Drugs and Alcohol Addiction

RESEARCH ARTICLE

Effect of Chinese Flavor Liquor and its Extract Consumption on Mice Gut Microbiota

Jingyi Hong[1,2], Qichan Gao[2], Shanshan Li[2], Bei Jiang[2], Guohao Zhang[2], Pingchang Yang[1,2], Zhigang Liu[1,2*]

[1]Department of Allergy, the Third Affiliated Hospital of Shenzhen University, Shenzhen, 518020, China.
[2]The Research Center of Allergy & Immunology, Shenzhen University School of Medicine, Shenzhen, 518060, China.

Abstract

Chinese flavor liquor (CFL) plays an important role in Chinese culture and people's daily lives. It is the first choice of most Chinese residents when drinking liquor, so the health problems of CFL consumption should be paid attention to. Gut microbiota plays a key role in host physiology and metabolism. Although alcohol feeding has been proved to produce evident intestinal microbial changes, most of these studies focus on pure ethanol (EtOH), and no comparative study of flavor liquor has been carried out, ignoring the role of the trace components in flavor liquor. In this study, different doses of EtOH, CFL and the extract from CFL were given to C57BL/6 mice by gastric perfusion for 3 weeks consecutively. The fecal samples were collected and the effects of EtOH, CFL and CFL extract on gut microbiota composition changes were analyzed using 16S rRNA method. Results revealed that mice fed with CFL extract had increased the richness and diversity of gut mirobiota compared to mice in normal control group. CFL extract also improved the proportion of intestinal probiotics such as *Lactobacillus and Bifidobacterium*. 3-weeks consumption of EtOH can alter gut bacterial communities, decrease the relative abundance of *Lactobacillus, Bifidobacterium* and *Akkermansia,* while increase the relative abundance of *Clostridium* in *a d*ose-dependent manner. The effect of CFL on the composition of gut microbiota was different from that of EtOH at middle and low doses.This might be contributed to the trace components in CFL. Therefore, the effects of molecular components in CFL extract on gut microbiota deserve further investigations.

Keywords: Chinese flavor liquor, Ethanol, Gut microbiota, Probiotics, and 16sRNA.

Introduction

Chinese flavor liquor (CFL), also known as Baijiu, is the national liquor of China and possesses a unique position in traditional Chinese culture. CFL is a clear and transparent fermented alcoholic beverage with a high ethanol (EtOH) content ranging from 38 to 65 vol%.[1] The strong alcoholic beverage is normally consumed straight by Chinese people, so the health problems of drinking excessive of CFL should be concerned. At the same time, the raw material, production process and the taste of CFL are different from those of other distilled spirits. For CFL production, jiuqu is mixed with grains to saccharify and ferment simultaneously, which produces EtOH and flavor compounds. [2] Therefore, CFL is rich in many flavor compounds, including organic acids, esters, phenols, terpenes, aromatic compounds, etc. [3,4] Furthermore, CFL also contains potential functional components, which are beneficial to humans, such as amino acids [5] and peptides. [6] Although excessive alcohol consumption has been proved to produce a variety of serious health problems, including alcoholic liver disease (ALD), [7] cirrhosis, [8] cancers [9] and neurologic impairment, [10] most of these studies only focus on pure EtOH, and no comparative study of CFL has been carried out, ignoring the role of the trace components in CFL.

Another potential and related health impact of alcohol ingestion may be on the gut microbiota. Alteration of the gut microbiota has been observed in many diseases, such as ALD, [11] irritable bowel syndrome, [12] food allergies [13] and so on. Accumulating studies have revealed that intestinal microbiome dysbiosis are common in patients who are abused in alcohol. The intestinal microbiome dysbiosis results in the translocation of bacteria and bacterial products. [14,15] These bacterial products may further induce intestinal inflammation. With the increasing rate of CFL consumption in China, the effect of different doses of CFL and the trace elements in CFL on gut microbiota and intestinal inflammation remain to be investigated. In this study, different doses of EtOH, CFL and CFL extract were given to C57BL/6 mice by gastric perfusion for 3 weeks consecutively. The intestine tissues and fecal samples were collected. 16S rRNA method was carried out to analyze their effects on gut microbiota composition changes, investigating the differences between EtOH and CFL at the same degree. This study may guide residents drinking CFL rationally and provide more information for CFL producers to improve their technology in order to produce high-quality CFL.

