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Seaweed polysaccharide relieves hexavalent chromium-induced gut microbial homeostasis

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Heavy metals released in the environment pose a huge threat to soil and water quality, food safety and public health. Additionally, humans and other mammals may also be directly exposed to heavy metals or exposed to heavy metals through the food chain, which seriously threatens the health of animals and humans. Chromium, especially hexavalent chromium [Cr (VI)], as a common heavy metal, has been shown to cause serious environmental pollution as well as intestinal damage. Thus, increasing research is devoted to finding drugs to mitigate the negative health effects of hexavalent chromium exposure. Seaweed polysaccharides have been demonstrated to have many pharmacological effects, but whether it can alleviate gut microbial dysbiosis caused by hexavalent chromium exposure has not been well characterized. Here, we hypothesized that seaweed polysaccharides could alleviate hexavalent chromium exposure-induced poor health in mice. Mice in Cr and seaweed polysaccharide treatment group was compulsively receive K2Cr2O7. At the end of the experiment, all mice were euthanized, and colon contents were collected for DNA sequencing analysis. Results showed that seaweed polysaccharide administration can restore the gut microbial dysbiosis and the reduction of gut microbial diversity caused by hexavalent chromium exposure in mice. Hexavalent chromium exposure also caused significant changes in the gut microbial composition of mice, including an increase in some pathogenic bacteria and a decrease in beneficial bacteria. However, seaweed polysaccharides administration could ameliorate the composition of gut microbiota. In conclusion, this study showed that seaweed polysaccharides can restore the negative effects of hexavalent chromium exposure in mice, including gut microbial dysbiosis. Meanwhile, this research also lays the foundation for the application of seaweed polysaccharides.

KEYWORDS

chromium, seaweed polysaccharides, gut microbiota, bacteria, heavy metals

Introduction

Industrial production releases a large amount of metal pollutants every year, such as lead, chromium, and copper, which are considered to be vital factors causing environmental contamination and animal metal poisoning (Wen et al., 2019; Zhao et al., 2019; Wang F. et al., 2022). Chromium is one of the most common heavy metals, which is widely used

in leather, fuel and steel production (Mamais et al., 2016; Kapoor et al., 2022). Early surveys indicated that the global annual consumption of chromium is more than 200,000 tons and its demand is still increasing (Li A. et al., 2021). However, large amounts of chromium waste may be directly discarded and reach the environment through multiple ways, seriously threatening the surrounding water and soil health (Vaiopoulou and Gikas, 2020; Prasad et al., 2021). Importantly, the released chromium could accumulate in soil, water and plants then transfer to aquatic and terrestrial animals *via* food chain, posing a serious threat to human health and food safety (Nguyen et al., 2017; Lee C. P. et al., 2019). Previous studies indicated that long-term exposure to hexavalent chromium can cause parenchymal organ injury such as gastrointestinal tract, liver, and kidney. Additionally, hexavalent chromium has also been shown to be associated with cancer, asthma and gut microbial dysbiosis (Yang Q. et al., 2020; Monteiro et al., 2018; Shaw et al., 2019).

Gut microbiota is a complicated and dynamic microecosystem that consists of approximately 100 trillion microorganisms involving over 2,000 diverse species (Egerton et al., 2018; Feng et al., 2018; Morris, 2018). The gut microbiota exhibits a symbiotic relationship with the host, exerting positive effects on host metabolism, intestinal homeostasis and immune system maturation (Yu et al., 2020; Zhang L. et al., 2021). Moreover, the other well-understood contributions of the gut microbial community is its key roles in the intestinal barrier maintenance and immune system maturation, which contribute to protecting the host from invasion by infectious pathogens (Sun et al., 2022; Wang R. et al., 2022). As essential biochemical converters, gut microbiota can also convert food into nutrients and metabolites (Zhang L. et al., 2021; Zhang X. et al., 2021; Yang J. et al., 2022). However, many factors associated with hosts and environment such as aging, oxidative stress, antibiotics and heavy metal could affect intestinal homeostasis and even induce gut microbial dysbiosis (Xia et al., 2018; Kakade et al., 2020; Ma et al., 2022). Numerous studies provided supporting evidence that gut microbial dysbiosis could impair intestinal mucosal barrier and gut mucosal immune system, potentially causing severe gastrointestinal infection, diarrhea, and colonitis (Liu et al., 2019; Li Y. et al., 2021; Xu et al., 2022). Additionally, gut microbial dysbiosis can also extend its negative effects beyond the gastrointestinal system and result in extraintestinal diseases such as autism, diabetes, obesity and NAFLD (Yang et al., 2021; Wan and Ma, 2022; Ye et al., 2022). Considering the systemic effects of gut microbial dysbiosis, it is also considered as a emerging participator in the pathophysiology of many diseases (Crusell et al., 2018).

Supplementation with antioxidants is regarded as a vital way to mitigate metal poisoning because metal contaminants can cause oxidative stress and decreased antioxidant capacity (He et al., 2020; Yang Y. et al., 2020; Paithankar et al., 2021). Currently, polysaccharides extracted from animals and plants have been shown to be promising antioxidants (Chen and Huang, 2018, 2019). Among many types of polysaccharides, seaweed polysaccharide has attracted mounting attention own to its several health benefits to the host (Tanna and Mishra, 2019; Bauer et al., 2021). Numerous studies indicated that seaweed polysaccharide has anti-inflammatory, antiviral, immunomodulatory and anti-tumor effects (Lomartire and Goncalves, 2022). Moreover, recent research on seaweed polysaccharide also showed its vital roles in the gastrointestinal disease and improve antioxidant ability (Fu et al., 2021). Although increasing evidence showed the positive role of seaweed polysaccharide on the host health, it remains unclear whether seaweed polysaccharide can alleviate gut microbial imbalance caused by hexavalent chromium. Thus, we investigated the protective effect of seaweed polysaccharide on hexavalent chromium induced gut microbial imbalance.

