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Original Article

Effect of Evodiamine in the Prevention and Treatment of 5-FU Induced Diarrhea in Swiss Albino Rats: A Preliminary Study

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ABSTRACT

Aim of the Study: To assess the antidiarrheal properties of Evodiamine in the prevention and treatment of Chemotherapy-Induced Diarrhea (CID) in experimental rats. **Materials and Methods:** The Swiss albino female rats (8-12 weeks) rats were treated with Evodiamine for 13 days and 5-FU was administered on day 4 to day 10 (7 consecutive days) for the induction of diarrhea. After 13 days of experiments, all rats were euthanized and thymus and spleen weights were measured. Bodyweight and diarrhea rate and score were recorded every day. **Results:** Our study resulted that Evodiamine significantly prevented and reduced the rate and intensity of diarrhea, body weight and thymus/spleen indexes in dose-dependently. The highest effects were observed with Evodiamine 50 and 100 mg/kg which exhibited a similar effect with that of loperamide (3 mg/kg). **Conclusion:** Our findings demonstrated the antidiarrheal activity of Evodiamine for the prevention of 5-FU induced diarrhea. This is the first-ever study reporting on the antidiarrheal potential of Evodiamine against chemotherapy-induced diarrhea.

Keywords: Evodiamine, Chemotherapy, Diarrhea, Phytomedicine, Swiss albino rat, *in vivo*.

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INTRODUCTION

Cancer is a prominent contributor to mortality worldwide.[1,2] Based on data from the International Agency for Research on Cancer, there were 18.1 million newly diagnosed incidences of cancer and 9.5 million deaths attributable to cancer globally in 2018. Even though chemotherapy has considerably revolutionized the survival rate and duration of cancer patients, the chemotherapeutic drugs utilized to treat cancers induce several toxicities and severe side-effects,[3] such as diarrhoea,[4] constipation,[5] nausea,[6] vomiting,[6] ulceration,[7] bloating,[4] hair loss,[8] bone marrow suppression,[9] loss of immunity,[10] and cardiotoxicity,[11] etc., In general, chemotherapy-induced toxicities and adverse-effects badly influence to compromise the clinical application of anticancer drugs.[12] Chemotherapy-Induced Diarrhea (CID) significantly hinders the modifications of chemotherapy treatment in around 60% of patients, resulting in dose decreases in 22% of patients, dose postponements in 28% of patients and therapy termination in 15% of patients.[13,14] This also leads to a decline in the Quality-of-Life (QOL) of cancer survivors.[15-17]

As per the research, the occurrence of post-treatment CID among cancer survivors was predicted to reach up to 49%. This has been found to long last nearly 10 years after the completion of chemotherapy.[16-19] Although the underlying mechanisms of chemotherapy-induced diarrhea could not understand clearly, it is assumed that the mucositis with ulceration and inflammation of the intestinal epithelium is the main contributor to CID.[20] CID can potentially cause severe and dangerous symptoms, such as electrolyte imbalances and dehydration. In some cases, it can even lead to death, even in patients who are in good physical condition, if prompt action is not done.[21,22] This suggests that more innovative approaches are necessary to contain and treat diarrhea and other side effects caused by chemotherapy.

The general approach for the treatment of diarrhea is to administer antimotility,[23] antisecretory agents,[24] opioids and their derivatives, such as diphenoxylate and loperamide,[25] and antimicrobial agents,[26] such as fluoroquinolones and third-generation cephalosporins in case of treatment of serious diarrhea.[27-29] But currently available antidiarrheal drugs have several limitations with adverse effects and contraindications

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including the development of drug-resistance, specifically against antibiotics used in diarrheal treatment.[30,31]

Traditional Chinese Medicine (TCM) has a long history of utilization to treat different types of ailments for more than 3000 years back.[32,33] Recently TCM have gained the research interests for the antidiarrheal drugs, more specifically for the treatment of chemotherapy-induced diarrhea.[34,35]

Evodia rutaecarpa Benth., is a small tree which belongs to Rutaceae family (genus Evodia) is mainly found in the Qinling or Szechuan Alps area in China.[36,37] The dried fruit of this plant is known as 'Evodiae Fructus' also called 'Wu-Zhu-Yu' in Chinese. It is one of the most popular herb which is ethnopharmacologically utilized in TCM to treat diarrhea, headache, abdominal pain, migraines, hemorrhage, dysentery, dysmenorrheal and hypertension among other diseases.[37-41] Scientific studies also demonstrated its anticancer,[42] antidiabetic,[39] protection and treatment of cardiovascular diseases,[43] antihyperlipidemic,[44] anti-inflammatory,[41] anti-microbial,[32] anti-nociceptive activity and anti-neurodegenerative activity including anti-Alzheimer's activities.[45,46] Phytochemical analysis resulted in the presence of large amounts of evodiamine, an indole alkaloid in the fruit of *Evodia rutaecarpa* Benth.[47,41]