Correspondence to: Zhigang Liu, PhD, Research Center of Allergy & Immunology, Shenzhen University School of Medicine.Room A7-509 in Xili Campus, Shenzhen University School of Medicine. 1066 Xueyuan Road, Shenzhen 518055, China. Tel:+852-86671907 E-mail: lzg195910[AT]126[DOT]com

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Materials and methods

Preparation of CFL extract without EtOH

Chinese flavor liquor (53%, EtOH, v/v) was supplied by Kweichow Moutai Co.Ltd (Guizhou, China). 50 mL of CFL were added to 50 mL plastic centrifuge tubes, and allowed to evaporate at room temperature for 7 days. Approximately 10 mg CFL *extract* was left after evaporation. CFL extract was stored at 4 °C in the dark until examined.

Animals and experimental design

6-8 weeks old female C57BL/6 mice were housed in a specific-pathogen-free and environmentally controlled room with constant temperature (22±1°C), humidity (55-60%) and a 12-hour light-dark cycle and were free to access standard diet and water. The animal studies were carried out in accordance with the Institutional Guidelines for Animal Care and Use of Laboratory Animals at Shenzhen University and approved by the Animal Ethic Committee at Shenzhen University.

During the one-week acclimation period, the mice were fed a rodent chow diet and water. The mice were then randomly divided into CFL group, EtOH group, CFL extract group (1.35 mg/kg) and normal control (NC) group. CFL and EtOH groups were divided into high, middle and low-dose groups (7.5mL/kg、5.0mL/kg、2.5mL/kg), respectively (n=6). All the mice were fed once every day continuously for 3 weeks. Body weight was recorded every other day during the experiment.

Determination of inflammatory factors in small intestine

The animals were euthanized with ether inhalation after fasting for 12 h. Small intestine tissues were lysed in RIPA buffer (Beijing Solarbio Science & Technology Co., Ltd) with proteinase inhibitors phenylmethanesulfonyl fluoride (PMSF) and homogenized using a tissue grinder (SCIENTZ-48, Ningbo Xingzhi Biotechnology Co, Ltd, China). Then the mixture was centrifuged at 10000 g for 5 min to collect the supernatant. Protein concentration of each sample was determined using BCA reagents (Thermo Scientific). Levels of cytokines interleukin-6 (IL-6), interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) in the intestinal tissue extracts were determined according to the instructions of the ELISA kit (Sino Biological, Beijing, China). The protein extracts were diluted to 1mg protein/mL. All biochemical indices were determined using an ELx808 absorbance microplate plate reader (BioTek, Shanghai, China).

DNA extraction, amplification and sequencing

After the last feeding, the fecal samples were collected and stored at -80°C. The total DNA from fecal samples was extracted by reported method [16]. The 16s rRNA was amplified and sequenced on the Ion Torrent Personal Genome Machine as reported in previous study [17].

Bioinformatic analysis

The data was treated with in-house pipeline developed based on motor v.1.33.3. [18] The community structure was calculated based on the membership and relative abundance of taxonomic groups in the sample. In this study, the Permutational multivariate analysis of variance (PERMANOVA) was used to assess the effect on operational taxonomic units (OTUs) profiles. A two-tailed Wilcoxon rank-sum test was used in the profile to identify the different OTUs and KEGG Orthologs (KOs). In addition, we used PICRUSt [19] to produce predicted KOs from the 16s rRNA gene sequence data.

Statistical analysis

Data are expressed as mean±SD. Statistical analysis was performed with SPSS 19.0 statistics software. Both Student's t test and ANOVA two ways test were used to evaluate the differences between groups, and $P < 0.05$ or less was considered significant.

