Polysaccharides isolated from *Laminaria japonica* attenuates gestational diabetes mellitus by regulating the gut microbiota in mice

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Abstract
The current study was aimed to explore the beneficial effects of polysaccharides isolated from *Laminaria japonica* (LP) on gestational diabetes mellitus (GDM) mice. The obtained results demonstrated that the LP improved serum biochemical index, body weight index, and glucose tolerance. Furthermore, the evidence also suggested that the beneficial effects of LP might be attributed to the alternation in gut microbiota by LP supplementation. Particularly, the *Turicibacter*, a short-chain fatty acids-producing bacterium, was found to be up-regulated. In conclusion, the obtained results indicated that the LP might serve as prebiotic, and might have a great potential to be used as food supplementation for GDM patients.

KEYWORDS
gut microbiome, *Laminaria japonica*, polysaccharides

1 | INTRODUCTION

The change in lifestyle has caused an increase in the number of elderly and/or obese pregnant women, which has led to an increase in the incidence of gestational diabetes mellitus (GDM) (Wang et al., 2021). GDM refers to the intolerance to carbohydrate during pregnancy (Patti et al., 2018). It is a special type of diabetes, which is caused by various factors (Dean et al., 2014). The advanced maternal age, prepregnancy obesity, and genetic inheritance of diabetes have been identified as the risk factors for GDM (Cho et al., 2016). Furthermore, the GDM can cause the disorder of glucose and lipid metabolism in both the mothers and fetus, which can lead to an increase in the perinatal morbidity and mortality (Diane et al., 2017). Currently, the dietary intervention is considered as an effective approach for the prevention and management of GDM, especially for the mild GDM patients. Polysaccharides are a class of bioactive compounds, which are widely present in the various tissues and organs of food plants. Increasing evidences have demonstrated their positive effects on health. Indeed, the polysaccharides and their complexes are the potential sources of antidiabetic compounds. Meanwhile, the human gut is now widely accepted as a unique organ that is colonized with different microbial species, which perform a variety of functions.
physiological functions (Tasse et al., 2010). Studies have shown that the disorders in gut can lead to diabetes and obesity (Andreas et al., 2010). In particular, changes in the distribution of intestinal microbiota in women have been shown during pregnancy, which make the pregnant women more likely to develop GDM (Gámez-Valdez et al., 2020). Koren et al. (2012) analyzed the intestinal microbiota of pregnant women and demonstrated that the diversity of intestinal flora decreased in the third trimester as compared to the early trimesters, and only the abundance of certain intestinal microbiota increased, such as Proteobacteria and Actinomycetes, which was consistent with the changes in intestinal microbiota of patients having obesity and metabolic syndrome. Therefore, restoring the balance of intestinal microbiota might be a promising strategy to combat GDM.

The Laminaria japonica polysaccharides (LP) have been demonstrated to have a great potential to alter the intestinal microbiota both in vitro and in vivo. Therefore, they are often used as carbon sources for the growth of beneficial bacteria during fermentation (Walsh et al., 2013; Wang et al., 2018). It has also been reported that the intervention of seaweed polysaccharides could promote the generation of short-chain fatty acids (SCFAs) in colon (Gao et al., 2019). Moreover, a number of studies also highlighted the antidiabetic properties of L. japonica (Li et al. 2012; Shang et al., 2017; Yang et al., 2017). Therefore, LP may be a promising healthcare food for GDM therapy or protection. However, to the best of our knowledge, the potential effects of LP on GDM have not been investigated yet. Hence, in the current study, the effects of LP on the improvement of GDM symptoms were investigated in mouse models, and the association between the changes in intestinal microbiota and their beneficial effects was also explored.

## 2 MATERIALS AND METHODS

### 2.1 Materials

Laminaria japonica were obtained from local supermarket (Fuzhou, Fujian) and stored immediately at -20°C until used. ICR mice were purchased from Wushi Experimental Animals Co., Ltd. (Fuzhou, Fujian, China). High-fat diet (HD001) was purchased from Biotech Co., Ltd. (Beijing, China). Streptozotocin was purchased from Sigma (St. Louis, MO, USA). The standard solutions of acetic acid, propionic acid, and butyric acid were purchased from Aladdin Reagent Co., Ltd. (Shanghai, China). Other reagents used in this study were of analytical grade.

