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Xiaobing Li[1], Shu Wang[2], Wenjing Chen[2], Mengting Zhao[2], Xueqing Kong[2], Xiaoyu He[2], Yan Chen[3], Wenyu Chen[3], Tong Wu[2], Chunlei Xu[2], Jun Huang[2] and Shuanzhu Song [2]

1 College of Basic Medicine, Henan University of Chinese Medicine, room A473, 156 Jinshui East St., Zhengzhou, China.
2 The First school of clinical medicine of Henan University of Traditional Chinese Medicine, Zhengzhou, China
3 The Second school of clinical medicine of Henan University of Traditional Chinese Medicine, Zhengzhou, China
Email: baishaoyao@163.com

Abstract. The present study was to investigate the effect of Pinellia Ageratum Decoction on vomiting induced by cisplatin in rats and its mechanism. The experiment was divided into blank control group, cisplatin model group, ondansetron hydrochloride group, Major Pinellia Decoction group and Pinellia Ageratum Decoction group. The vomiting model was established by intraperitoneal injection of cisplatin in rats. At the end of the experiment, the amount of kaolin consumption, food intake, gastric residual rate, gastric binding mucus volume and small intestinal propulsion rate were observed and measured. Serum 5-hydroxytryptamine (5-HT) and dopamine levels were detected by ELISA. The results demonstrated that compared with the blank group, the amount of kaolin consumption in the model group increased significantly and the food intake decreased significantly. Compared with the model group, the amount of kaolin consumption in pinellia ageratum decoction group decreased significantly, the food intake increased significantly, the amount of gastric-binding mucus increased significantly, the rate of small intestinal propulsion increased significantly, and the differences were significant ($P < 0.05$), level of 5-HT decreased slightly, there was no significant difference, the level of dopamine decreased significantly, and the difference was significant ($P < 0.05$)pinellia ageratum decoction group has a therapeutic effect on cisplatin-induced vomiting in rats, and its mechanism may be related to its reduction of dopamine levels in rats.

1. Introduction

The cisplatin vomiting rate during tumor chemotherapy is as high as 90%. Strong nausea and vomiting not only affect the patient's eating and living, but also cause the body's electrolyte and acid-base balance disorder and exhaustion. General anti-vomiting drugs are difficult to work, easy to produce anxiety, depression and other emotions, is an important reason why many cancer patients can not tolerate chemotherapy [1]. Pinellia Ageratum Decoction comes from “The theory of the plague” and has a good anti-vomiting effect. It has been used in the treatment of vomiting for hundreds of years. This study explored the effect and mechanism of Pinellia Ageratum Decoction on chemotherapy-induced vomiting.

2. Materials and Methods

2.1. Animals

Healthy male SD, Weight 230-300 grams, were provided by the experimental animal center of Henan University of Chinese Medicine

2.2. Experimental Materials

2.2.1. Experimental Reagents. Pinellia ternate, ginseng, honey, pogostemon cablin, dried ginger, licorice root, white poria cocos, Guang tangerine, rhizoma atractylodis macrocephalae stir-fired with bran,(Development of Guangdong Efong Pharmaceutical Co., Ltd.), Cisplatin injection (Development of Jiangsu Haosen Pharmaceutical Group Co., Ltd., Batch Number: Guo Yao Zhun Zi H20040813), Ondansetron hydrochloride (Development of Qilu Pharmaceutical Co., Ltd., Batch Number: Guo Yao Zhun Zi H10970062), Alcian blue dyes (Development of Wuhan Saiwei Biotechnology Co., Ltd., Ltd., Item Number: G1027), Rats 5HT ELISA Kit, Rats DA ELISA Kit (96T,Wuhan Chundu Biotechnology Co., Ltd. ,Item Number: DRE20055).

2.2.2. Experimental Instruments. Laboratory animal clean breeding cabinet YX-1 type, electronic balance, enzyme mark instrument,722 type spectrophotometer, thermostat water bath.