Results and Discussions

The alpha-diversity change of gut microbiota

Chao [16, 20] are usually used to compute community richness; the higher score, the more richness. Simpson metrics are commonly used to calculate community diversity [21]. The higher Simpon index indicates the lesser community diversity. We used these two kinds of alpha diversity parameters to compare the microbiologic species richness and diversity changes (Figure 1). Student's t-test showed that the Chao

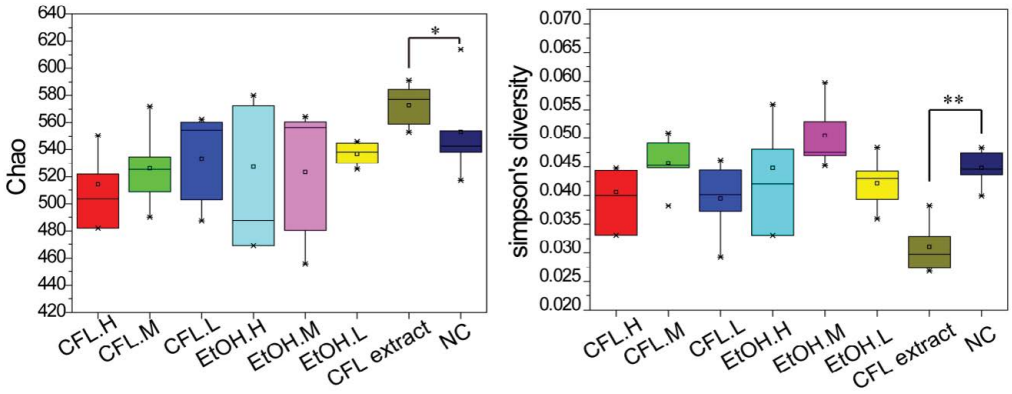

Figure 1: CFL extract increased the richness and diversity of gut microbiota. Alpha diversity of CFL, EtOH, CFL extract and NC groups was demonstrated in boxplot. L, M, H represents for low-dose group, middle-dose group and high-dose group, respectively. Chao, simpson are two kinds of alpha diversity metrics. *p < 0.05, **p < 0.01 when compared with NC group. CFL and EtOH ingestion altered gut bacterial communities in mice.

index of CFL extract group was higher than that of NC group ($P<0.05$). The simpson index of CFL extract group was significantly lower than that of NC group ($P<0.01$). There were no significant differences in Chao and Simpon index between CFL and EtOH treated group. The above results indicated that daily administration of CFL extract can increase the richness and diversity of gut microbiota. The alternation of the gut microbiota diversity was correlate with some diseases [22]. For example, low-diversity microbiota, with increases in proportions of facultative anaerobes, has been observed with liver disease [23, 24]. On the contrary, the high diversity of gut microbiota might maintain the stable environment of intestine and protect the liver from the attack of endotoxin and bacteria.

CFL and EtOH ingestion altered gut bacterial communities in mice

The principal component analysis (PCA) gives a measure of bacterial genus community relatedness so that the samples with similar bacterial communities are localized in similar positions in the diagram. As shown in Figure 2, PCA based on the relative abundance of OTUs showed that even low-dose of CFL and EtOH exposure were divergent in comparison to NC group on the basis of the first two principal component (PC) scores, let alone middle and high-dose of groups. Meanwhile, low-dose of alcohol exposure, no matter CFL or EtOH, are quite different from middle and high-dose groups in the composition of bacterial communities. Significance of the structural shift of gut microbiota in the progression of diseases has been highlighted by several recent publications. Alterations of gut microbiota have been suggested to occur in Crohn's disease patients, [25] ulcerative colitis patients, [26] infants suffering from allergic inflammation, etc. [27] Fecal samples of CFL extract group and NC group showed similar bacterial communities, which are localized in similar positions.

Effects of CFL, EtOH and CFL extract on the intestinal microbial composition

The taxonomic structure was calculated based on the relative abundance of OTUs. We found that the *Bacteroidetes* and *Firmicutes* are two major bacterial phyla of the gut microbiota in all the groups. CFL and EtOH high-dose treated groups showed an obvious decrease in *Bacteroidetes* (Figure 3). The