### 2.2 Preparation of L. japonica polysaccharides

According to previous study (Li et al., 2012; Zeng et al., 2017), the L. japonica were washed with tap water and deionized water, and air-dried at 65°C temperature. The L. japonica were then crushed using a grinder (IKA A11 basic, IKA, Staufen, Germany), and stored at room temperature (25°C) until used. The powder form of L. japonica was mixed with deionized water at a ratio of 1:70 (w/v), and heated in a water bath at 70°C temperature for 1 h. The mixture was blended using Sevag reagent (added at a ratio of 4:1). The Sevag reagent consisted of n-butyl alcohol and chloroform (added at a ratio of 1:4). The mixture was shocked in a water bath for 30 min before being centrifuged (Allegra X-30R, Beckman Coulter Inc., Brea, USA) at 10,000 g for 20 min in order to remove proteins. The supernatant was freeze-dried, stored in a dryer, and were called L. japonica polysaccharides (LP).

### 2.3 Animal models and study design

The 4-week-old ICR mice (specific pathogen-free [SPF] grade, body weight ranging from 20–24 g) were ordered from Wushi Experimental Animals Co., Ltd. (Fuzhou, Fujian, China). The mice were acclimated for 1 week. The female mice were mated with male mice at a ratio of 2:1 at 13 weeks of age, and the next day was designated as gestation day (GD) 0. Then, diabetes was induced in high-fat diet-fed mice with a single intraperitoneal injection of streptozotocin (STZ; Sigma) at a dose of 35 mg/kg bodyweight according to the previous reports to mimic the GDM status (plasma glucose levels > 11 mmol/L) (Wang, 2013; Zeng et al., 2017). For LP intervention, LP was added into diet at 1% (w/w) according to previous research (Li et al., 2012, 2020; Wang, 2013; Zeng et al., 2017). The maternal mice were housed one per cage at room temperature (25±2°C) and moderate humidity (50±10%) with a 12/12 h of light/dark cycle till spontaneous delivery. The mice were sacrificed on lactation day 21.

### 2.4 Measurement of serum biochemical index and body index

The serum biochemical index was measured as previously described with slight modification (Lin et al., 2019). The body and viscera weights were measured on lactation day 21.

### 2.5 Intra-peritoneal glucose tolerance test and postprandial glucose

The intraperitoneal glucose tolerance tests (IPGTT) were conducted on gestation day 10 and lactation day 21. For IPGTT, the maternal mice were fasted overnight, and glucose was administered with intraperitoneal injection at a dose of 1 g/kg glucose, as described previously (Nicholas et al., 2020). The blood samples were collected from the tail vein at 0, 30, 60, 90, and 120 min after glucose administration. The postprandial glucose levels were measured at gestation day 10.

### 2.6 Analysis of intestinal microbiota

A slightly modified form a previously described method was used for the analysis of intestinal microbiota (Zhang et al., 2019). Briefly, the microbial genomic DNAs were extracted from maternal mice feces using OMEGA bacterial DNA Kit (Omega Bio-tek, Norcross,
GA, USA) and DNA quality was checked using 2% agarose gel electrophoresis. Then, 16S rRNA gene amplicon sequencing was performed on Illumina sequencing platform using the bacterial primer pair 338F–806R (338F:ACTCCTACGGGAGGCAGCAG; 806R:GGACTACHVGGGTWTCTAAT). Operational taxonomic assignment was performed using 16S silva138/16s_bacteria database. The analysis of microbiota was processed at classification different levels, including Phylum and Genus.

2.7 Determination of fecal SCFAs

The SCFAs were determined as described previously with slight modifications (Wang et al., 2020). In brief, the freeze-dried feces were mixed with deionized water at a ratio of 1:8 (w/w) and stirred well using a vortex mixer. To remove the insoluble materials, the mixture was centrifuged at 8000 g for 30 min at 4°C before the supernatants were filtered through a 0.45 µm filter. Then the filtrate was transferred into chromatographic sampling bottles and loaded onto a high-performance liquid chromatography (e2695; Waters, Milford, MA, USA) equipped with a UV detector (2489 UV/Vis; Waters) and a Zorbax SB-Aq chromatographic column (5 µm, 4.6 mm × 150 mm; Agilent, Santa Clara, CA, USA). The column was maintained at 30°C. Detection was carried out at 215 nm. The mobile phase used for elution was 0.02 mol/L KH2PO4 (pH at 2.8 ± 0.05) and methanol at 98:2 (V/V). The flow rate was set as 1 mL/min and the injection volume was 20 µl. The standard curves of SCFAs with the concentration as abscissas (x) and the peak area as ordinate (Y) were obtained by fitting the data generated using acetic acid, propionic acid, and butyric acid solutions at known concentration. The contents of SCFAs were then calculated according to the standard curves.

2.8 Statistical analysis

All data was presented as mean ± standard error of mean (SEM) and the statistical differences between groups were analyzed using one way ANOVA followed by Tukey’s post hoc test Duncan’s test and student’s t-test. The values of p < 0.05 were considered to be statistically significant.

