Drug Design, Development and Therapy

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Effects of ondansetron and [6]-gingerol on pica and gut microbiota in rats treated with cisplatin

This article was published in the following Dove Press journal:
Drug Design, Development and Therapy

Xiaodi Feng[1,*]
Qianqian Cheng[1,*]
Qi Meng[2]
Yanhong Yang[3]
Ke Nie[1]

[1]School of Chinese Materia Medica, Guangdong Pharmaceutical University, Guangzhou 510006, People's Republic of China; [2]School of Chinese Medicine, Shandong University of Traditional Chinese Medicine, Jinan 250355, People's Republic of China; [3]The First Affiliated Hospital (School of Clinical Medicine), Guangdong Pharmaceutical University, Guangzhou 510080, People's Republic of China

*These authors contributed equally to this work

Purpose: [6]-gingerol is one of the main components of ginger with many biological activities. In this study, the effects of ondansetron and [6]-gingerol on pica and gut microbiota in rats injected with cisplatin were evaluated.

Materials and methods: Rat model of cisplatin-induced pica was established, and the effects of ondansetron and [6]-gingerol on the gut microbiota were further studied by 16S rDNA gene analysis.

Results: The results showed that the total intake of kaolin of the rats injected with cisplatin was significantly increased, and treatment of ondansetron and [6]-gingerol in advance could significantly ameliorate the pica induced by cisplatin. The body weight of the rats injected with cisplatin was decreased compared with the control group. The 16S rDNA gene analysis has shown that ondansetron, [6]-gingerol and cisplatin could increase the relative abundance of *Bacteroidetes* and decrease *Firmicutes* on phylum level.

Conclusion: [6]-gingerol was as effective as ondansetron in the treatment of pica induced by cisplatin in rats, and it seemed that [6]-gingerol had the potential to ameliorate the alteration of gut microbiome, but it needs further study.

Keywords: [6]-gingerol, ondansetron, kaolin, pica, gut microbiota, cisplatin

Introduction

Chemotherapy-induced nausea and vomiting (CINV) are the most common adverse reactions of chemotherapy, which seriously influenced the quality of cancer patients' life, even reduced their compliance with chemotherapy. For example, cisplatin is a widely used chemotherapeutic agent due to its affinity for DNA. Despite its anti-cancer activities, cisplatin has several toxicities such as ototoxicity, neurotoxicity, nephrotoxicity and nausea/emesis.[1] Most of the patients experience acute or delayed nausea and vomiting after cisplatin treatment. Therefore, it is urgent to develop effective medicines to deal with chemotherapy-induced emesis.

Chemotherapeutic medicine, such as cisplatin, could also lead to intestinal mucositis and microbiota dysbiosis, and it has been reported that cisplatin could result in high relative abundances of *Deferribacteres* and *Proteobacteria* and the diversity of the microbiota was reduced.[2] Gui et al reported that cisplatin combined with ABX (vancomycin, ampicillin, and neomycin) could destroy the microflora of the Lewis lung cancer mouse model, while probiotics cotreatment could enhance the anti-cancer effects of cisplatin.[3] To study the alterations and mechanisms of gut microbiota after chemotherapy treatment could help to find new methods to prevent and reduce CINV and other chemotherapy-related adverse reactions.

Correspondence: Yanhong Yang
The First Affiliated Hospital (School of Clinical Medicine), Guangdong Pharmaceutical University, Nong-Lin-Xia Road 19#, Yue-Xiu District, Guangzhou 510080, People's Republic of China
Tel +86 203 935 3115
Fax +86 203 935 2606
Email 1764941457@qq.com

Ke Nie
School of Chinese Materia Medica, Guangdong Pharmaceutical University, 280 Waihuan East Road, Panyu District, Guangzhou 510006, People's Republic of China
Tel +86 203 935 2557
Email nicknk@hotmail.com

submit your manuscript | www.dovepress.com
DovePress
http://doi.org/10.2147/DDDT.S211845

Ondansetron is a kind of 5-HT3R antagonists, and widely used in the treatment of nausea and vomiting of chemotherapy.[4] It has been shown that a single oral dose of ondansetron could reduce the recurrent vomiting of children with acute gastroenteritis.[5] Ondansetron is also used in the treatment of nausea and vomiting during pregnancy, so it is important to know the accurate safety information about its use during pregnancy.[6] Natural compounds have many biological and pharmaceutical activities, characterized by high safety, availability, accessibility and low cost, and have been widely used in the treatment of many diseases, such as inflammation and tumors.[7] Ginger (*Zingiber officinale*) is an ancient spice, normally used as flavoring agent for food, and is listed on the FDA's "generally regarded as safe" list.[8] [6]-Gingerol, a major component of *Zingiber officinale*, has several biological and pharmaceutical activities. It has been reported that [6]-gingerol could decrease cardiomyocyte apoptosis and ameliorate myocardial ischemia/reperfusion (I/R) injury.[9] [6]-Gingerol also exhibits anticancer effects, and it can enhance the cisplatin sensitivity of gastric cancer cells by inhibition of proliferation, migration and invasion.[10] Ginger and its extracts have also been widely used in treatment of gastrointestinal discomfort such as diarrhea, dyspepsia, nausea, and vomiting.[11,12] However, since some results about ginger are controversial,[11,12] the mechanism of ginger's anti-emetic effect is not clear yet, and needs further study.