The scientific investigations for the antidiarrheal activity of *Evodia rutaecarpa* Benth or its bioactive compound 'evodamine' have not yet been explored for the justification of the ethnopharmacological use of Evodia to develop new pharmaceuticals for diarrhea. On the other hand, currently available antidiarrheal drugs have several limitations with adverse-effects and contraindications, including the development of drug-resistance, specifically against antibiotics used in diarrheal treatment.[48,49] As *Evodia rutaecarpa* Benth fruit has ethnopharmacological use in the treatment of diarrhea and it's scientific studies have not yet performed, the current work was intended to assess the pharmacological potential and toxicological studies of 'evodamine', to treat the CID in experimental rats. This approach offers a new perspective to prevent and treat the CID that can be effective in controlling other side effects.

MATERIALS AND METHODS

Chemicals and Reagents

Loperamide was procured from Shandong Yihong Chemical Co. Ltd., China. 5-Fluorouracil (5-FU), Ketamine-HCl and xylazine-HCl were procured from Sigma-Aldrich, USA.

Collection of *Evodia rutaecarpa* Benth extract

Evodia rutaecarpa Benth extract (commercial name 'Evodia') with a potency of 80% evodiamine (determined by HPLC analysis) was purchased from Bolise Co. Ltd., China. The followings were specification of the extract:

Loss on drying: 3.64%, Residue on Ignition: 3.12%, residual solvents: ≤0.05% heavy metal: ≤20 ppm, residual pesticide: negative, Salmonella: negative, *E. coli*: negative

Experimental animals

The assays were performed using Swiss Albino female rats,[50-53] aged 8-12 weeks with body weight between 162-203 g/rat. The rats were procured from Shanghai Laboratory Animal Center (SLAC, Shanghai, China) and caged polypropylene confines, maintained with 12/12 hr light-dark series and provided standard pellet diet and water *ad libitum*. The environmental modifications were meticulously regulated and before conducting any assays, a one-week acclimation period was provided for all animals to adapt to the new environment. The inductions of diarrhea and treatment pattern of evodiamine are illustrated in Figure 1.

Ethical Approval

The animal ethical approval was taken from Animal Ethics Committee of Northwest University First Hospital (Approval Number: 20230211). All the assays were conducted as per the verified protocols of the ethics committee and following the regulations of Shaanxi prefecture of China and as per the Guidelines for Care and Use of Laboratory Animals published by the US National Institutes of Health.The Federation of European Laboratory Animal Science Associations (FELASA) guidelines were adopted to mitigate the pain of the experimental rats. After the completion of treatments, the animals were euthanized with Ketamine HCl (100 mg/kg) and xylazine (10 mg/kg).[54]

Analysis of acute toxicity of Evodia extract (80% Evodiamine)

Oral acute toxicity research was conducted to determine the LD_{50} of Evodia extract, which has a potency of 80% as Evodiamine. The study followed the OECD protocol no. 420, known as the Fixed Dose Procedure, as described previously.[55] The rats were distributed into four groups. Group 1 was control (received 5% CMC-Na aqueous solution only), groups 2, 3 and 4 administered Evodiamine at 300, 1000 and 2000 mg/kg concentrations, respectively. The rats underwent an overnight period of fasting from food (but not water) before to receiving the doses and then fasted from food for 3-4 hr after the doses were administered. The rats were monitored separately for the initial 30 min following administration, with particular emphasis on the first 4 hr. Subsequently, repeated observations were made within the first 24 hr to detect any potential harmful effects in the rats. Throughout the whole 14-day observation period, the animals were closely examined for any alterations in behavior, body weight, urine, food and water intake, tremors, constipation, alterations in eye and skin pigmentation, as well as any instances of animal death.

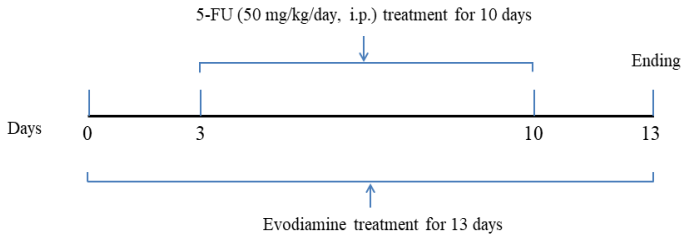

Figure 1: Induction of diarrhea and treatment pattern of Evodiamine.