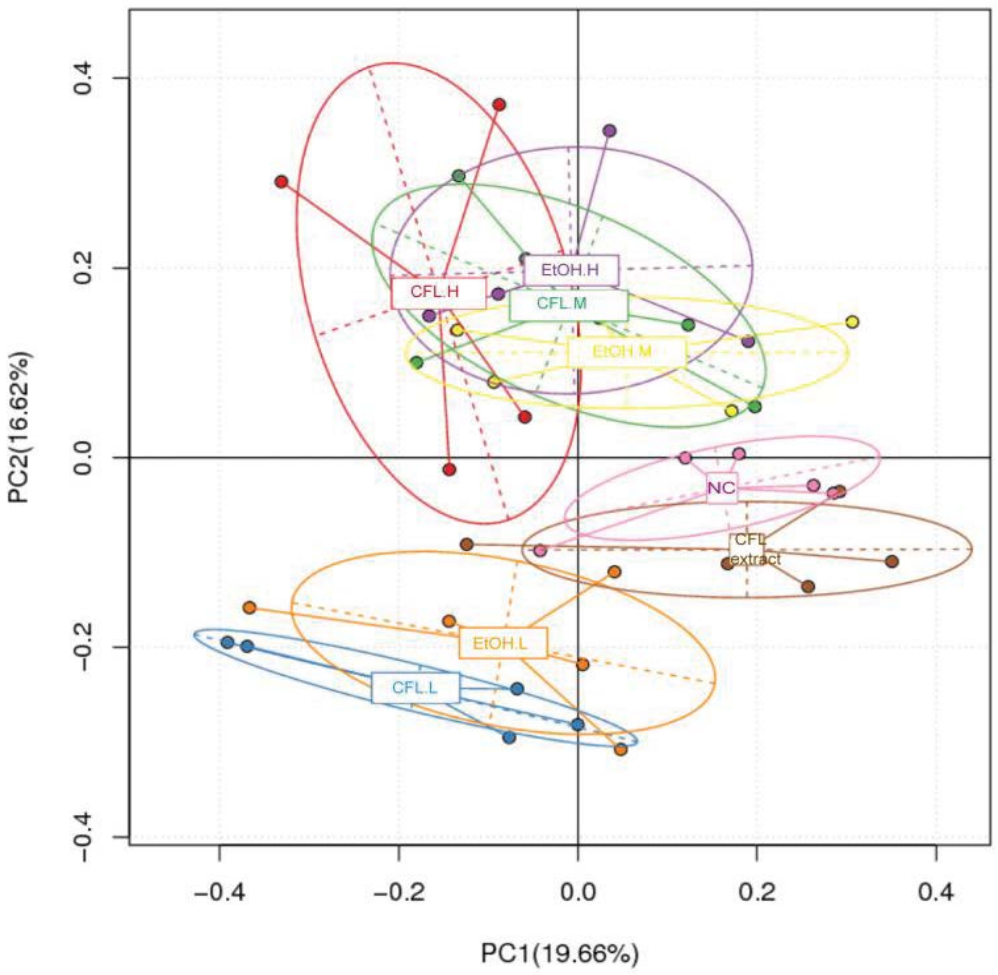

Figure 2: Principal component analysis (PCA) scores plot based on the relative abundance of OTUs (97% similarity level). L, M, H represents for low-dose group, middle-dose group and high-dose group, respectively. The samples from NC group and alcoholic groups (CFL and EtOH) show a clear separation in OUT levels, demonstrating an obviously difference in the bacterial community.

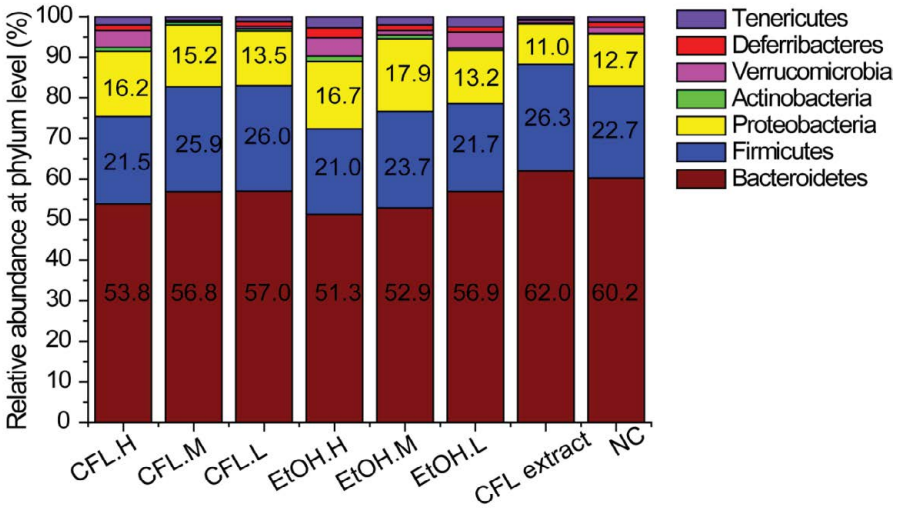

Figure 3: The relative abundance of bacteria phylum. The phylum abundance is indicated by the color bars. The exact percentage of Bacteroidetes, Firmicutes and Proteobacteria's relative abundance is given by the numbers on the bars.

