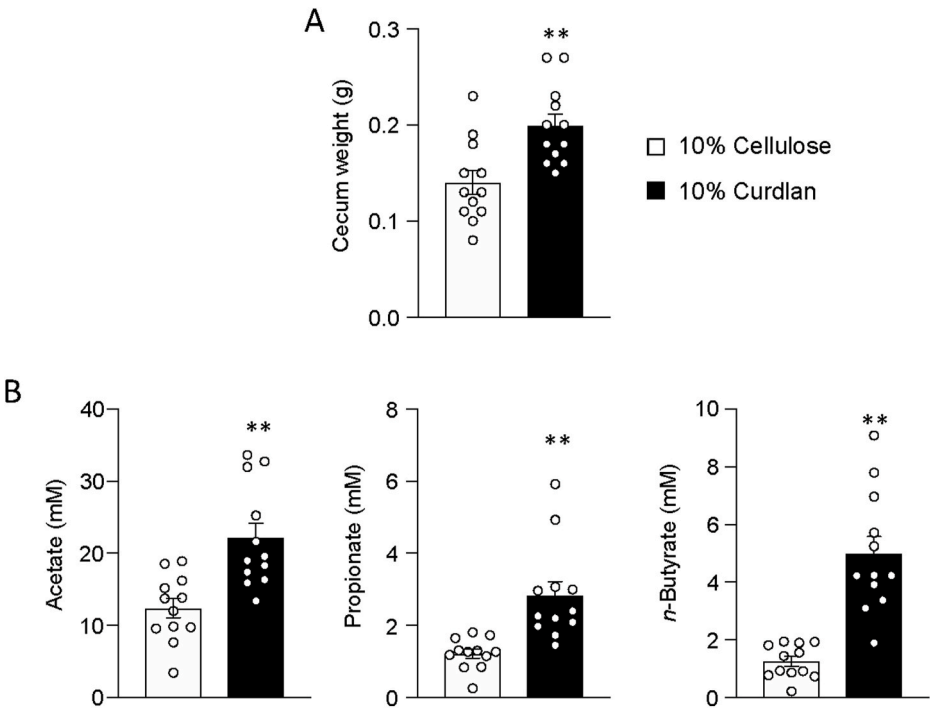

Fig. 2. Short-chain fatty acid (SCFA) production by curdlan supplementation. (A) Weight of cecum in mice fed a high-fat diet (HFD) supplemented with cellulose or curdlan for 12 weeks. (B) Amounts of acetic, propionic and butyric acids among SCFAs extracted from fecal samples collected during a 5-h fast after 12 weeks of cellulose or curdlan supplementation determined using GC-MS. Data are expressed as means ± SEM (Cellulose-supplementation group: n = 12, Curdlan-supplementation group: n = 12. $P < 0.05$ was considered statistically significant (**$P < 0.01$).

analyzed on an Acquity UPLC system and a Waters Xevo TQD MS (Waters). The analytes were quantified using external standards, and calibrators were prepared in methanol–acetonitrile (1:1, v/v) within a range of 0.001–1.0 μg/mL, with quality controls at 0.1 and 1.0 μg/mL.

2.9. Statistical analysis

All values are presented as mean ± SEM. Differences between groups were examined for statistical significance using a two-tailed unpaired Student's *t*-test (two groups). Permutational multivariate analysis of variance (PERMANOVA) tests were used to analyze the similarity of microbiomes. The alpha diversity of each group was measured using Shannon diversity. The FDR *q*-values in 16S rDNA sequencing were analyzed. The false discovery rate (FDR; *q*-value) was estimated using the Benjamini–Hochberg procedure. The 16S rDNA sequencing data were analyzed using a Student's *t*-test with FDR correction. Differences were considered statistically significant at $P < 0.05$ and $q < 0.05$.