2.3. Animal Treatment

The experiment was divided into blank control group, cisplatin model group, ondansetron hydrochloride group, Major Pinellia Decoction group and Pinellia Ageratum Decoction group.The vomiting animal model was established by intraperitoneal injection of 3mg/kg cisplatin 1hour prior to administration. The heterophilic behavior of mice was obvious, and the intake of kaolin increased compared with the blank control group, indicating successful modeling [2]. Mice with successful modeling were randomly assigned to the blank control group, the cisplatin model group, the ondansetron hydrochloride group, the Major Pinellia Decoction group and the Pinellia Ageratum Decoction group. The mice in ondansetron hydrochloride group were administered daily at a dose of 2.6mg/kg (gavage), the mice in Major Pinellia Decoction group were administered daily at a dose of 1.6g/kg (gavage) and the mice in Pinellia Ageratum Decoction group were administered daily at a dose of 1.6g/kg (gavage). The mice in blank control group and the mice in cisplatin model group were intragastrically administered with an equal volume of saline. Animals were sacrificed on the fifth day of the experiment.

2.4. Observations

2.4.1. The Amounts of Kaolin Eaten by Mice.

2.4.2. Gastric Residual Rate [3]. Dissolved 10g of sodium carboxymethyl cellulose in 250ml of distilled water, then added 16g of milk powder, 8g of sugar, 8g of starch and 2g of activated carbon, stirring evenly, finally configured into 300ml black semisolid Paste, about 300ml.Then put it in the refrigerator and kept it ready. Before the last administration, the mice in each group were fasted but water was given for 24 hours and after 30 minutes of the last administration, the mice in each group were given a nutritive semi-solid paste at a perfusion volume of 1ml/100g. After 30 minutes, anesthesia was performed, then the neck was sacrificed, the abdominal cavity was opened, and the stomach was separated. Cut the stomach from the pylorus and called the stomach full weight (M1), then cut the stomach along the big curve of the stomach, washing the stomach contents in physiological saline and wiping the water with the filter paper, finally weighed the stomach net weight (M2) and calculated the gastric residual rate.

Gastric residual rate = (M1-M2) / M1 × 100%

2.4.3. Detection of Gastric Binding Mucus Volume [4]. After collecting the gastric juice, the stomach was cut along the greater curvature of the stomach, rinsed, and the filter paper absorbs moisture. Then the stomach was immersed in the Alisin blue dye solution (10 ml) and incubated for 2 hours, and then the supernatant was collected by centrifuging the incubation solution at 3000 r/min for 15 minutes. The absorbance value (OD 650 nm) of each well was measured with the enzyme-labeling instrument, and the amount of gastric-bound mucus was calculated from the amount of the bound dye.

2.4.4. Detection of Small Intestine Propulsion Rate [3]. After taking the stomach, use the tweezers to gently extract the upper end to the pylorus, the lower end to the ileocecal intestine tube, spread on the experimental bench, without pulling, gently pull the small intestine into a straight line, and measure the small intestine propulsion index with a ruler. The small intestine propulsion rate was calculated by measuring the length of the small intestine (L1) and the length of the anterior end of the pylorus to charcoal (L2). Small intestine propulsion rate (%) = L2 / L1 × 100%

2.4.5. Detection of 5-hydroxytryptamine (5-HT) and dopamine levels in serum. Test according to the kit instructions

2.5. Statistical Analysis
Data are presented as the mean ± SD. Differences were evaluated using Statistical Package for Social Science 21.0. Statistical analysis was performed using One-way ANOVA followed by least-significant difference (LSD). $p < 0.05$ was considered to be statistically significant.

3. Results

3.1. Effect of Pinellia Ageratum Decoction on the Amount of Kaolin Consumption of Rats
Compared with the normal group, the amount of kaolin consumption in the model group was significantly increased in 24-28h and 48-72h, and the model group had significant statistical difference ($P<0.05$).Compared with the model group, the amount of kaolin consumption in the Major Pinellia Decoction and the Pinellia Ageratum Decoction was significantly decreased.