effects of alcohol on fecal Bacteroidetes are not constant. *Bull-Otterson et al* [28] reported that the abundance of *Bacteroidetes* was decreased while *Yan et al* [29] reported a relative increase of *Bacteroidete* after the ingestion of alcohol. This discrepancy might depend on the different methods of alcohol feeding. An expansion of *Proteobacteria* and *Actinobacteria* phyla was also observed in CFL and EtOH groups in a positive dose-dependent manner. *Proteobacteria* and *Actinobacteria* phyla were reported to play a pathogenic role in the development of ALD. Our result was in parallel with the previous reports. [28, 29] However, the phylum *Proteobacteria* decreased in CFL extract group compared with NC group (11.017 vs 12.744, $p<0.05$). There were no significant differences in *Bacteroidetes* and *Actinobacteria* between CFL extract group and NC group.

The distribution of gut bacterial family and genus was shown in Table 1. With the increasing dose of CFL and EtOH, the proportion of *Porphyromonadaceae* and *Bacteroidaceae* decreased. It has been reported that *Porphyromonadaceae* was negatively correlated with TNF-α expression in the liver in ALD. [30] *Mutlu et al.* reported that the mean abundance of *Bacteroidaceae* was significantly decreased in the alcoholic groups compared with the healthy controls, [31] which was in consistent without study. However, CFL extract group

Table 1: Effects of CFL, EtOH and CFL extract on changes of fecal microbial composition in family and genera levels

Bacterial targets	Relative Abundance (%)							
	NC	CFL.H	CFL.M	CFL.L	EtOH.H	EtOH.M	EtOH.L	CFL extract
Family								
Porphyromonadaceae	47.044	37.323	41.079	49.697	33.644	40.267	45.809	49.826
	±	±	±	±	±	±	±	±
	5.991	9.898	8.417	11.102	5.447*	6.243	14.264	7.121
Bacteroidaceae	2.949	1.089	1.582	2.202	0.674	1.104	1.121	5.905
	±	±	±	±	±	±	±	±
	0.588	0.260*	0.124	1.073	0.095**	0.138*	0.332*	1.907*
Genus								
Clostridium	0.020	0.142	0.085	0.028	0.441	0.090	0.425	0.012
	±	±	±	±	±	±	±	±
	0.005	0.106*	0.037	0.025	0.133***	0.062**	0.246***	0.009
Akkermansia	4.294	0.626	1.185	4.223	0.093	0.662	1.477	6.763
	±	±	±	±	±	±	±	±
	1.200	0.586**	0.245*	1.475	0.059***	0.607**	0.740*	1.265
Lactobacillus	3.155	1.213	1.865	2.079	1.085	1.254	1.690	4.530
	±	±	±	±	±	±	±	±
	0.189	0.466*	0.459	0.730	0.731*	0.221*	0.716	0.842*
Bifidobacterium	0.829	0.361	0.305	0.749	0.125	0.332	0.420	1.850
	±	±	±	±	±	±	±	±
	0.111	0.294	0.082	0.355	0.058*	0.109	0.241	0.178**

Data are presented as the means ± SD (n = 6). L, M, H represents for low-dose group, middle-dose group and high-dose group, respectively. *p < 0.05, **p < 0.01, ***p < 0.001 when compared with NC group.

exhibited an increased level of *Porphyromonadaceae* (not significant) and *Bacteroidaceae* (5.90% vs 2.92%, P<0.05) compared with NC group.