3. Results

3.1. Curdlan intake improves gut microbial composition

Dysbiosis caused by an HFD exacerbates obesity, which can be mitigated by dietary fiber intake, improving the metabolic functions of the host by affecting the intestinal environment [27]. Hence, we first examined changes in gut microbial composition following curdlan supplementation in HFD-fed mice. After comparing cellulose (non-fermented fiber)- and curdlan-supplemented HFD-fed mice for 12 weeks (Supplementary Table S1), we confirmed that curdlan supplementation altered gut microbial composition, as indicated by the PCA and α-diversity based on taxonomic datasets. Upon PCA analysis, although no difference in PC distribution was seen along PC 2, a significant difference was observed along PC 1 ($P = 0.003$, Fig. 1A). The α-diversity analysis also showed a significant difference between two groups (Fig. 1A). Taxonomic analysis of the fecal microbiota showed an increased abundance of Bacteroidetes, whereas a reduction in the population of Firmicutes, Deferribacteres, and Proteobacteria was noted in the curdlan-supplemented group (Fig. 1B). The relative abundance of Bacteroidetes was significantly higher in the curdlan-supplemented group than in the cellulose-supplemented group ($P = 0.0029$), whereas the relative abundance of Firmicutes, Deferribacteres, and Proteobacteria significantly decreased ($P = 0.0292$, $P = 0.0133$, and $P = 0.0263$, respectively; Fig. 1B). Curdlan supplementation did not significantly affect the relative abundance of any other phyla. Furthermore, the hierarchical clustering of individual families in the curdlan-supplementation group showed an increase in the Bacteroidales S24-7 group, Prevotellaceae (phylum Bacteroidetes), and Erysipelotrichaceae (phylum Firmicutes) (Fig. 1C). In particular, in the curdlan-supplementation group, the abundance of the genera *Muribaculum, Paramuribaculum,* and *Duncaniella* in the Bacteroidales S24-7 family (Fig. 1D), and the genus *Catenibacterium* in the Erysipelotrichaceae family (Fig. 1E) were markedly increased compared with the cellulose-supplementation group. Thus, curdlan supplementation improved the aggravation of gut microbial composition in a HFD-model.

3.2. Curdlan intake increases fecal SCFA levels

Dietary fiber intake increases intestinal SCFA concentrations at various levels by changing the gut microbial composition, depending on the structure of indigestible polysaccharides [7,27]. Hence, we investigated intestinal SCFA production following curdlan intake. After 12 weeks of HFD intake, the cecum weight in the curdlan-supplemented HFD-fed mice was significantly higher than that in the cellulose-supplemented group (Fig. 2A). This result indicates that curdlan is fermented in the cecum compared with cellulose, because in mice, dietary fibers are mainly fermented in the cecum, and ingestion of fermentable feed causes enlargement of the cecum [28]. Consequently, fecal SCFAs in curdlan-supplemented HFD-fed mice were significantly higher than those in cellulose-supplemented HFD-fed mice (Fig. 2B). Thus, curdlan intake markedly increased the levels of intestinal SCFAs, particularly butyrate.

3.3. Curdlan intake improves HFD-induced hyperglycemia

Since an increase in intestinal SCFAs affects host energy homeostasis [7,29], we investigated the beneficial metabolic effects of curdlan