Pica is the behavior characterized by the consumption of non-nutritional substances such as kaolin (china clay), and pica induced by some substance such as cisplatin in rats can be used as model for nausea and vomiting.[13,14] In the current study, the vomiting model of rats was established by intraperitoneal injection of cisplatin, and the effects of ondansetron and [6]-gingerol on nausea and vomiting were checked by assessing the amount of kaolin intake as the index of vomiting degree. In addition, effects of ondansetron and [6]-gingerol on gut microbiota were also investigated. The above results may improve our understanding of the functions and mechanisms of [6]-gingerol, and help to assess [6]-gingerol as a complementary and alternative medicine for treatment of CINV.

Materials and methods

Preparation of kaolin pellets

The 2% Arabic gum solution was slowly added into the kaolin powder (China Pharmaceutical Chemical Reagents Company, China), stirred to thick paste, and shaped into pellets similar to the rats' normal laboratory diet, then dried at room temperature.

Animal treatment

All the animal experiments were approved by the Committee on Laboratory Animal Care and Use of Guangdong Pharmaceutical University (Guangzhou, China), in accordance with the National Institutes of Health guide for the care and use of laboratory animals. The SD rats (200–230 g) (purchased from the Laboratory Animal Center of Guangzhou University of Chinese Medicine, Guangzhou, China) were housed in a temperature-controlled room (23±2°C), and the relative humidity was 50%±10%. The ventilation was good and the alternating time of day and night was 12 hrs/12 hrs. The rats had free access to standard diet and water.

Measurement of kaolin consumption and drug administration

The kaolin pellets were introduced into the rats 3 days prior to drug administration. Most of the rats did not take kaolin anymore on the third day, and the rats that were still interested in kaolin were excluded. The rest rats were randomly divided into six groups and each group had 6 rats. Group 1 was the normal control group (Con); group 2 was the rats treated with ondansetron (the ondansetron control group, O-con); group 3 was the rats treated with [6]-gingerol (the [6]-gingerol control group, G-con); group 4 was the cisplatin model group (Model); group 5 was the rats treated with ondansetron before injection of cisplatin (the ondansetron-treated model group, O-treated); group 6 was the rats treated with [6]-gingerol before injection of cisplatin (the [6]-gingerol-treated model group, G-treated).

On the day of drug administration, the ondansetron control group and the ondansetron-treated model group were given ondansetron (1.3 mg/kg (body weight), Qilu Pharmaceutical Company, China) by gavage, respectively. The [6]-gingerol control group and the [6]-gingerol-treated model group were given [6]-gingerol (25 mg/kg (body weight), Chengdu Must Biotechnology Company, China) by gavage, respectively. The control group and the cisplatin model group were given vehicle of 3% Tween-80 by gavage. After 1 hrs, the cisplatin model group, the ondansetron-treated model group and the [6]-gingerol treated model group were injected intraperitoneally (i.p.) with cisplatin (Qilu Pharmaceutical Company) at the

concentration of 6 mg/kg (body weight), and the other groups were injected i.p. with saline of equal volume.

The general conditions of rats were closely observed every day, including activities, fur, appetite, breath and stool. The weight and kaolin intake of rats were measured every 24 hrs, and recorded until 24 hrs after the establishment of the model.

16S rDNA gene analysis

After cisplatin modeling for 24 hrs, fecal samples were collected, genomic DNA was extracted, and the V3+V4 region of 16S rDNA was amplified. Then, the product of PCR amplification was collected by gel cutting and quantified by Life Invitrogen Qubit 3.0 fluorometer. The purified-amplified products were mixed in equal amount, connected with sequencing connectors, and the sequencing libraries were constructed. Fecal bacterial DNA extraction, 16S rDNA gene PCR amplification, sequencing and analysis were carried out by Gene Denovo Biotechnology Company (Guangzhou, China).

Statistical analysis

Statistical differences were determined by using SPSS 23.0 software (SPSS Inc., Chicago, IL, USA). Data were expressed as mean ± SE Two-way ANOVA was performed when more than two groups were compared, *P*-value <0.05 was considered to be significant.

Results

Effect of ondansetron and [6]-gingerol on cisplatin-induced kaolin ingestion

On the first day of kaolin release, almost all rats took kaolin, and then the amount of kaolin intake gradually decreased. At the fourth day, almost all animals did not take kaolin anymore. After injected intraperitoneally of cisplatin, the total intake of kaolin in the model group was significantly higher than that of the control group ($P<0.001$). The intake of kaolin in the ondansetron and [6]-gingerol treated groups was decreased in varying degrees 24 hrs after modeling ($P<0.05$), indicating that both ondansetron and [6]-gingerol can ameliorate pica induced by cisplatin in rats. The data are shown in Table 1.

After cisplatin injection, the body weight of rats in the model group, the ondansetron and [6]-gingerol treatment group was decreased significantly ($P<0.05$) (Table 2). There was no significant difference of the body weight between the model group and the ondansetron and [6]-gingerol treated groups, indicating that ondansetron and [6]-gingerol had no significant effect on the body weight of cisplatin-treated rats (Table 2).

Overview of the 16S rDNA gene analysis

To investigate the effects of ondansetron and [6]-gingerol on the gut microbiota of cisplatin-treated rats, 16S rDNA gene analysis was conducted. The total tags and operational taxonomic units (OTUs) of each group were shown in Table 3. The Ace and Chao index (showing the richness of bacteria) and the Shannon and Simpson index (showing the diversity of bacteria) are also demonstrated in Table 3. The Shannon rarefaction curves for each group have reached the saturation plateau, indicating that the samples had enough sequence coverage (Figure 1A). The Venn diagram showed that there were 805 common OTUs in the 6 groups of rats (Figure 1B–C).