Materials and methods

Animal experiments

Sixty 28-day-old Kunming mice with similar weight and background were used for this research. These selected mice were housed in a standard environment and health assessments were performed on all mice to ensure that the experiments ran smoothly. After acclimatization for 3 days, these mice were randomly divided into three groups namely control group (Con), Cr (VI)-induced group (Cr), seaweed polysaccharide treatment group (SP, 200 mg/kg). The dosage of seaweed polysaccharide and Cr (VI) refers to the previous research with slight improvements (Ben et al., 2016; Fu et al., 2021). The proportion of male and female in each groups was 1:1. The mice in the Con, Cr and SP groups were provided adequate feed and water. In addition, mice in Cr (VI) and SP treatment group was compulsively receive $K_2Cr_2O_7$ (75 mg/kg). Moreover, the SP treatment group was compulsively gavaged with 0.2 ml of SP. On the day 29 of the experiment, we euthanized all the mice and collected colonic contents. The collected samples were snap-frozen in liquid nitrogen and stored at-80°C until further investigation.

DNA extraction and illumine MiSeq sequencing

The acquired samples of each group were separately homogenized and then performed DNA extraction using QIAamp DNA Mini Kit (QIAGEN, Hilden, Germany) following suggested instructions of manufacturer. After ensuring the extracted DNA met the requirements for subsequent analysis, we amplified the V3/V4 variable regions using the primers (338F: ACTCCTAC GGGAGGCAGCA and 806R: GGACTACHVGGGTWTCTAAT) synthesized from conserved regions. The conditions and volumes of PCR reactions were determined as per previous studies (Zhang et al., 2020). Before building the libraries, some processing products including fragment recovery, quantitation and quality

appraisal were performed to obtain qualified products. The constructed libraries were subsequently performed quality evaluation. The libraries with only one peak and concentration greater than 2 nM were considered qualified. The qualified libraries were subjected to paired-end sequenced (2 × 300 bp) on MiSeq sequencing machine following the standard protocols. The original data containing short sequences, chimera and mismatched primers preduced from amplicon sequencing were performed quality evaluation and filtration to acquire effective sequence. The effective sequences were clustered and OTUs partitioned based on 97% similarity. To further dissect the effects of thiram exposure on gut microbiota, we calculated five alpha diversity indices and generated PCoA plots that reflected beta diversity. The differential bacteria were identified through the Metastats analysis and LEfSe. *p*-values (means ± SD) <0.05 were considered statistically significant.

Results

Data collection and analysis

To investigate the protective effect of seaweed polysaccharide on Cr (VI)-induced mice, we explored changes in the gut microbiota of mice during polysaccharide supplementation. Results indicated that a total of 735,152 (Con = 256,535, Cr = 222,963, SP = 255,654) raw sequences were obtained from three groups (Table 1). Subsequently, we performed quality assessment on the raw data and obtained 502,400 (Con = 183,752, Cr = 138,389, SP = 180,259) valid sequences. Results of the rarefaction curves, which can reflect the sequencing depth, show that the species coverage and sequencing depth are qualified (Figures 1A–C). The valid sequences of three groups were clustered into 358 OTUs (Con = 298, Cr = 182, SP = 269), ranging from 76 to 193 OTUs per sample (Figures 1D,E). Furthermore, the Con, Cr and SP groups have 69, 9, and 35 unique OTUs, respectively.

Seaweed polysaccharide recovered the changes of gut microbial diversity induced by Cr (VI)

We further calculated changes in gut microbial diversity based on the abundance of OTUs in each sample. Results of Good's coverage indicated that almost all bacterial phenotypes were found in this amplicon sequencing. The gut microbial diversity indices such as Chao1 (170.75 ± 15.79 vs. 87.00 ± 9.55, $p = 0.00029$), ACE (170.75 ± 15.79 vs. 87.00 ± 9.55, $p = 0.00029$), Shannon (4.64 ± 0.68 vs. 2.64 ± 0.64, $p = 0.0055$), and Simpson (0.88 ± 0.060 vs. 0.63 ± 0.15, $p = 0.035$) in the hexavalent chromium exposure group were significantly lower than those in the control group, indicating that hexavalent chromium markedly reduced the diversity and abundance of gut microbiota. However, seaweed polysaccharide administration reversed the hexavalent chromium-induced decrease in gut diversity indices (Figures 2A–D). PCoA plots indicated that all the samples were clustered together, indicating no differences in the major components of the gut microbiota (Figures 2E,F).

Seaweed polysaccharide altered gut microbial composition in Cr (VI)-induced mice

The gut microbial composition and abundance in different taxonomical levels were evaluated and observed significant variations. In this amplicon sequencing, a total of 10 phyla and 91 genera were identified in 12 samples, ranging from 7 to 10 phyla and 37 and 69 genus per sample. *Proteobacteria* (13.49, 40.43%), *Campylobacterota* (23.70, 21.54%), *Firmicutes* (20.47, 13.58%) and

TABLE 1 The raw sequence information generated from amplicon sequencing.