Further analysis also revealed that CFL, EtOH and CFL extract treatment resulted in a change in fecal microbiota composition at genus level. Table 1 showed that *Lactobacillus* (4.53% vs 3.16%, P<0.05) *and Bifidobacterium* (1.85% vs 0.83%, P<0.01) were prominent in CFL extract treated group compared to NC group. *Lactobacillus and Bifidobacterium* were defined as probiotics for their health-promoting properties. [32, 33] Kirpich et al. found that *Lactobacillus and Bifidobacterium* restored the bowel flora and improved liver enzyme in human alcohol-induced liver injury. [34] Forsyth et al. also reported that *Lactobacillus* treatment ameliorated alcohol-induced intestinal oxidative stress, gut leakiness and liver injury in a rat model. [35] These results suggest that CFL extract may possess prebiotic potential effects. However, EtOH exposure decreased the abundance of *Lactobacillus and Bifidobacterium* in a dose-dependent manner, which is consistent with previous study and clinical study. [36, 37] The relative abundance of *Lactobacillus* also decreased in CFL groups, but there were no significant differences between middle/low-dose exposure group and NC group. *Clostridium* increased much more in EtOH groups than CFL groups. It has been reported that *Clostridium* was a kind of disease-associated bacteria. The shifts and an overgrowth of *Clostridium* in the gut have been associated with increased intestinal permeability, contributing to increased endotoxin levels [38] and the pathogenesis of alcohol-related diseases. [39] *Akkermansia* decreased significantly in EtOH groups compared to NC group, but not in CFL low-dose group (4.22% vs 4.59%, P>0.05). The loss of *Akkermansia* was defined as as an early marker of alcohol-induced changes in the gut microbiome in previous studies. [40] Besides, *Akkermansia* has also been found to decrease the obesity and type-2 diabets in mouse models. [41]

Changes of body weight and inflammatory factors levels in small intestine

During the experiments, the mice body weight change in each group was measured to compare the toxicity of EtOH and CFL (Figure 4A). The body weight change curves for mice in CFL extract group, low-dose group (2.5 mL/kg) of CFL and EtOH groups were similar to that of NC group, suggesting good tolerance and less harm. The mice in middle-dose group (5 mL/kg) of CFL group displayed continuous weight increase in time. However, mice that received 5 mL/kg of EtOH experienced a severe weight loss and then recovered, indicating a potential toxicity. The mice in high-dose group (7.5 mL/kg) of EtOH group experienced continuous weight loss, dropping to only 0.73 times their starting body weight. While the mice weight in 7.5 mL/kg of CFL group almost kept the same as the first day.

Chronic inflammation develops with excessive and uncontrolled production of pro-inflammatory cytokines,