(8-12 weeks) were pre-treated with Evodiamine doses at 12.5, 25, 50 and 100 mg/kg or loperamide (3 mg/kg) orally for the first 3 days of experiments before the induction of diarrhea. Then 5-FU (50 mg/kg/day, i.p.) was injected to rats for 7 consecutive days. Evodiamine or loperamide was administered 30 min before the injection of 5-FU chemotherapy. At the end of 5-FU therapy, the rats were further treated with Evodiamine and loperamide for 3 more consecutive days. At the end of 13 days experiments, all the rats were sacrificed.

Experiment design

The experimental method was designed as mentioned previously. Forty Swiss Albino female rats were distributed into seven groups:

Group-1: Non-Diarrheal Control (NDC)-rats administered 5% CMC-Na aqueous solution only.

Group-2: Diarrheal Control (DC)-rats received 5-FU (50 mg/kg/day, i.p.) dissolved in 5% CMC-Na aqueous solution without Evodiamine treatment.

Group-3: Rats treated with 5-FU+Evodiamine (12.5 mg/kg).

Group-4: Rats treated with 5-FU+Evodiamine (25 mg/kg).

Group-5: Rats treated with 5-FU+Evodiamine (50 mg/kg).

Group-6: Rats treated with 5-FU+Evodiamine (100 mg/kg).

Group-7: Rats treated with 5-FU+Loperamide (3 mg/kg).

The rats were administered with the prescribed above-mentioned doses of Evodiamine or loperamide for 13 days of experiments. Five-Fluorouracil (5-FU) (50 mg/kg/day, i.p.) was treated at day 3 and ended at day 10. Evodiamine was dissolved in 0.5% Carboxymethylcellulose Sodium (CMC-Na) solution. Rats were orally administrated with Evodiamine or loperamide 30 min before the administration of 5-FU chemotherapy.

Clinical observations and diarrheal assessment

Both diarrhea conditions and body weight were monitored daily. All rats were checked 4-times/day and diarrhea monitored as per the grading mentioned by Stringer *in vitro* 2006. The grading was as follows based on clinical symptoms of diarrhea:

No diarrhea=0.

Mild diarrhea (staining of the anus)=1.

Moderate diarrhea (staining over top of legs and lower abdomen)=2.

Severe diarrhea (staining over legs and higher abdomen, often with continual anal leakage)=3.

All diarrhea tests were performed blindly by 2 persons (XZ and CQ). The rate of diarrhea was calculated based on the following formula:

$$\text{Diarrhea rate (\%)} = \frac{\text{Number of diarrheal rats}}{\text{the number of rats in each group}} \times 100$$

24 hr after the final treatment, the fecal sample of each rat was gathered in a sterile tube and stored at -80°C. The rats were euthanized by anesthesia overdose and then immune organs were collected. The spleen and thymus index of each rat was determined as per the following equation:

$$\text{Spleen/thymus index} = \text{Spleen/Thymus weight/Body weight (mg/g)}$$

Statistical analysis

he values are examined by one-way ANOVA using SPSS software, followed by Dunnett's-T3 test to assess the significance level between treatment groups. The data are depicted as mean±SEM of triplicates. The $p<0.05$ was fixed as significant.

RESULTS

Oral acute toxicity study of Evodiamine in laboratory rats

An oral acute toxicity study of Evodiamine was performed as per the OECD guidelines. There were no instances of death recorded during the 14-day treatment period using a restricted dosage of 2000 mg/kg of Evodiamine. The treated animals exhibited tolerance to the doses of Evodiamine and there was no significant disparity in body weight between the treatment groups. The rats showed no signs of abnormalities or significant changes in behavior, such as difficulty breathing, abnormal movement, shaking, excessive drooling, diarrhea, unusual sleep patterns, walking backwards, reactions to being handled, prolonged muscle stiffness, unconsciousness, or any toxic symptoms. These observations were made both immediately after treatment and during the 14-day period of post-treatment observation. Therefore, it may be concluded that the LD_{50} for orally administering Evodiamine is greater than 2000 mg/kg body weight. Therefore, the used doses of Evodiamine (12.5-100 mg/kg) were well tolerated by the rats.

Five-Fluorouracil (5-FU) induced diarrhea in Swiss albino rats

The treatment of 5-FU (on day 4 on 13 days experiment) at the 50 mg/kg concentration (i.p.) successfully induced mild diarrhea to 40% rats of diarrheal control group 8 hr after administration of 5-FU. The peak incidence of diarrhea was induced to 100% of test animals in a diarrhea control group on day 7 (on 4th day of 5-FU treatment) which continues up to the 10th day of experiment. However, after stopping of 5-FU treatment, the rate of diarrhea

Table 2: Effect of Evodiamine on the rate of the incidence of diarrhea induced by 5-FU in Swiss albino female rats.