Sample	Raw reads	Clean reads	Denoised reads	Merged reads	Effective reads	Effective (%)
Con1	63,877	48,706	47,825	46,605	44,712	69.99
Con2	52,984	42,083	41,786	41,500	41,298	77.94
Con3	68,338	56,977	56,209	55,487	54,201	79.31
Con4	71,336	54,244	51,810	48,256	43,541	61.03
Cr1	57,184	45,048	44,317	43,248	36,645	64.08
Cr2	43,218	33,053	32,877	32,630	32,505	75.21
Cr3	64,568	50,981	50,095	48,996	40,654	62.96
Cr4	57,993	44,484	43,224	41,448	28,585	49.29
SP1	72,200	55,611	54,193	52,194	46,092	63.83
SP2	59,875	48,195	47,982	47,741	46,954	78.42
SP3	68,315	52,716	50,800	48,336	43,504	63.68
SP4	55,264	44,248	44,016	43,778	43,709	79.09

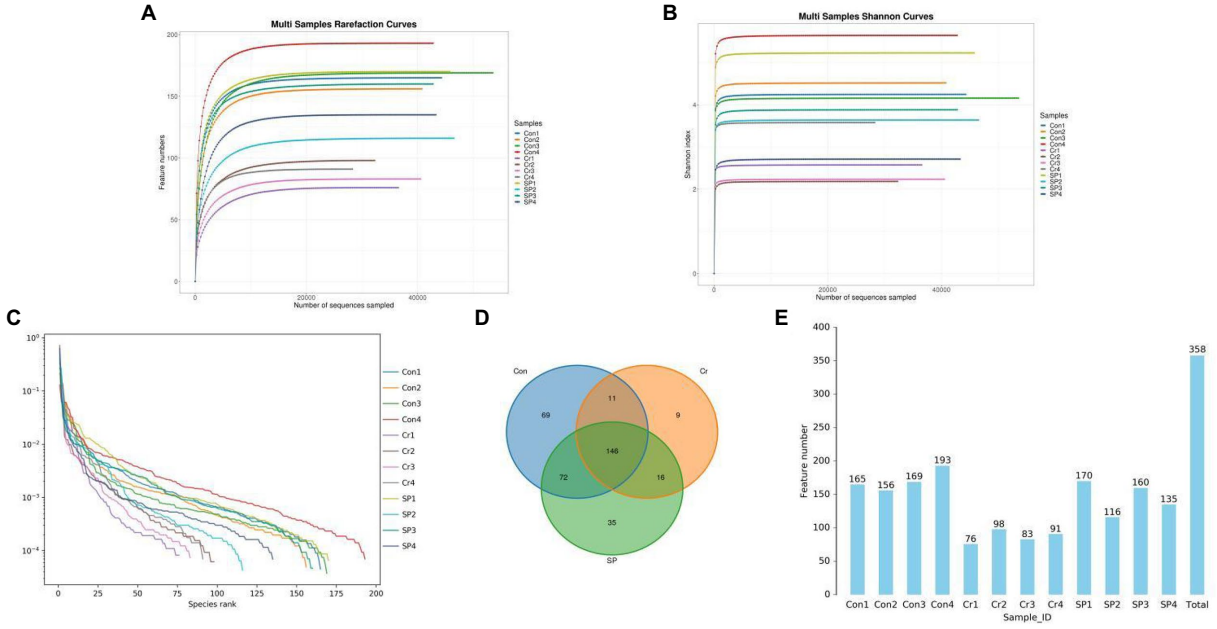

FIGURE 1
Feasibility assessment and OTU distribution. **(A,B)** Rarefaction curves. **(C)** Rank abundance curve. **(D)** Venn diagram. **(E)** OTUs distribution histogram.