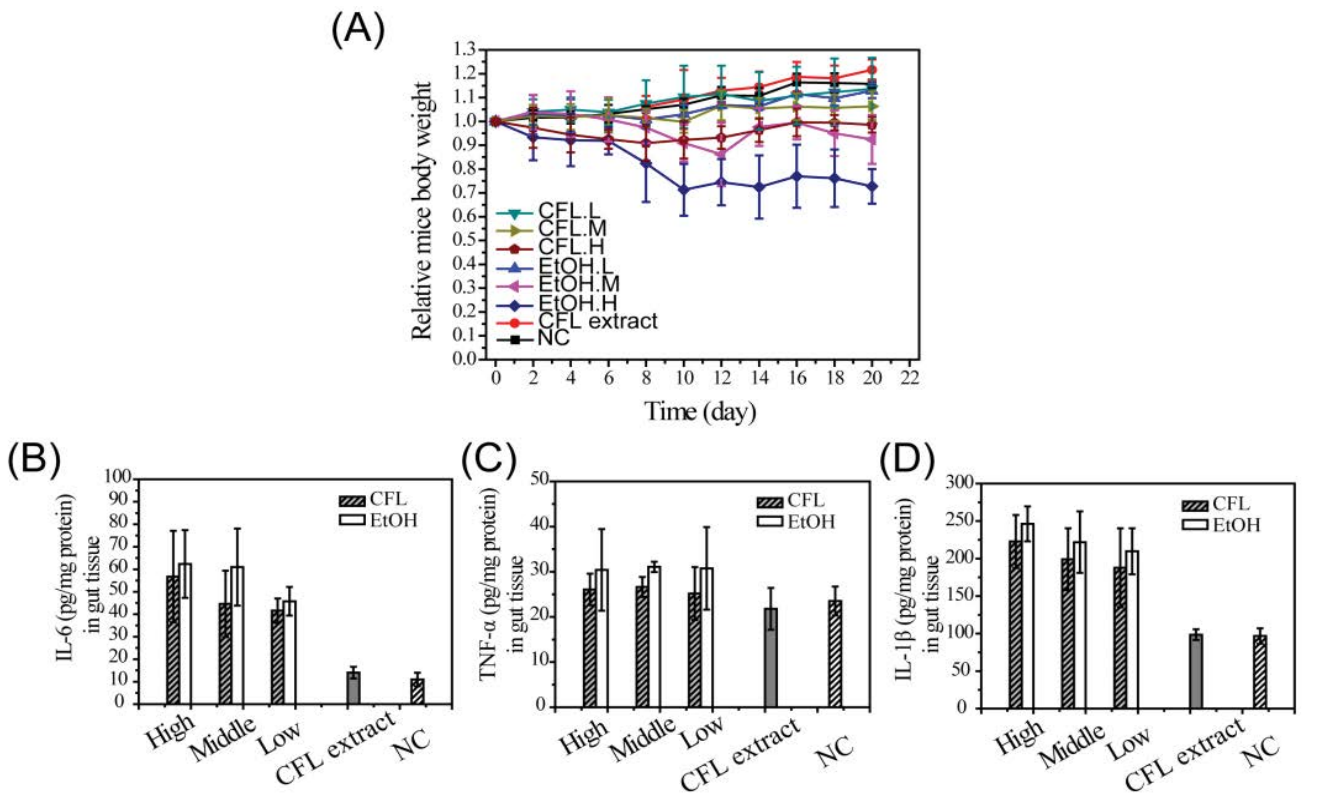

Figure 4: Effect of CFL and EtOH consumption on body weight changes and inflammatory factors levels in mice. (A) Mice body weight changes; (B) intestinal IL-6 level; (C) intestinal TNF-α level; (D) intestinal IL-1β level. L, M, H represents for low-dose group, middle- dose group and high-dose group, respectively. Data are presented as mean±SD.

such as IL-6, TNF-α, IL-1β. As illustrated in Figure 4B-4D, CFL extract group remained similar inflammatory factors levels with NC group. Intestinal IL-6 and IL-1β levels of both EtOH and CFL groups were remarkably increased at all doses compared with NC group ($P<0.001$), indicating the intestine inflammation. Compared with EtOH group, CFL group induced lower level of pro-inflammatory cytokines, but there were no significant differences in these groups. This discrepancy might be contributed to the improved abundance of intestinal probiotics induced by the trace compounds in CFL, but the effects are not obvious.

In summary, our study found that CFL extract ingestion can increase the richness and diversity of gut microbiota. CFL and EtOH ingestion altered gut bacterial communities in mice. An expansion of *Proteobacteria* and *Actinobacteria* phyla was observed in CFL and EtOH groups in a positive dose-dependent manner. CFL extract treatment enhanced the relative abundance of probiotics known to be beneficial to the host, such as *Lactobacillus and Bifidobacterium* while CFL and EtOH exposure decreased the relative abundance of *Lactobacillus and Bifidobacterium* in a dose-dependent manner. But there were no significant differences between CFL groups at middle/low-doses compared with NC group. Moreover, CFL groups induced lower level of pro-inflammatory cytokines compared with EtOH groups, although there were no significant differences. These results might be contributed to some beneficial trace components in CFL. For example, Geranials, β-Caryophyllene, E-nerolidol and linaloo were significant odor active terpenes in Maotai, which was one of the famous CFL. [42] The pathogenic gut bacteria like *Clostridium* could be inhibited by geraniol in vitro. But beneficial commensal colonic bacteria like *Lactobacillus and Bifidobacterium* were less affected. [43, 44] β-Caryophyllene, E-nerolidol, linalool were also reported to have great potential of selective anti-bacterial properties. [45-47] They can play a beneficial role to increase the relative abundance of probiotics. Furthermore, CFL contains amino acids and peptides, which are beneficial to humans. A tetrapeptide (Ala-Lys-Arg-Ala) and tripeptide (Pro-His-Pro) have been identified in CFL and showed preventive effects against oxidative stress and antihypertensive activity. [48] These flavor compounds in CFL extract may contribute to maintain intestinal homeostasis and decrease the susceptibility to bacterial endotoxins. Therefore, the effects of molecular components in CFL extract on gut microbiota and human health deserve further investigations.

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Disclosure

The authors report no conflicts of interest in this work.

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