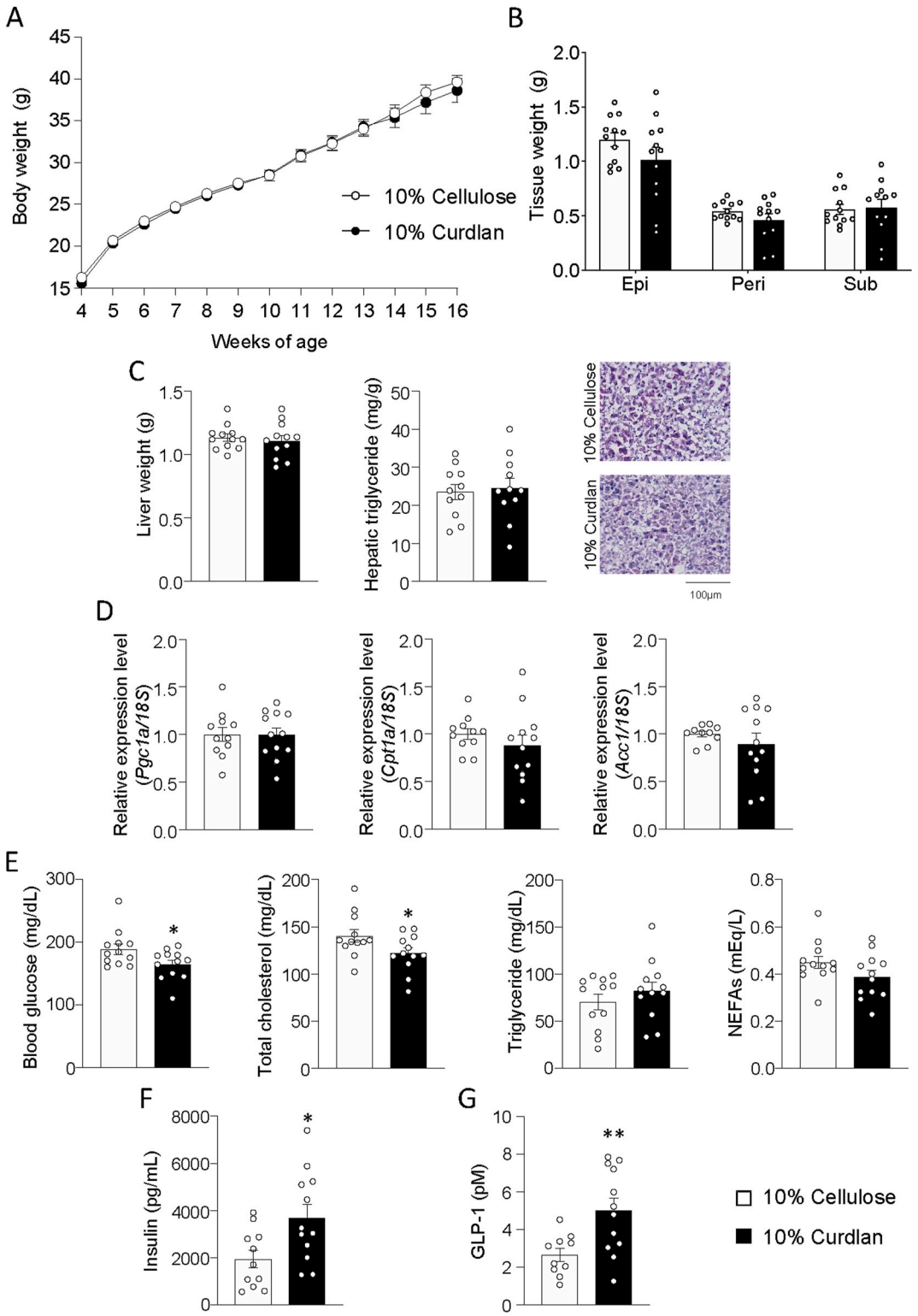

Fig. 3. Improvement of metabolic function by curdlan supplementation. (A) Body weight gain. (B) Weight of white epididymal (epiWAT), perirenal (periWAT), and subcutaneous (subWAT) adipose tissues. (C) Weight of liver. Hepatic triglyceride, and hematoxylin and eosin (H&E) staining of hepatocytes in cellulose or curdlan group. (D) Relative mRNA expressions involved in energy expenditure (*Pgc1a*), β-oxidation (*Cpt1a*), and fatty acid synthesis (*Acc1*) in the liver. (E) Blood glucose, plasma total cholesterol, triglyceride, non-esterified fatty acids (NEFAs), (F) plasma insulin, and (G) plasma GLP-1 levels were measured after fasting for 5 h. (B–G) Mice fed a HFD diet supplemented with cellulose or curdlan for 12 weeks. Data are expressed as means ± SEM. $P < 0.05$ was considered statistically significant (*$P < 0.05$ and **$P < 0.01$). Cellulose-supplementation group: n = 10–12; Curdlan-supplementation group: n = 11–12. Each cage contained two mice. Epi, epididymal; Peri, perirenal; Sub, subcutaneous; WAT, white adipose tissue.