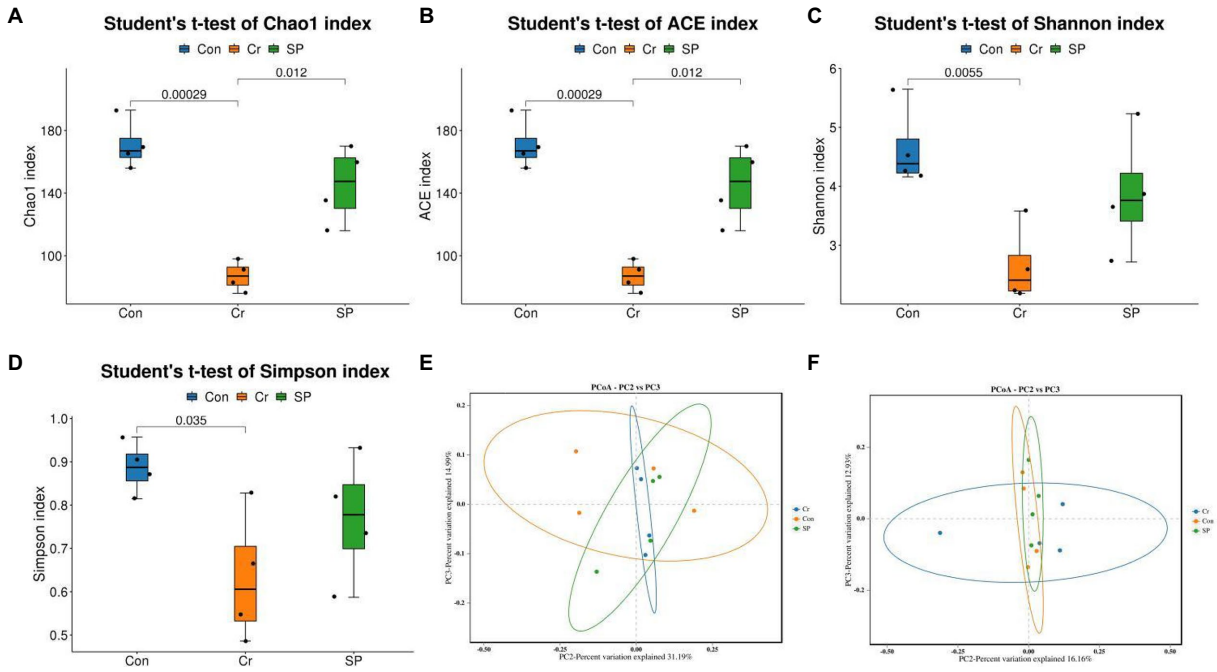

FIGURE 2
Seaweed polysaccharide administration restored the changes in gut microbial diversity induced by hexavalent chromium exposure. **(A)** Chao1. **(B)** ACE. **(C)** Shannon. **(D)** Simpson. **(E,F)** PCoA plots based on the weighted and unweighted UniFrac distance.

Bacteroidota (23.43, 17.17%) were the most preponderant bacteria in Con and SP groups, whereas *Proteobacteria* (64.11%), *Campylobacterota* (8.41%), *Firmicutes* (19.43%), and *Actinobacteriota* (1.58%) were abundantly present in the Cr groups (Figure 3A). However, the abundances of *Deferribacterota* (3.18, 0.42, 1.57%), *Verrucomicrobiota* (2.94, 0.82, 0.22%),

Patescibacteria (0.97, 0.021, 0.31%), and *Cyanobacteria* (0.033, 0.00, 0.00%) are lower in Con, Cr and SP groups. *Escherichia_Shigella* (10.71, 33.45%) and *Helicobacter* (23.70, 21.54%) were the most dominant genus in the Con and SP groups, whereas *Escherichia_Shigella* (57.75%) and *Ligilactobacillus* (14.24%) were abundantly present in the Cr group (Figure 3B). However, the proportions of *Enterorhabdus* (4.94, 1.41, 2.71%), *Desulfovibrio* (6.07, 0.89, 1.43%), *unclassified_Enterobacteriaceae* (0.43, 4.05, 3.52%), and *Bacillus* (2.63, 1.57, 2.06%) were lower in gut microbiota of Con, Cr, and SP groups. The specific bacterial species and abundance are also shown in the heatmap (Figure 3C).

At the phylum level, the abundances of *Proteobacteria* was observably more preponderant in Cr group than in the Con group, whereas the abundances of *Bacteroidota*, *Patescibacteria*, and *Actinobacteriota* were lower. At the genus level, the abundances of *Escherichia_Shigella* and *Enterococcus* in Cr group was observably predominant than Con group, whereas the *unclassified_Lachnospiraceae*, *Prevotellaceae_UCG_001*, *unclassified_Desulfovibrionaceae*, *Bilophila*, *Stenotrophomonas*, *Lachnoclostridium*, *Rikenellaceae_RC9_gut_group*, *Rhodococcus*, *Microbacterium*, *Candidatus_Saccharimonas*, *Enterorhabdus*, *unclassified_Erysipelotrichaceae*, *Sphingobacterium*, *unclassified_Anaerovoracaceae*, *Anaerotruncus*, *unclassified_Ruminococcaceae*, and *Acinetobacter* were lower (Figure 4). However, seaweed polysaccharide administration could reverse these bacterial changes. A comparison of the Cr and SP showed a distinct decrease in the abundances of *Bacteroides*, *Alloprevotella*, *unclassified_Desulfovibrionaceae*, *unclassified_Ruminococcaceae*, *Odoribacter*, *GCA_900066575*, *unclassified_Lachnospiraceae*, *Anaerotruncus*, and *Alistipes*. LEfSe analysis further revealed bacteria that differed between groups (Figure 5).

Correlation network analysis

Alistipes was positively related to *unclassified_Muribaculaceae* (0.79). *Prevotellaceae_UCG_001* was positively related to *Alloprevotella* (0.83), *unclassified_Erysipelotrichaceae* (0.77) and *unclassified_Lachnospiraceae* (0.66). *Rikenellaceae_RC9_gut_group* was positively related to *unclassified_Erysipelotrichaceae* (0.72) and *unclassified_Clostridia_UCG_014* (0.67) (Figure 6).

Discussion

The environmental contamination caused by heavy metal discharge and the negative impact on public health have attracted increasing attention (Drzezdzon et al., 2018; Yuan et al., 2020). In addition, the accumulation of heavy metals in animals and plants also seriously affects animal production and human health (Quina et al., 2019; Bao et al., 2021). Studies have shown that chromium could be absorbed by the host in many ways such as the digestive system, epidermis and respiratory system (Zhang et al., 2020). Moreover, chromium ingested by the digestive tract can enter other organs such as liver, kidney, and intestine through blood circulation, which further threatens the health of the host (Cardenas-Gonzalez et al., 2016; Andleeb et al., 2020). Early investigations showed that long-term chromium exposure can cause a significant decrease in growth performance and perturb gut microbial homeostasis in broilers (Li Y. et al., 2021). In addition, chromium exposure has also been shown to cause significant gastrointestinal symptoms (Zhang et al., 2022). It is widely known that the intestine plays an important role in nutrient absorption and host health, which in turn depends on normal gut microbiota structure (Brussow, 2015; Coelho et al., 2019). Although gut microbiota inhabits the intestine, it can cause systemic effects. Therefore, the maintenance of gut microbial homeostasis is critical for host health (Greenhill, 2018; Ma et al., 2020). Chromium intake through the digestive tract inevitably affects the gut microbiota and causes kidney damage, but whether seaweed polysaccharides with various biological properties can restore the gut microbiota is still unknown. Therefore, we systematically explored the protective effects of seaweed polysaccharides on hexavalent chromium-induced gut microbiota in mice.