Table 1. Effect of Pinellia Ageratum Decoction on the amount of kaolin consumption of rats

group	before the experiment	0-24h	24-48h	48-72h
normal group	0.80±0.1	0.30±0.05	0.14±0.16	0.11±0.17
model group	0.71±0.01	2.93±2.10	3.03±0.74*	2.00±1.76*
western medicine group	0.73±0.10	2.67±1.53	2.50±1.64	1.27±0.59
Major Pinellia Decoction group	0.71±0.10	2.55±1.43	1.79±1.73	1.05±0.82
Pinellia Ageratum Decoction group	0.74±0.28	2.50±1.69	2.35±2.62	1.65±0.92

Note: Compared with the normal group, $^{**}P<0.01$,$^{*}P<0.05$; Compared with the model group, $^{\#\#}P<0.01$, $^{\#}P<0.05$.

3.2. Effect of Pinellia Ageratum Decoction on Rat Appetite
Compared with the normal group, the model group of rat appetite on 24h,24-48h and 48-72h were significantly reduced(*P<0.01*).Compared with the model group, the major pinellia decoction group of rat appetite was significantly increased(*P<0.01*), pinellia ageratum decoction group was significantly increased(*P<0.01*)

Table 2. Effect of pinellia ageratum decoction on rat appetite (g, $\bar{x} \pm s$)

group	before the experiment	0-24h	24-48h	48-72h
normal group	31.73±1.89	30.87±2.45	33.50±0.80	31.00±1.57
model group	32.73±1.37	20.00±2.86**	16.93±3.71**	13.40±2.19**
western medicine group	30.53±1.60	20.47±2.30	18.23±3.80	19.00±1.56#
Major pinellia decoction group	32.03±2.00	21.70±1.85	18.63±7.22	18.83±3.32#
pinellia ageratum decoction group	33.10±0.42	23.20±4.10	19.90±3.54	20.31±2.57##

Note: Compared with the normal group **P<0.01, *P<0.05, compared with the model group ##P<0.01, #P<0.05.

3.3. Effect of Pinellia Ageratum Decoction on Gastric Residual Rate of Rats

Compared with the normal group, gastric residual rate in the model group was significantly increased, and the model group had significant statistical difference (P<0.01).Compared with the model group,the gastric residual rate in the Pinellia Ageratum Decoction group was decreased.

Table 3. Effect of Pinellia Ageratum Decoction on gastric residual rate of rats ($\bar{x} \pm s$)

group	*gastric residual rate*
normal group	42.20 ± 1.83
model group	74.50 ± 2.04**
western medicine group	70.97 ± 3.37
major pinellia decoction group	78.60 ± 2.62
pinellia ageratum decoction group	73.56 ± 18.63

Note: Compared with the normal group, **P<0.01,*P<0.05; Compared with the model group, ##P<0.01, #P<0.05

3.4. Effect of Pinellia Ageratum Decoction on Gastric Binding Mucus Volume

Compared with the normal group, the model group of gastric binding mucus volume was significantly reduced (P<0.05). Compared with the model group, each drug administration group of gastric binding mucus volume was significantly increased (P<0.05), major pinellia decoction group was slightly lower than pinellia ageratum decoction group.

Table 4. Effect of pinellia ageratum decoction on gastric binding mucus volume (mg,$\bar{x} \pm s$)

group	*gastric binding mucus volume*
normal group	0.79±0.05
model group	0.52±0.13*
western medicine group	0.78±0.04#
major pinellia decoction group	0.77±0.03#
pinellia ageratum decoction group	0.79±0.05#

Note: Compared with the normal group **P<0.01, *P<0.05, compared with the model group ##P<0.01, #P<0.05.