The effects of ondansetron and [6]-gingerol on gut microbiome of cisplatin-treated rats

Figure 2A is the box diagram of Chao index, and Figure 2B shows the principal coordinates analysis,

Table 1 Effects of ondansetron and [6]-gingerol on kaolin consumption in cisplatin-treated rats

	($\bar{x}$±SE, g)			
	−48 hrs	−24 hrs	0 hr	24 hrs
Con	0.272±0.069	0.076±0.046	0.011±0.001	0.024±0.005
O-con	0.379±0.098	0.135±0.099	0.020±0.014	0.027±0.003
G-con	0.196±0.082	0.113±0.078	0.010±0.002	0.017±0.004
Model	0.364±0.170	0.072±0.032	0.022±0.013	0.547±0.119^{aaa}
O-treated	0.485±0.123	0.171±0.033	0.025±0.009	0.195±0.084^{b}
G-treated	0.503±0.101	0.134±0.027	0.034±0.007	0.210±0.098^{b}

Notes: $^{aaa}P<0.001$, compared with Con, $^{b}P<0.05$, compared with model. Cisplatin (6 mg/kg (weight), i.p.) was administered at t=0.

Abbreviations: Con, the normal control group; O-Con, the rats treated with ondansetron; G-con, the rats treated with [6]-gingerol; Model, the rats injected intraperitoneally with cisplatin; O-treated, the ondansetron-treated model group; G-treated, the [6]-gingerol-treated model group.

Table 2 Effects of ondansetron and [6]-gingerol on body weight of cisplatin-treated rats

	($\bar{x}$ ±SE, g)			
	−48 hrs	−24 hrs	0 hr	24 hrs
Con	239.57±5.94	247.08±6.17	253.17±6.23	262.08±5.77
O-con	239.48±5.80	247.48±6.34	254.25±7.08	264.93±6.09
G-con	237.23±4.96	243.97±5.46	251.17±5.88	262.65±6.02
Model	244.20±4.03	250.07±4.59	255.33±4.37	240.80±4.34[a]
O-treated	240.35±3.68	247.47±4.32	253.03±4.79	239.72±3.54[a]
G-treated	233.65±6.00	242.32±5.70	247.82±5.37	237.27±5.47[a]

Notes: [a]$P<0.05$, compared with Con . Cisplatin (6 mg/kg (weight), i.p.) was administered at t=0.
Abbreviations: Con, the normal control group; O-Con, the rats treated with ondansetron; G-con, the rats treated with [6]-gingerol; Model, the rats injected intraperitoneally with cisplatin; O-treated, the ondansetron-treated model group; G-treated, the [6]-gingerol-treated model group.

Table 3 Diversity estimation of the 16S rDNA gene library of the rats from the sequencing

Groups	Total tags	OTUs	Chao	Ace	Shannon	Simpson
Con	174,026±7358	1475±35	2042.06±56.24	2033.43±47.55	6.48±0.06	0.96±0.00
O-con	147,637±6760	1334±36	1860.08±63.12	1839.85±59.76	5.48±0.29	0.87±0.02
G-con	150,682±5433	1393±21	2032.71±34.71	1975.16±40.75	6.17±0.17	0.94±0.01
Model	128,393±5022	1318±31	1855.02±40.80	1829.92±37.17	6.37±0.20	0.96±0.01
O-treat	113,317±2810	1273±28	1848.81±37.18	1826.19±45.25	6.06±0.21	0.93±0.01
G-treat	112,045±4851	1184±103	1721.70±134.29	1697.2±123.03	6.24±0.24	0.96±0.00

Abbreviations: Con, the normal control group; O-Con, the rats treated with ondansetron; G-con, the rats treated with [6]-gingerol; Model, the rats injected intraperitoneally with cisplatin; O-treated, the ondansetron-treated model group; G-treated, the [6]-gingerol-treated model group; OTUs, operational taxonomic unit.

indicating that there was obvious difference between the 6 groups of gut microbiome.

Figure 2C–D demonstrated the relative abundance of gut microbiota on phylum level and *Bacteroidetes, Firmicutes* and *Proteobacteria* had high abundance in all the samples. The abundance of *Bacteroidetes* was increased in the ondansetron control group, the ondansetron-treated model group and the model group ($P<0.05$) (Figure 2D). The abundance of *Bacteroidetes* was also elevated in the [6]-gingerol control group and the [6]-gingerol-treated model group, although not statistically significant (Figure 2D). The abundance of *Firmicutes* was significantly decreased in the ondansetron control group, the ondansetron-treated model group, the [6]-gingerol control group, the [6]-gingerol-treated model group and the model group ($P<0.05$) (Figure 2D). The ondansetron control group and the ondansetron-treated model group, the [6]-gingerol control group and the [6]-gingerol-treated model group, and the model group, had increased *Bacteroidetes* and decreased *Firmicutes* compared with the control group.

Line Discriminant Analysis Effect Size (LEFse) analysis showed the specific and predominant bacteria of the control group, the model group, the ondansetron-treated model group and the [6]-gingerol-treated model group: *Butyricimonas_synergistica* was predominant in the model group; *Porphyromonadaceae* and *parabacteroides* were specific for the ondansetron-treated model group; *Ruminococcaceae_UCG_010* and *Butyricimonas* were specific for [6]-gingerol-treated model group; the control group was characterized by Clostridiales, Fusobacteria, Cetobacterium, etc. (Figure 3A).

The Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis demonstrated the top 20 pathways for each group. The nitrogen metabolism pathway was up-regulated in the model group, and in the [6]-gingerol-treated model group, pathways related with aminoacyl-tRNA biosynthesis, purine metabolism, ribosome, flagellar assembly, cell cycle, Caulobacter, oxidative phosphorylation and peptidoglycan biosynthesis were up-regulated (Figure 3B).

Discussion

Chemotherapy is one of the main means of cancer treatment at present. CINV, one of the common clinical complications of chemotherapy, is a complicated process mediated by several factors such as serotonin, substance P and dopamine.[15] Nausea and vomiting occurring within

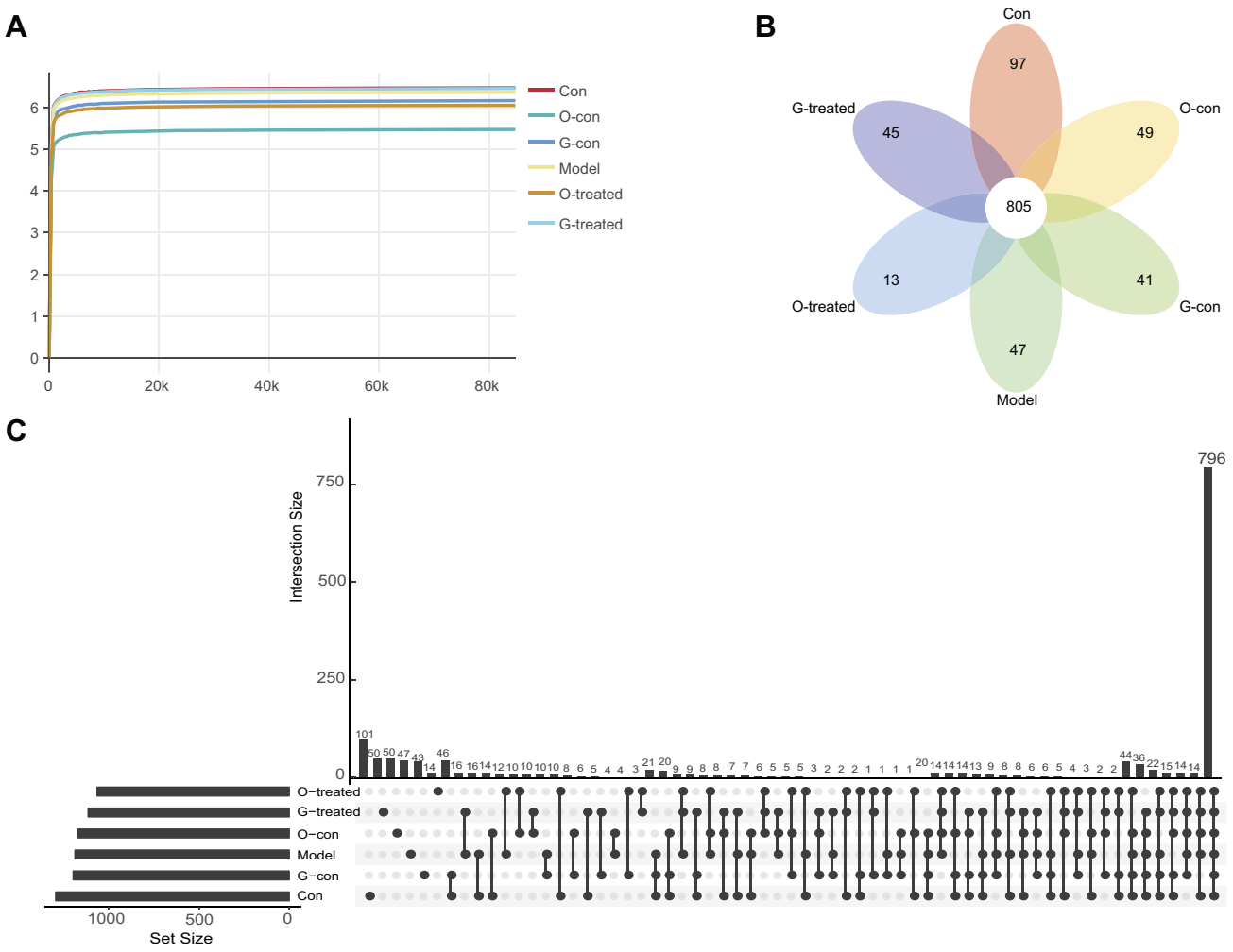

Figure 1 Overview of the 16S rDNA gene analysis: (**A**) the Shannon rarefaction curves for each group and (**B–C**) the distribution of OTUs in the 6 groups.
Abbreviations: Con, normal control group; O-con, the ondansetron control group; G-con, the [6]-gingerol control group; Model, the cisplatin model group; O-treated, the ondansetron-treated model group; G-treated, the [6]-gingerol-treated model group; OTUs, operational taxonomic units.

24 hrs after chemotherapy is acute CINV, which is caused by the binding of serotonin to 5-HT3 receptors in peripheral vagal afferents in the intestine.[15] If not treated in advance, patients will have serious nausea and vomiting after taking chemotherapeutic drugs, which will have adverse effects on patients in the followed treatment. In this study, the effects of ondansetron and [6]-gingerol on CINV were investigated based on the cisplatin-induced CINV rats model, and the alterations of gut microbiota caused by ondansetron and [6]-gingerol were further checked by 16S rDNA gene analysis.