As the main channel for various substances to enter the body, the intestinal own health and the gut microbiota inhabiting the intestine are also more susceptible to external factors (Sadeq et al., 2021; Zheng et al., 2021). Generally, the gut microbiota is in a dynamic balance under the action of various factors, but intestinal function does not change significantly (Michaudel and Sokol, 2020). In addition, the stability of the gut microbiota is also necessary to maintain the host health and the intestinal function (Li et al., 2016). However, environmental pollutants such as heavy metals, microplastics and pesticides can damage the intestine and various parenchymal organs, causing gut microbial imbalance and systemic effects (Lu et al., 2019; Qiao et al., 2019). Additionally, dysbiosis in the gut microbiota also affects the digestion and absorption of nutrients and growth performance (Chi et al., 2021). Previous study showed that long-term hexavalent chromium exposure leads to dysbiosis of the gut microbiota, accompanied by a significant reduction in microbial diversity (Li A. et al., 2022). Additionally, Yao et al. (2019) also found similar conclusions, demonstrating the negative impact of hexavalent chromium on gut microbes. In this study, we observed significant decrease in gut microbial diversity of mice during hexavalent chromium exposure. However, seaweed polysaccharide administration could restore the gut microbial dysbiosis caused by chromium exposure. Studies have shown that gut microbial dysbiosis and reduced diversity are considered important drivers of various diseases such as diarrhea, obesity and diabetes (Stephens et al., 2018; Lee P. et al., 2019). Moreover, decreased gut microbial diversity also affects intestinal barrier function and immune system maturation, which may reduce host immunity and increase permeability (Burcelin, 2016; Van Averbeke et al., 2022). In this case, the host is more sensitive to external pathogenic factors and more prone to other diseases. Increased intestinal permeability may also cause the passage of harmful intestinal metabolites or pathogenic bacteria across the

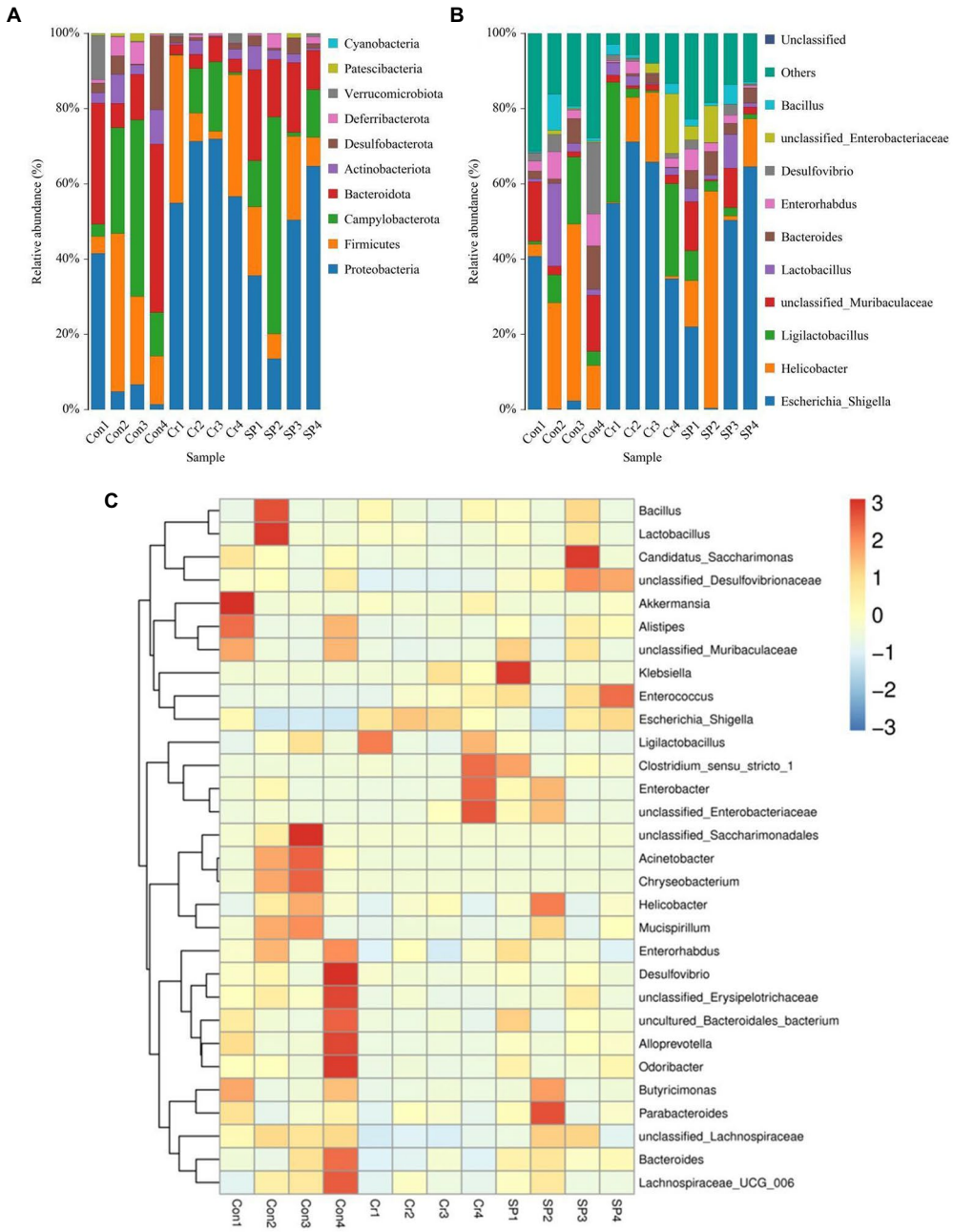

FIGURE 3
Seaweed polysaccharide administration restored gut microbial composition in hexavalent chromium-induced mice. **(A,B)** The preponderant bacteria at the phylum and genus levels. **(C)** Heat map of bacterial distribution.