3.5. Effect of Pinellia Ageratum Decoction on Small Intestinal Propulsion Rate of Rats

Compared with the normal group, the small intestinal propulsion rate in the model group was significantly decreased, and the difference between groups had significant statistical difference (P<0.01). Compared with the model group, the small intestinal propulsion rate in the western medicine group and the Pinellia Ageratum Decoction group was significantly increased, and the difference between groups had significant statistical difference (P<0.05).

Table 5. Effect of Pinellia Ageratum Decoction on small intestinal propulsion rate of rats($\bar{x} \pm s$)

group	small intestinal propulsion(%)
normal group	100.00 ± 0.00
model group	$40.70 \pm 2.40^{**}$
western medicine group	$67.40 \pm 7.00^{\#}$
major pinellia decoction group	55.43 ± 21.81
pinellia ageratum decoction group	$70.70 \pm 9.32^{\#}$

Note: Compared with the normal group, $^{**}P$<0.01,$^{*}P$<0.05; Compared with the model group, $^{\#\#}P$<0.01, $^{\#}P$<0.05

3.6. Effect of Pinellia Ageratum Decoction on Serum 5-hydroxytryptamine and Dopamine Levels of Rat.

Compared with the normal group, the model group of Serum 5-hydroxytryptamine and dopamine levels were significantly increased (P<0.01). Serum 5-hydroxytryptamine level was significantly increased in Major pinellia decoction group and pinellia ageratum decoction group (P<0.05).

Table 6. Effect of pinellia ageratum decoction on Serum 5-hydroxytryptamine and dopamine levels of rat. ($\bar{x} \pm s$)

group	Serum DA(ng/L)	Serum 5-TH(ng/ml)
normal group	33.34 ± 2.81	64.09 ± 5.29
model group	$52.31 \pm 2.40^{**}$	$90.95 \pm 10.22^{**}$
western medicine group	42.53 ± 4.57	82.73 ± 12.62
major pinellia decoction group	$37.48 \pm 6.57^{\#}$	75.42 ± 8.75
pinellia ageratum decoction group	$38.66 \pm 1.63^{\#}$	75.56 ± 3.95

Note: Compared with the normal group $^{**}P$<0.01, $^{*}P$<0.05, compared with the model group $^{\#\#}P$<0.01, $^{\#}P$<0.05.

4. Discussion

Cisplatin can cause heterophile in a dose-dependent manner, i.e., ingestion of an inalimental substance such as kaolin. Studies have clearly pointed out that rats with heterophilic behavior can be equivalent to other nausea and vomiting reactions in animals with vomiting. Experimental chemotherapy vomiting and exercise vomiting often use the rat heterophilic model [5].

Studies have shown that the heterogeneity of kaolin in the Pinellia Ageratum Decoction group is lower than that in the model group, and its heterogeneity is close to half of the model group, indicating that Pinellia Ageratum Decoction can significantly improve the heterophilic behavior of rats and improve their vomiting symptoms. Studies have shown that Pinellia Ageratum Decoction can increase the food intake of vomiting rats, increase the amount of gastric-bound mucus, and increase the rate of small intestinal propulsion. It indicates that Pinellia Ageratum Decoction can enhance the

gastrointestinal motility of rats with vomiting and alleviate the damage of gastrointestinal mucosa caused by cisplatin.

Dopamine is an important neurotransmitter in the body. The gastrointestinal mucosa is stimulated by chemotherapeutic drugs can release excess dopamine. After binding to the dopamine receptor, the signal is transmitted to CTZ via the vagus nerve. CTZ is impulsive and releases dopamine, which binds to the central dopamine receptor. Signaling to the vomiting center causes vomiting. 5-HT is another important vomiting signal and neurotransmitter that mediates chemotherapy-vomit. It is closely related to mental activity and participates in many physiological processes. The experimental results showed that compared with the model group, Pinellia Ageratum Decoction can lower serum 5-HT levels and significantly reduce serum dopamine content. It is suggested that the anti-vomiting effect of Pinellia Ageratum Decoction may be related to the regulation of dopamine neurotransmitter levels.

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