Our results showed that when treated with ondansetron and [6]-gingerol in advance, the intake of kaolin of rats injected intraperitoneally with cisplatin was significantly reduced compared with the model group, indicating that ondansetron and [6]-gingerol were effective in prevention of CINV. Clinically ondansetron is usually used for treatment of CINV alone or combined with other medicines such as olanzapine and dexamethasone.[16,17] The ginger extract has similar effects to 5-HT3 antagonists, neurokinin 1 receptor antagonists and antihistamines, and it has been reported that intake of ginger could control the acute vomiting of CINV.[18,19] Qian et al reported that the therapeutic effects of gingerol on cisplatin-induced pica are potentially mediated by inhibiting central or peripheral dopamine by inhibiting dopamine D2 receptor, tyrosine hydroxylase and accelerating dopamine transporter, and gingerol could also modulate gastrointestinal motility.[20] Our result demonstrated that [6]-gingerol was as effective as ondansetron for control the pica of rats induced by cisplatin.

We further checked the effects of ondansetron and [6]-gingerol on the intestinal flora of rats, and our results showed that on phylum level, ondansetron, [6]-gingerol

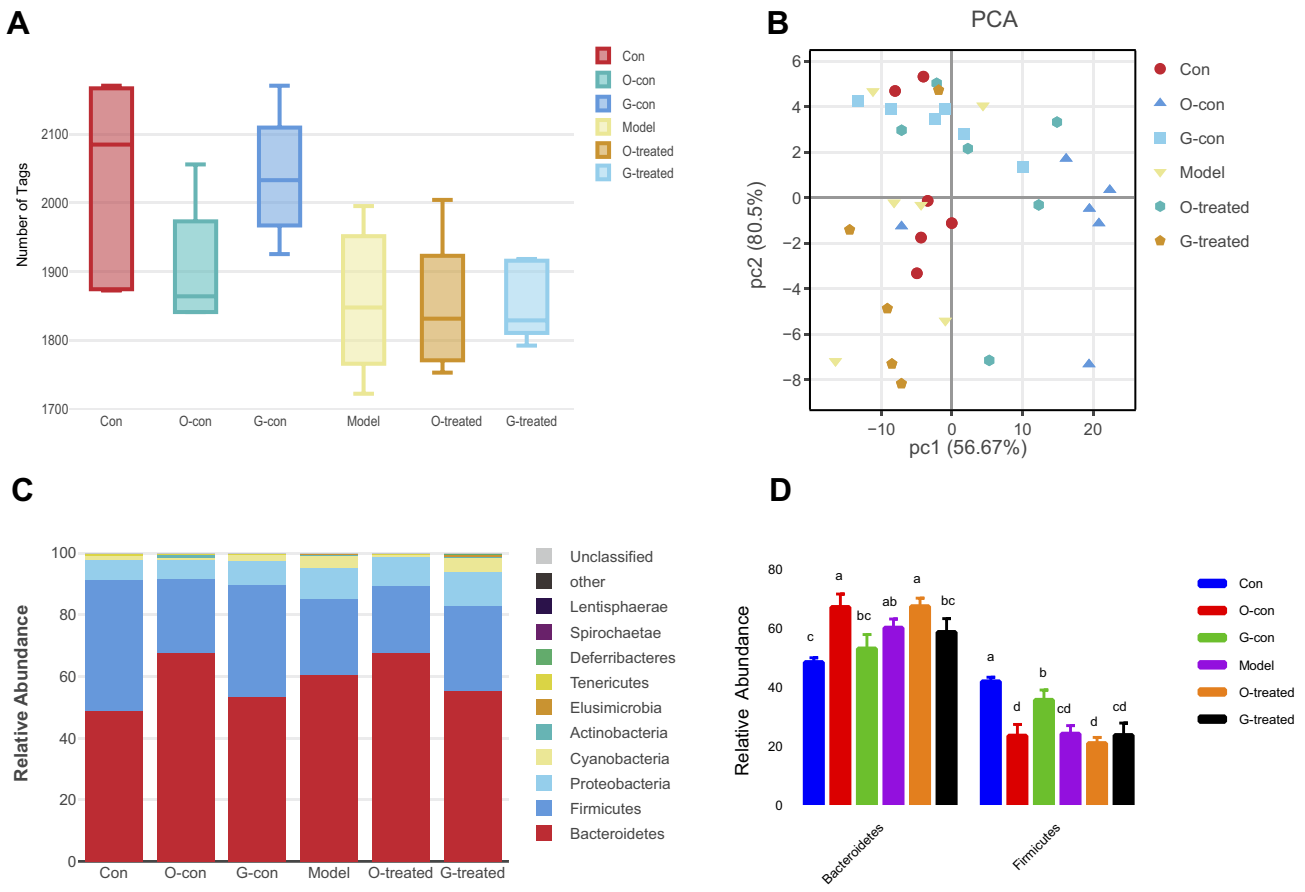

Figure 2 The Unifrac analyses, relative abundances and heat map of the dominant bacterial communities of the gut microbiota in the 6 groups. (**A–B**) The Unifrac analyses, and (**C–D**) the relative abundances of the gut microbiota on the bacterial phylum level. Boxes with a different letter above the error bars were significantly different ($P<0.05$).
Abbreviations: Con, normal control group; O-con, the ondansetron control group; G-con, the [6]-gingerol control group; Model, the cisplatin model group; O-treated, the ondansetron-treated model group; G-treated, the [6]-gingerol-treated model group; OTUs, operational taxonomic units.