intestinal barrier, leading to damage to other organs such as liver and kidney (Adolph and Tilg, 2018; Wahlstrom, 2019). More importantly, some opportunistic pathogens may also become pathogenic during this period (Nishida et al., 2018). Therefore, maintaining the balance of gut microbiota is also considered to be an important condition to ensure the health of the host. In addition, we also performed beta diversity analysis to explore the differences in the main components of the gut microbiota. Results showed that all the samples were clustered together, indicating that there were no differences in the main components of the gut microbiota.

As the most complex micro-ecosystem, the gut microbiota is composed of a large number of microorganisms, of which bacteria account for approximately 98% (Qin et al., 2022; Yakabe et al., 2022). Intestinal bacteria play key roles in intestinal function and homeostasis by interacting with the host or producing some beneficial metabolites (Haase et al., 2020; Zhou et al., 2022). Consistent with previous studies, we observed that hexavalent

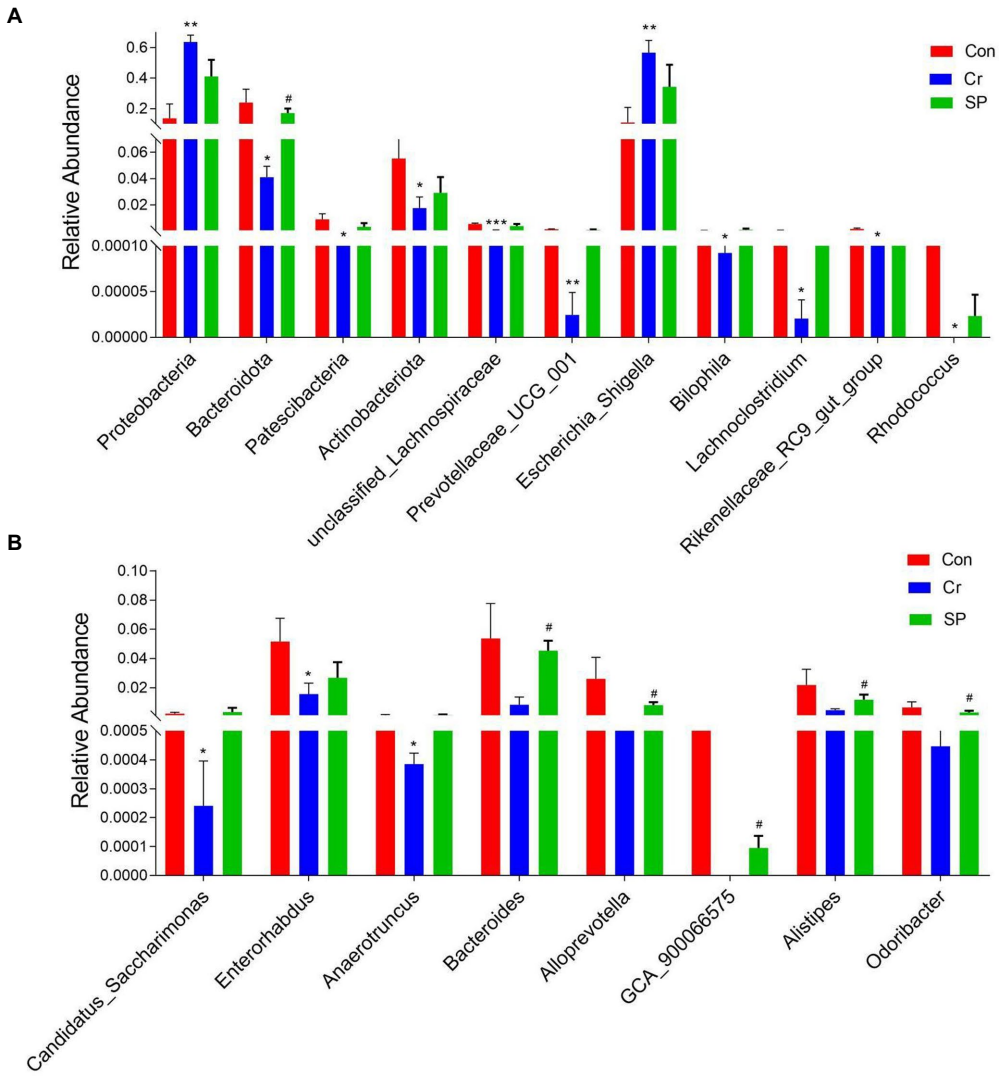

FIGURE 4
Statistical analysis of differential bacteria. **(A)** Relative Abundance at genus level. **(B)** Relative Abundance at phylum level. All data was indicated as mean±SD. *p<0.05, **p<0.01, ***p<0.001 compared with Con group, $^{\#}p$<0.05 compared with Cr group.