3 RESULTS AND DISCUSSION

3.1 Establishment of GDM models

As shown in Figure 1, the fasting serum glucose levels of all the mice were kept below 5 mmol/L before injection with STZ (Tian et al., 2015). In contrast, the mice injected with STZ demonstrated the up-regulation of fasting serum glucose levels to over 11 mmol/L at the sixth day of injection; while the control group maintained their glucose levels at around 5 mmol/L during the process of establishment, which showed the successful establishment of GDM mouse models.

3.2 Effects of LP on body index during gestation and lactation

The changes occurred in mice body weights after the administration of LP during gestation are shown in Figure 2(a). The mice body weights increased gradually in all the mice group during pregnancy. Moreover, there were no significant differences between the weights of normal diet-fed mice and GDM mice, as reported previously (Sha, Zeng, Zhao, & Jin, 2019). Furthermore, the LP administration did not significantly alter the mice body weights. Although no significant differences were found in the mice body weights, the visceral weights in maternal mice significantly changed in GDM mice. On the other hand, the LP administration reversed the increasing trend of liver and kidney weights in GDM mice as compared to normal diet-fed mice (Figures 2(c) and 2(d)). The pancreas weight showed a similar trend among all the groups but the changes were relatively smaller (Figure 2(e)).

3.3 Effects of LP on serum biochemical indices

The effects of LP administration on serum biochemical indices were further analyzed on lactation day 21, which included total serum cholesterol (TCh), serum triglyceride (TG), glutamic-oxalacetic transaminase (AST), glutamic-pyruvic transaminase (ALT), serum high-density lipoprotein (HDL) and serum low-density lipoprotein (LDL). As shown in Figure 3(a)-3(f), GDM mice showed the up-regulation of TCh, TG, AST, ALT, HDL-C, and LDL-C, and down-regulation of HDL-C/LDL-C ratio as compared to the GD group (Figure 3(g)). Notably, the LP administration lowered the increasing rate of TCh, TG, AST, ALT, HDL-C, and LDL-C in GDM mice. These results indicated that the abnormal serum biochemical indices, induced by GDM, could be relieved by the supplementation of LP.
FIGURE 2  Effects of LP on body indices during gestation and lactation. (a) Growth curve of gestational weight during pregnancy. (b) body weight, (c) liver weight, (d) kidney weight, and (e) pancreas weight measured on lactation day 21. Data are presented as mean ± SEM. Different letters indicate that significant difference in the body weight and the viscera weight of each group at $p < 0.05$.

3.4  Effects of LP on IPGTT and postprandial glucose

The effects of LP on blood glucose levels were determined using IPGTT and postprandial glucose tests. As shown in Figures 4(a) and 4(b), the LP-treated groups showed a decrease in the blood glucose levels by LP supplementation as compared to non-treated group on gestation day 10. Furthermore, the AUC of serum glucose also slightly decreased by the LP supplementation (Figure 4(c)). Similar trends were also observed on lactation day 21, which showed that the LP supplementation could improve glucose tolerance after delivery (Figures 4(d) and 4(e)). Again, the AUC of serum glucose supported the above findings (Figure 4(f)). Moreover, the postprandial glucose levels in treated groups also decreased as compared to not-treated groups (Figure 4(g)).
FIGURE 3  Effects of LP on serum biochemical indices. (a) Total serum cholesterol (TCh), (b) serum triglyceride (TG), (c) glutamic-oxalacetic transaminase (AST), (d) glutamic-pyruvic transaminase (ALT), (e) serum high-density lipoprotein (HDL), (f) serum low-density lipoprotein (LDL), and (g) the ratio of HDL to LDL (HDL/LDL) were measured on lactation day 21. Data are presented as mean ± SEM. Different letters indicate that significant difference in the serum biochemical indices of each group at $p < 0.05$.

3.5 Effects of LP on relative abundance of gut microbiota

The effects of LP on the changes in the relative abundance of gut microbiota were explored. As presented in Figures 5(a) and 5(b), Shannon index (diversity) and Chao index (richness) based on the OTU numbers in GD and GD_LP groups were calculated. Both the indices for the GD_LP group were down-regulated as compared to the GDM group without LP administration. This was consistent with a previous study, which reported that the polysaccharides decreased species diversity (Li et al., 2016). In addition, previous study (Yue et al., 2016) showed that high resistant starch exert the prebiotic in pig by downregulating the diversity. Furthermore, the Venn diagram showed that the GD group shared 189 OTU levels with the GD_LP group, while in 43 and 72
FIGURE 4 Effects of LP on IPGTT and Postprandial glucose levels. The serum glucose levels in (a) NP and NP_LP groups, (b) GD and GD_LP groups and (c) AUC of serum glucose tested on gestation day 10; the serum glucose levels in (d) NP and NP_LP groups, (e) GD and GD_LP groups, (f) AUC of serum glucose tested on lactation day 21, and (g) postprandial glucose levels in all the groups tested on gestation day 10. Data are presented as mean ± SEM. ##p < 0.01, #p < 0.05 were compared to the NP group. *p < 0.05 was compared to the GD group.
FIGURE 5 Effects of LP on gut microbiota between GD and GD_LP groups. (a) Shannon index, (b) Chao index, (c) Venn diagram, and (d) PCoA analysis based on OTU levels. (e) Firmicutes/Bacteroidetes ratio, (f) key phylum levels, and (g) key genus levels were tested on lactation day 21. Data are presented as mean ± SEM. *p < 0.05, **p < 0.01, ***p < 0.001.
FIGURE 6   Effects of LP on fecal SCFAs: (a) acetic acid, (b) propionic acid, (c) butyric acid, and (d) total SCFAs in feces were measured on lactation day 21. Data are presented as mean ± SEM. ## $p < 0.01$ was compared to the NP group.