and cisplatin could increase the relative abundance of *Bacteroidetes* and decrease *Firmicutes* compared with the control group (Figure 2C–D). The gut microbiota is a complex ecosystem that can connect to the immune and hormone system, to the gut–brain axis and to host metabolism via microbiota-derived metabolites, and the alternations of gut microbiota are associated with a number of diseases, including obesity, inflammatory diseases and behavioral and psychological abnormalities.[21] Wu et al reported that cisplatin increased the abundances of *Bacteroides caccae, Bacteroides uniformis, Escherichia coli*, etc, while decreasing the abundance of *Lactobacillus* in Wistar rats,[2] which is similar to our results in cisplatin-treated SD rats in the current study. Perales-Puchalt et al restored the gut microbiota altered by cisplatin treatment via fecal-pellet gavage in mice, and found that reversal of dysbiosis could promote the healing of the damaged intestinal epithelium induced by cisplatin and inhibit the systemic inflammation, indicating that fecal microbiota transplant could ameliorate the gastric and intestinal symptoms caused by chemotherapy.[22] Pica is a kind of compulsive eating of non-nutritive substances, such as clay, and its pathophysiology is not clear yet.[23] In the current study, cisplatin treatment increased the relative abundance of *Bacteroidetes* and decreased *Firmicutes*, and the altered gut microbiota may change the metabolites and affect the gut–brain axis, leading to pica. Green tea and ginger are the main ingredients of oil tea, contains high concentrations of tea polyphenols and [6]-gingerol, which is often used for treating various diseases in traditional Chinese medicine.[24] Lin et al reported that the abundance of *Lachnospiraceae* increased after oil tea treatment in mice with diabetes, and *Lachnospiraceae* was significantly correlated with fasting blood glucose, total cholesterol and LDL-cholesterol levels, so oil tea (tea polyphenols and [6]-gingerol) could improve the abnormal glucose and lipid metabolism via modulation of gut microbiota.[24] In this study, although not significant in statistics, it seemed that [6]-gingerol had the potential to ameliorate the alteration of gut microbiome caused by

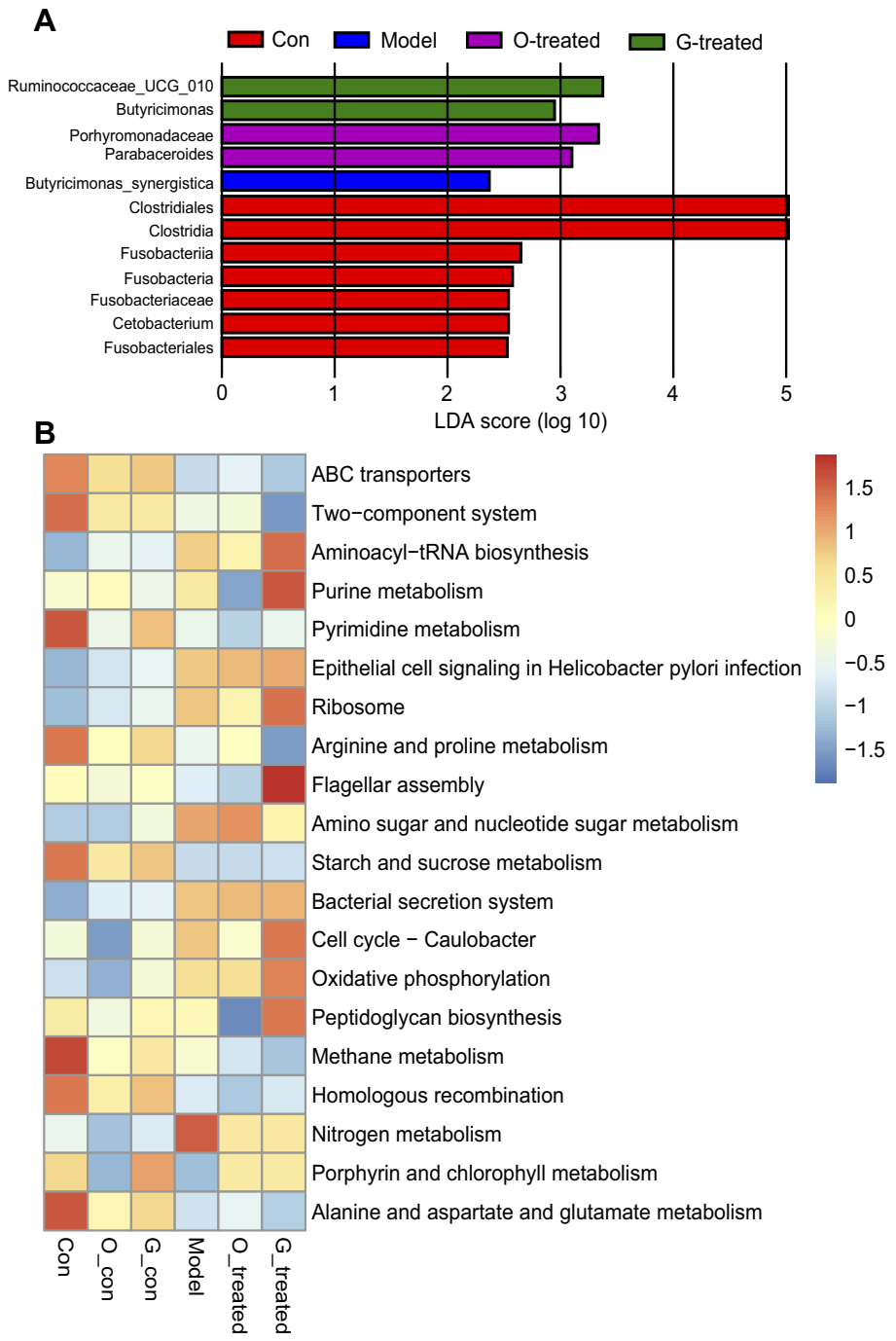

Figure 3 LEFse analysis and KEGG assignments of the 6 groups. (**A–B**) LEFse analysis identified the predominant taxons of each group, and (**C**) the presentation of KEGG assignments of the altered pathways in each group.