chromium exposure could cause significant changes in gut microbial composition, indicating the disruption of gut microbial homeostasis. Specifically, hexavalent chromium exposure led to a significant increase in gut pathogenic bacteria (*Enterococcus* and *Escherichia_Shigella*) and a significant decrease in beneficial bacteria (*Alistipes*, *Lachnospiraceae*, *Prevotellaceae_UCG_001*, *Alloprevotella*, *Bacteroides* and *Rikenellaceae_RC9_gut_group*). However, seaweed polysaccharide administration significantly improved the composition of the gut microbiota in mice. Studies have shown that *Alistipes* and *Lachnospiraceae* could produce short-chain fatty acids (SCFAs; Wu et al., 2020). Many investigations indicate that SCFAs played vital roles in relieving intestinal inflammation, oxidative stress, opportunistic infections as well as maintaining gut microbial homeostasis, intestinal permeability and intestinal epithelial cells morphology (Marino et al., 2017; Schwarz et al., 2017; Ikeda et al., 2022). Moreover, SCFAs has also been shown to regulate energy intake, regulate cell apoptosis and decrease cholesterol (Murugesan et al., 2018; Prasad and Bondy, 2018; Yang J. et al., 2022; Yang X. et al., 2022). *Prevotellaceae* in the intestine could digest pectin, hemicellulose and high carbohydrate foods, indicating its key roles in digestion and absorption (Li A. et al., 2022; Li C. et al., 2022). *Alloprevotella* could secrete acetate and succinate and these beneficial metabolites are critical for intestinal homeostasis and decreased cardiovascular disease risk (Yuan et al., 2021). *Bacteroides* could decompose polysaccharides, showing a key role in intestinal ecosystem (Schwalm et al., 2016; Schwalm and Groisman, 2017). *Rikenellaceae* could alleviate inflammation by activating T-regulatory cell differentiation

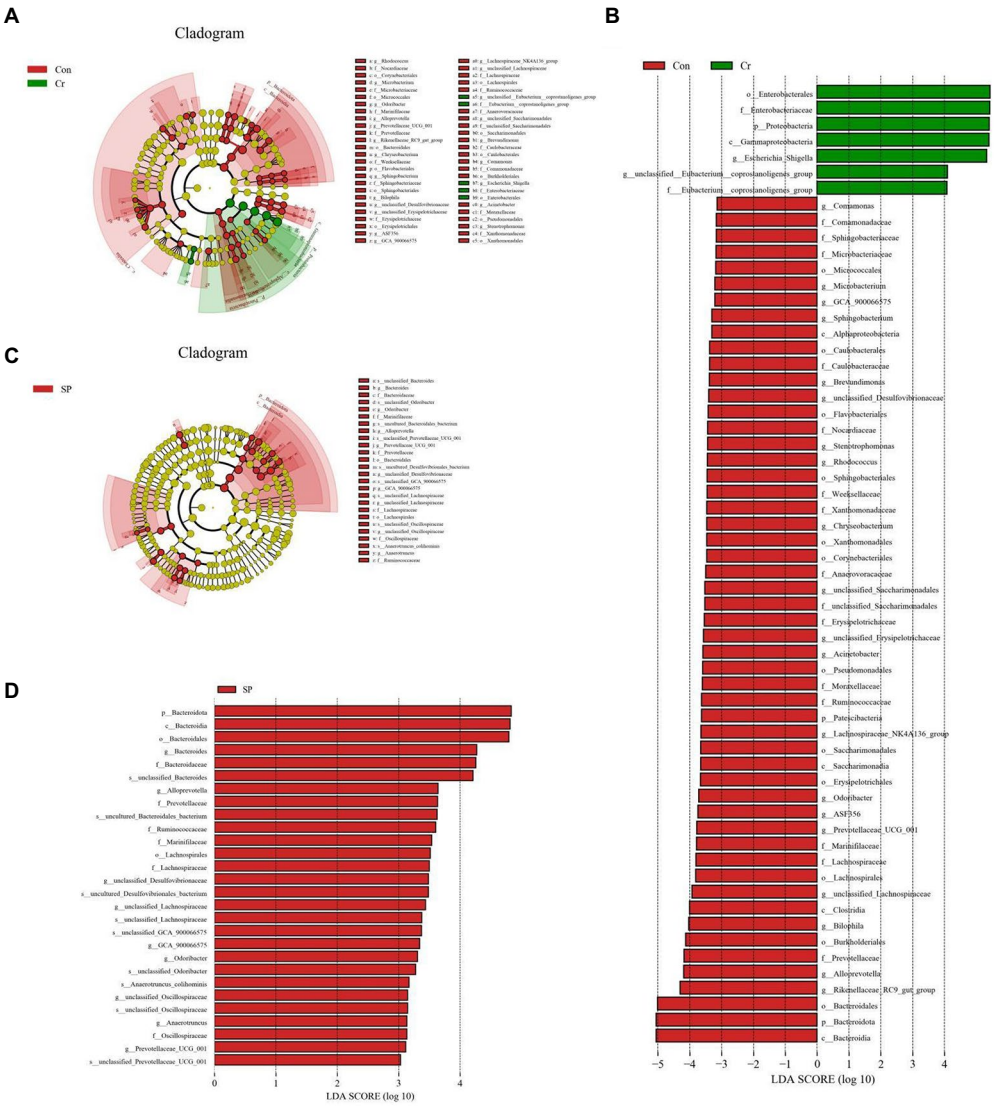

FIGURE 5
Identification of differential bacteria by LEfSe and LDA scores. **(A,C)** Cladogram of phylogenetic distribution of differential bacteria. **(B,D)** LDA scores >2 were considered significantly different.