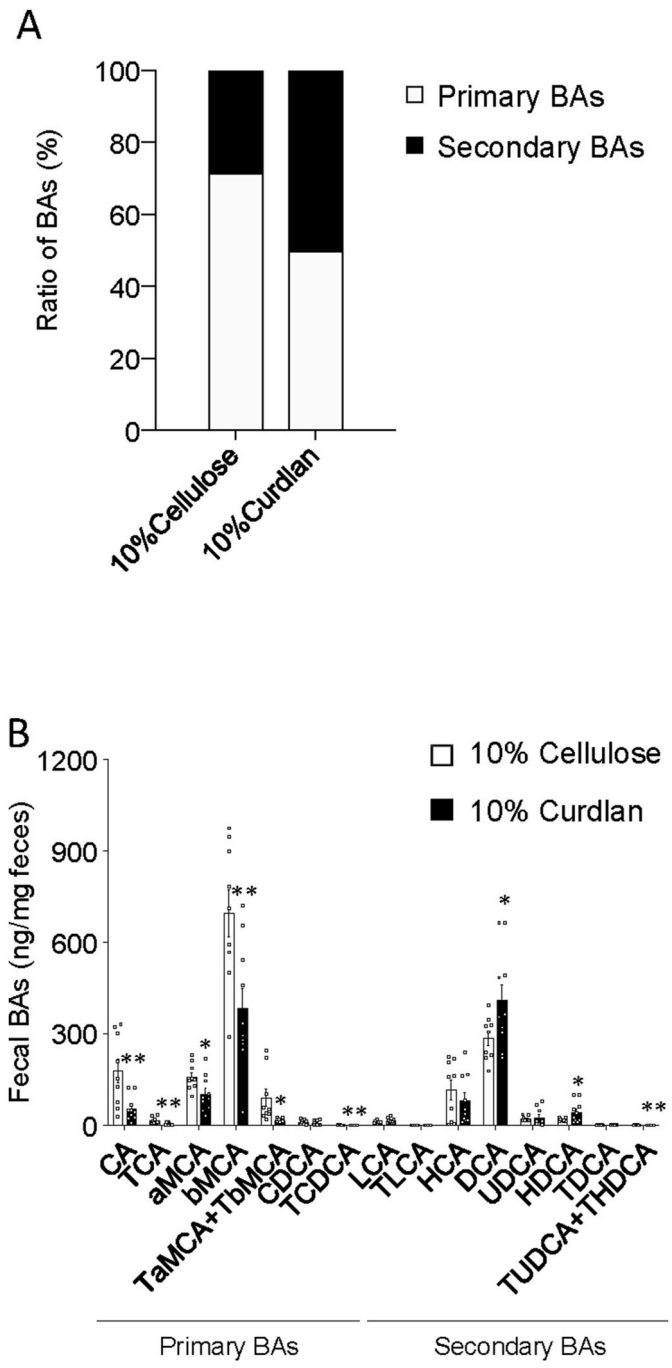

Fig. 4. Changes in the bile acid (BA) profile of mice supplemented with curdlan. (A) Ratio of primary and secondary BAs. (B) Individual BAs. Data are expressed as mean ± SEM. Cellulose-supplementation group: n = 9; Curdlan-supplementation group: n = 10. $P < 0.05$ was considered statistically significant (*$P < 0.05$ and **$P < 0.01$). CA, cholic acid; TCA, tauro-cholic acid; aMCA, α-muricholic acid; bMCA, β-muricholic acid; TaMCA, tauro-α-muricholic acid; TbMCA, tauro-β-muricholic acid; CDCA, chenodeoxy cholic acid; TCDCA, tauro-chenodeoxy cholic acid; LCA, lithocholic acid; TLCA, tauro-lithocholic acid; HCA, hyocholic acid; DCA, deoxycholic acid; UDCA, ursodeoxycholic acid; HDCA, hyodeoxycholic acid; TDCA, tauro-deoxycholic acid; TUDCA, tauro-ursodeoxycholic acid; THDCA, tauro-hyodeoxycholic acid.

supplementation in HFD-induced obese mice. HFD-induced increases in body weight and fat mass were comparable between cellulose and curdlan-supplemented HFD-fed mice (Fig. 3A and B). Additionally, HFD-induced hepatic steatosis and changes in metabolic enzymes such as energy expenditure (*Pgc1a*), β-oxidation (*Cpt1a*), and fatty acid synthesis (*Acc1*) in the liver were also comparable between cellulose and curdlan-supplemented HFD-fed mice (Fig. 3C and D). On the other hand, the blood glucose and plasma total cholesterol levels of curdlan-supplemented HFD-fed mice were significantly lower than those of cellulose-supplemented HFD-fed mice; however, plasma triglyceride and NEFA levels were similar between cellulose and curdlan-fed mice (Fig. 3E). Plasma insulin and incretin GLP-1 levels in curdlan-supplemented HFD-fed mice were significantly higher than those in cellulose-supplemented HFD-fed mice (Fig. 3F and G). The gut hormone GLP-1 is related to an increase in pancreatic β-cell growth and glucose-dependent insulin secretion [9]. Thus, curdlan intake improves hyperglycemia, along with increased plasma insulin and GLP-1 levels.