Abbreviations: Con, normal control group; O-con, the ondansetron control group; G-con, the [6]-gingerol control group; Model, the cisplatin model group; O-treated, the ondansetron-treated model group; G-treated, the [6]-gingerol-treated model group; OTUs, operational taxonomic units.

cisplatin; it slightly reduced the elevated abundance of Bacteroidetes caused by cisplatin (Figure 2C–D). The effects of [6]-gingerol on the gut microbiome of CINV animal models still need further study, maybe try different dosages and different treat time.

Our result demonstrated that the body weight of the 3 groups of rats injected with cisplatin was significantly decreased compared with the control group (Table 2). Yamamoto et al reported that cisplatin at a dose of 6 mg/kg could induce severe anorexia, and the behavior continued for

5 days;[25] therefore, it can be assumed that the decrease of food consumption is one of the reasons for the weight loss. It has been reported that obesity was associated with a reduced ratio of *Firmicutes* to *Bacteroidetes*.[26,27] Our results demonstrated that cisplatin-treated rats had increased ratio of *Firmicutes* to *Bacteroidetes*, contrary to the intestinal flora change of obesity, and this alternation of gut microbiota may also be linked with the body weight loss caused by cisplatin. As one of the essential component of digestion, gut microbiota produced a lot of potentially both beneficial and toxic metabolites that affect many physiological and pathological processes, depending on the concentration and location of the metabolite.[28] Gu et al reported that obese mice showed a reduced ratio of *Firmicutes* to *Bacteroidetes* and increased *Proteobacteria*, and the alternation of gut microbiota was related with the changes of metabolites involved in glycolysis, lipids, amino acids and the tricarboxylic acid cycle.[27] In this study, cisplatin-treated rats had increased ratio of *Firmicutes* to *Bacteroidetes*, which could affect the glucose and lipid metabolism via metabolites, leading to weight loss.

Extracts from fresh and dried ginger root had different components, thus had different functions, and the efficacy of ginger may be associated with the dose.[18] Here a standardized bioactive compound, [6]-gingerol was studied for its function in the prevention of CINV, compared with ondansetron. [6]-Gingerol was as effective as ondansetron in the treatment of pica induced by cisplatin in rats, and it seemed that [6]-gingerol had the potential to ameliorate the alteration of gut microbiome, but it needs further study. As a natural compound from ginger, [6]-gingerol had potential to collaborate with other antiemetic drugs to ameliorate CINV, with less adverse effects.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (No. 81673779, No. 81803912), the Scientific Research Project of the Administration of Traditional Chinese Medicine of Guangdong Province (No. 20182079), the Characteristic Innovation Project (Natural Science) of the Education Department of Guangdong Province and the "Innovation Strong School Project" of Guangdong Pharmaceutical University (No. 2017KTSCX102), and the Science and Technology Project of Yue-Xiu District of Guangzhou (No. 2018-WS-011).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Trendowski MR, El Charif O, Dinh PC, Travis LB, Dolan ME. Genetic and modifiable risk factors contributing to cisplatin-induced toxicities. *Clin Cancer Res*. 2019;25(4):1147–1155. doi:10.1158/1078-0432.CCR-18-2244
2. Wu CH, Ko JL, Liao JM, et al. D-methionine alleviates cisplatin-induced mucositis by restoring the gut microbiota structure and improving intestinal inflammation. *Ther Adv Med Oncol*. 2019;11:1758835918821021. doi:10.1177/1758835918821021
3. Gui QF, Lu HF, Zhang CX, Xu ZR, Yang YH. Well-balanced commensal microbiota contributes to anti-cancer response in a lung cancer mouse model. *Genet Mol Res*. 2015;14(2):5642–5651. doi:10.4238/2015.May.25.16
4. Zulkifli MH, Viswenaden P, Jasamai M, Azmi N, Yaakob NS. Potential roles of 5-HT3 receptor (5-HT3R) antagonists in modulating the effects of nicotine. *Biomed Pharmacother*. 2019;112:108630. doi:10.1016/j.biopha.2019.108630
5. Romano C, Dipasquale V, Scarpignato C. Antiemetic drug use in children: what the clinician needs to know. *J Pediatr Gastroenterol Nutr*. 2018;1. doi:10.1097/MPG.0000000000002225
6. Haas DM. Helping pregnant women and clinicians understand the risk of Ondansetron for nausea and vomiting during pregnancy. *JAMA*. 2018;320(23):2425–2426. doi:10.1001/jama.2018.19328
7. Ortiz LM, Lombardi P, Tillhon M, Scovassi AI. Berberine, an epiphany against cancer. *Molecules*. 2014;19(8):12349–12367. doi:10.3390/molecules190812349
8. Ryan JL, Heckler CE, Roscoe JA, et al. Ginger (*Zingiber officinale*) reduces acute chemotherapy-induced nausea: a URCC CCOP study of 576 patients. *Support Care Cancer*. 2012;20(7):1479–1489. doi:10.1007/s00520-011-1236-3
9. Zhang W, Liu X, Jiang Y, Wang N, Li F, Xin H. 6-Gingerol attenuates ischemia-reperfusion-induced cell apoptosis in human AC16 cardiomyocytes through HMGB2-JNK1/2-NF-κB pathway. *Evid Based Complement Alternat Med*. 2019;2019:8798653. doi:10.1155/2019/8798653
10. Luo Y, Zha L, Luo L, et al. [6]-Gingerol enhances the cisplatin sensitivity of gastric cancer cells through inhibition of proliferation and invasion via PI3K/AKT signaling pathway. *Phytother Res*. 2019;33:1353–1362. doi:10.1002/ptr.6325
11. Nikkhah Bodagh M, Maleki I, Hekmatdoost A. Ginger in gastrointestinal disorders: a systematic review of clinical trials. *Food Sci Nutr*. 2018;7(1):96–108. doi:10.1002/fsn3.807
12. Haniadka R, Rajeev AG, Palatty PL, Arora R, Baliga MS. Zingiber officinale (ginger) as an anti-emetic in cancer chemotherapy: a review. *J Altern Complement Med*. 2012;18(5):440–444. doi:10.1089/acm.2010.0737
13. Yamamoto K, Yamatodani A. Strain differences in the development of cisplatin-induced pica behavior in mice. *J Pharmacol Toxicol Methods*. 2018;91:66–71. doi:10.1016/j.vascn.2018.01.559
14. Liu YL, Malik N, Sanger GJ, Friedman MI, Andrews PL. Pica – a model of nausea? Species differences in response to cisplatin. *Physiol Behav*. 2005;85(3):271–277. doi:10.1016/j.physbeh.2005.04.009
15. Aapro M, Zhang L, Yennu S, LeBlanc TW, Schwartzberg L. Preventing chemotherapy-induced nausea and vomiting with netupitant/palonosetron, the first fixed combination antiemetic: current and future perspective. *Future Oncol*. 2019;15:1067–1084. doi:10.2217/fon-2018-0872
16. Wang W, Lou G, Zhang Y. Olanzapine with ondansetron and dexamethasone for the prevention of cisplatin-based chemotherapy-induced nausea and vomiting in lung cancer. *Medicine (Baltimore)*. 2018;97(37):e12331. doi:10.1097/MD.0000000000012331
17. Kim HJ, Shin SW, Song EK, et al. Ramosetron versus ondansetron in combination with aprepitant and dexamethasone for the prevention of highly emetogenic chemotherapy-induced nausea and vomiting: a multicenter, randomized phase III trial, KCSG PC10-21. *Oncologist*. 2015;20(12):1440–1447. doi:10.1634/theoncologist.2015-0128