(Cui et al., 2018). Numerous evidence demonstrate that *Enterococcus* could cause many diseases such as meningitis, sepsis, and cardioperiostitis (Su et al., 2016; Subramanya et al., 2019). Additionally, *Enterococcus* infection is difficult to cure because of inherent and acquired resistance (Chanderraj et al., 2020; Ekore et al., 2022). *Escherichia_Shigella* was considered as a vital factor for causing diarrhea (Li et al., 2018). Hexavalent chromium exposure may further adversely affect host health by disrupting gut microbial homeostasis. However, seaweed polysaccharide can maintain the gut microbial balance and this may be one of the modes of action of seaweed polysaccharides. Microorganisms inhabiting the intestine could interact in a synergistic, antagonistic or symbiotic relationship to form a stable intestinal environment (Li A. et al., 2022; Li C. et al., 2022). In this study, we observed significant correlations among some bacteria through correlation network analysis. For instance, *Alistipes* and *Prevotellaceae_UCG_001* were associated with *unclassified_Muribaculaceae* and *Alloprevotella*, respectively. Therefore, these altered bacteria may further affect the function of other bacteria through the interaction between bacteria.

Conclusion

In conclusion, this research explored the protective effect of seaweed polysaccharide administration on the gut microbiota of hexavalent chromium-exposed mice. Results showed that seaweed polysaccharide administration could alleviate hexavalent chromium exposure induced gut microbiota dysbiosis. Our study shows that seaweed polysaccharides can be used as an effective drug to mitigate the negative effects of

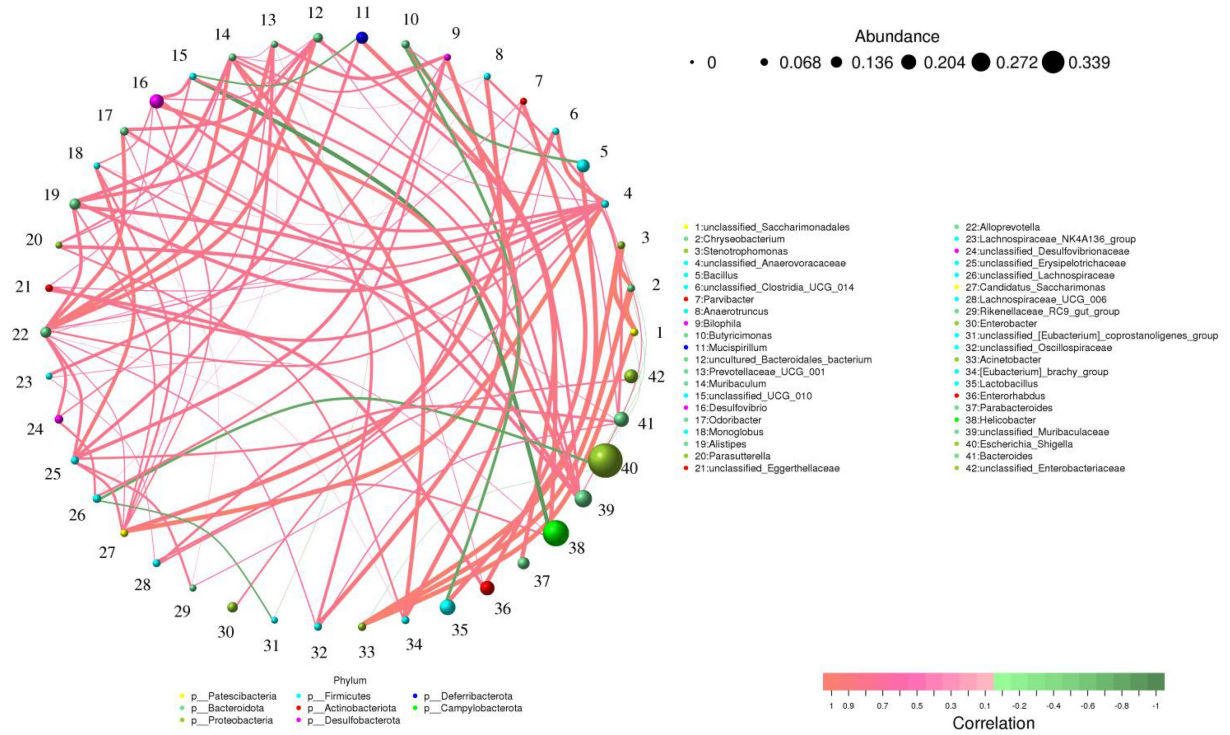

FIGURE 6
Correlation network analysis of gut microbiota. The green and red lines indicate the negative and positive correlation, respectively.

hexavalent chromium exposure on host health. Meanwhile, maintaining the homeostasis of gut microbiota may be one of the ways that seaweed polysaccharides exert their pharmacological effects.

Data availability statement

The original sequence data was submitted to the Sequence Read Archive (SRA) (NCBI, USA) with the accession no. PRJNA902534.

Ethics statement

The animal study was reviewed and approved by the study was conducted under the guidance and approval of the Animal Welfare and Ethics Committee of Henan university of Animal Husbandry and Economy.

Author contributions

JM, ZG, and XM provided the idea. XiuW, XueW, YF, and XL contributed reagents, materials, and analysis tools. JM wrote the manuscript. XueW, YF, XL, FZ, GH, and XM revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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