3.4. Curdlan intake alters fecal BA profiles

SCFAs affect glucose homeostasis by promoting insulin and GLP-1 secretion via the SCFA receptors GPR41 and GPR43 [7,30]. However, changes in the gut microbiota affect GLP-1 secretion not only through SCFA production but also through secondary BA increases by changing the profiles of BAs [13–16]. Hence, we examined the fecal primary and secondary BAs to clarify the relationship between curdlan intake and plasma GLP-1 increase in addition to SCFAs. The ratio of fecal primary to secondary BA was higher in curdlan-supplemented HFD-fed mice than in cellulose-supplemented HFD-fed mice (Fig. 4A). The level of β-muricholic acid, the most abundant primary BA in rodents, was greatly reduced in curdlan-supplemented HFD-fed mice compared with that in cellulose-supplemented HFD-fed mice. In contrast, the level of deoxycholic acid (DCA), a major secondary BA, was significantly increased in curdlan-supplemented HFD-fed mice compared with that in cellulose-supplemented HFD-fed mice (Fig. 4B). These results suggest that the increase in secondary BAs by curdlan intake is also related to an increase in plasma GLP-1 levels.

4. Discussion

Curdlan intake affects intestinal microbial composition and improves metabolic and immune functions [23]. However, the beneficial metabolic effects of intestinal SCFA production by curdlan intake remain unclear. In this study, we found that curdlan supplementation in HFD-induced obese mice reduced blood glucose levels and plasma total cholesterol levels. Additionally, the effect of curdlan supplementation on blood glucose reduction depends on gut microbial SCFA production and BA transformation.

Curdlan supplementation improved the aggravation of gut microbial composition caused by HFD. Our study demonstrated that the Bacteroidales S24-7 and Erysipelotrichaceae families were significantly increased by curdlan supplementation. *Muribaculum*, *Paramuribaculum,* and *Duncaniella* genera of the Bacteroidales S24-7 family are known to have propionate- and butyrate-producing properties [31,32]. Hence, levels of SCFAs in feces were significantly increased by curdlan supplementation, and *Muribaculum*, *Paramuribaculum,* and *Duncaniella* were partly responsible for the increase in fecal SCFA. Alternatively, the *Catenibacterium* genus, of the Erysipelotrichaceae family, is known to have a bile salt hydrolase (BSH) gene [33]. Since BSH is an important enzyme in secondary BA production, an increase in metabolic efficiency to secondary bile acids may lead to an increase in fecal secondary BAs by curdlan supplementation, thereby increasing plasma GLP-1 levels. However, further studies are needed to clarify the curdlan intake-mediated molecular mechanism of secondary BA increase and regulation of GLP-1 secretion.

Curdlan supplementation did not affect changes in body weight, fat mass, glucolipid metabolism-related kinase expression levels, and morphological changes in the liver. However, it affected the increase in plasma insulin and GLP-1 levels. In general, dietary fiber intake improves obesity conditions, such as body weight, fat mass gain, hepatic metabolic functions, and hyperglycemia [27,34,35]. This result may

depend on other factors such as energy harvest, except for SCFA production by curdlan. Moreover, suppression of plasma cholesterol by curdlan supplementation may be related to changes in fecal BA profiles, because cholesterol acts as a substance for BA synthesis [36]. However, further studies using SCFA receptor-deficient mice are needed to clarify the detailed mechanism of the curdlan intake-mediated cholesterol suppression effect.

5. Conclusion

In this study, we showed that curdlan supplementation exerts inhibitory effects on HFD-induced hyperglycemia and improves the intestinal environment. These effects may occur as a result of the promotion of GLP-1 secretion through the production of gut microbial metabolites SCFAs and secondary BAs. Our results may contribute to the development of food additives for the prevention of metabolic disorders, such as obesity and diabetes.

Author contributions

K.W. performed the experiments and wrote the paper; M.Y. performed the experiments and interpreted data; Y.M. performed the experiments and interpreted data; R.O-K. performed the experiments and interpreted data; I.K. supervised the project, interpreted data, and wrote the paper; I.K. had primary responsibility for the final content. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbrep.2021.101095.

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