18. Chang WP, Peng YX. Does the oral administration of ginger reduce chemotherapy-induced nausea and vomiting?: A meta-analysis of 10 randomized controlled trials. *Cancer Nurs*. 2018;1. doi:10.1097/NCC.0000000000000648
19. Konmun J, Danwilai K, Ngamphaiboon N, Sripanidkulchai B, Sookprasert A, Subongkot S. A phase II randomized double-blind placebo-controlled study of 6-gingerol as an anti-emetic in solid tumor patients receiving moderately to highly emetogenic chemotherapy. *Med Oncol*. 2017;34(4):69. doi:10.1007/s12032-017-0931-4
20. Qian W, Cai X, Wang Y, et al. Effect of gingerol on cisplatin-induced pica analogous to emesis via modulating expressions of dopamine 2 receptor, dopamine transporter and tyrosine hydroxylase in the vomiting model of rats. *Yonago Acta Med*. 2016;59(2):100–110.
21. Schroeder BO, Bäckhed F. Signals from the gut microbiota to distant organs in physiology and disease. *Nat Med*. 2016;22(10):1079–1089. doi:10.1038/nm.4185
22. Perales-Puchalt A, Perez-Sanz J, Payne KK, et al. Frontline science: microbiota reconstitution restores intestinal integrity after cisplatin therapy. *J Leukoc Biol*. 2018;103(5):799–805. doi:10.1002/JLB.5HI1117-446RR
23. Borgna-Pignatti C, Zanella S. Pica as a manifestation of iron deficiency. *Expert Rev Hematol*. 2016;9(11):1075–1080. doi:10.1080/17474086.2016.1245136
24. Lin R, He X, Chen H, et al. Oil tea improves glucose and lipid levels and alters gut microbiota in type 2 diabetic mice. *Nutr Res*. 2018;57:67–77. doi:10.1016/j.nutres.2018.05.004
25. Yamamoto K, Asano K, Tasaka A, et al. Involvement of substance P in the development of cisplatin-induced acute and delayed pica in rats. *Br J Pharmacol*. 2014;171(11):2888–2899. doi:10.1111/bph.12629
26. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature*. 2006;444(7122):1027–1031. doi:10.1038/nature05414
27. Gu Y, Liu C, Zheng N, Jia W, Zhang W, Li H. Metabolic and gut microbial characterization of obesity-prone mice under a high-fat diet. *J Proteome Res*. 2019;18(4):1703–1714. doi:10.1021/acs.jproteome.8b00945
28. Oliphant K, Allen-Vercoe E. Macronutrient metabolism by the human gut microbiome: major fermentation by-products and their impact on host health. *Microbiome*. 2019;7(1):91. doi:10.1186/s40168-019-0704-8