OUTs were specifically found in GD and GD_LP groups, respectively, suggesting that LP treatment profoundly altered the gut microbiota (Figure 5(c)). However, the PCoA analysis showed remarkable clusters between the GD_LP and GD groups, respectively (Figure 5(d)), indicating that bacterial community of samples from mice with LP treatment were distinct from those in the control group.

The relative abundances of gut microbiota at phylum and genus levels were further explored. As shown in Figure 5(f), the predominant phyla in gut microbiota were Firmicutes, Bacteroidetes, and Proteobacteria. In particular, the LP improved the gut microbiota by decreasing the abundance of Proteobacteria, which was consistent with the previous study (Yan et al., 2017). According to previous report (Larsen et al., 2017), the ratio of Firmicutes to Bacteroidetes has is often correlated with obesity and abnormal glucose metabolism. However, the ratio of Firmicutes to Bacteroidetes decreased (Figure 5(f)). In addition, the ratio showed no significant differences upon LP supplementation. Notably, relatively small number of mice in the current study may limited the results reaching significance. We will improve this by increasing the mice number in our future experiment.

As shown in Figure 5(g), at genus level, the administration of LP significantly up-regulated the relative abundance of Turicibacter, which is a type of anaerobic gram-positive bacteria, belonging to the order Bilidobacterium (Bosshard, Reinhard, & Martin, 2002). Our result was also in agreement with a previous study, which reported that the random blood glucose showed negative correlation with Turicibacter (Zhou et al., 2019). In addition, another study also showed that high resistant starch diet could significantly increase Turicibacter abundance in gut(Yue et al., 2016). Considering that high resistant starch acts as generator of SCFAs, this may also highlight the beneficial effects of increasing Turicibacter abundance. Furthermore, a related study also showed that Turicibacter was an important genus for the generation of SCFAs (Fak et al., 2015). However, more investigation is needed before a clear conclusion can be reached. Meanwhile, our data also indicated that the relative abundance of Lactobacillus was significantly down-regulated as compared to the nontreated group. This finding is consistent with early research that lower abundance of Lactobacillus was observed in control subjects, when compared to diabetic subjects (Sato et al., 2014). This indicated that the LP might relieve GDM by down-regulating the abundance of Lactobacillus. Furthermore, this study also showed that Enterorhabdus was significantly down-regulated by the LP supplementation. Interestingly, a previous study indicated that the Enterorhabdus up-regulated in lean subjects, but not in diabetic subjects (Geurts et al., 2011). Therefore, further investigations are needed to explain the
correlation between LP-induced decrease in the abundance of Enterorhabdus and its beneficial effects on GDM.

3.6 Effects of LP on fecal SCFAs

The potential effects of LP administration on fecal SCFAs were further explored. As presented in Figures 6(a) and 6(b), the amount of acetic acid and propionic were all up-regulated by the LP supplementation. In contrast, the amount of butyric acid seemed to be unaffected by the LP supplementation (Figure 6(c)). In conclusion, these results suggested that, in addition to the induction of changes in the composition of gut microbiota, the LP could further influence the SCFAs-producing gut bacteria.

4 CONCLUSIONS

In this study, the effects of LP in maternal GDM mice were explored. In brief, the LP supplementation regulated maternal GDM mice, as evaluated from their body weight index, serum biochemical indices, glucose tolerance tests and gut microbiota. The possible underlying mechanisms may involve the regulatory effects of LP on composition of gut microbiota and short-chain fatty acids in mice. Particularly, the production of SCFAs was induced by LP, which may be associated with the alternation in the abundance of Turicibacter. In summary, the hyperglycemic state in maternal GDM mice was attenuated by the modification of gut microbiota, which provided a theoretical basis for the development of LP-based functional foods.

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CONFLICT OF INTEREST

The authors confirm that they have no conflict of interest to declare for this publication.

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