Sl. No.	Treatment group of animals	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13
1	NDC	0	0	0	0	0	0	0	0	0	0	0	0	0
2	DC	0	0	0	40%	60%	80%	100%	100%	100%	100%	80%	80%	60%
3	Evodiamine 12.5 mg/kg	0	0	0	20%	40	40	60	60	80	80	60	40	20
4	Evodiamine 25 mg/kg	0	0	0	20%	40	40	40	60	60	40	40	20	20
5	Evodiamine 50 mg/kg	0	0	0	0%	20	40	20	20	40	40	20	0	0
6	Evodiamine 100 mg/kg	0	0	0	0%	20	20	20	20	40	20	20	0	0
7	Loperamide (3 mg/kg)	0	0	0	0%	20	40	20	20	20	40	20	0	0

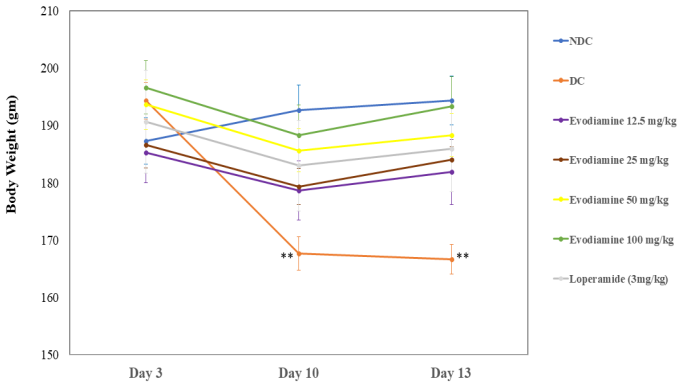

Figure 2: Effect of Evodiamine on the change of body weight induced by 5-FU treatment.

Swiss albino female rats (8-12 weeks) were pre-treated with Evodiamine (12.5, 25, 50 and 100 mg/kg) or loperamide (3 mg/kg) for the first 3 days. Then 5-FU (50 mg/kg/day, i.p.) was injected to rats for 7 consecutive days starting from day 4 to day 10. At the end of 5-FU therapy, the rats were further treated with Evodiamine and loperamide for 3 more consecutive days up to day 13. The body was recorded everyday but statistical analysis was performed for body weights on just before and after 5-FU treatment and at the end of the experiment. The data are S.E.M. of five animals in each group. $^{**}p<0.01$ compared to day 4 among the group.

reduced to 80% on the next day and ended at 60% on 13th day of experiment (Table 2).

Evodiamine improved 5-FU induced body weight loss in experimental rats

Treatment of experimental Swiss albino rats with 5-FU (50 mg/kg) decreased body weight of rats in diarrheal control group every day for seven days of 5-FU treatment. However, after the ending of the 5-FU treatment, the weight loss has stopped and the rats gradually started to regain weight on day 13 of the treatment. The influence of Evodiamine on the 5-FU induced weight loss in Swiss albino female rats have presented in Table 1 and Figure 2.

Everyday weights were recorded and the weight records before starting 5-FU treatment (experiment day 3), on 5-FU ending day and the whole experiment ending day were statistically analyzed. As we can see in Table 1 and Figure 2, 5-FU treatment significantly reduced body weight of rats on day 7 of 5-FU treatment ($^{**}p<0.01$, weight loss 13.72%) and 3 days after stopping of 5-FU treatment (experiment day10) ($^{**}p<0.01$, weight loss 14.33%) compared to that of 0 days of 5-FU administration. However, the treatment of various concentrations of Evodiamine (12.5, 25, 50 and 100 mg/kg) and loperamide (50 mg/kg) prevented the remarkable decrease of body weight in 5-FU induced experimental rats. However, a marginal insignificant decrease of body weight was noted in Evodiamine treated groups which has been reversed on the next day just after the ending of 5-FU treatment.

Evodiamine ameliorates the incidence of 5-FU induced diarrhea in rats

The incidences of diarrhea have been presented in Table 2 and Figure 3. The 5-FU induced diarrhea among 40% of experimental rats on the 1st day of treatment and the incidence of diarrhea has increased everyday of 7 days treatment with 5-FU. The highest incidence (rate of the diarrheal case: 100%) of diarrhea was observed on day 4 of 5-FU treatment which continues for 7 days up to the end of 5-FU treatment. However, treatment of diarrheal rats with Evodiamine (12.5, 25, 50 and 100 mg/kg) dose-dependently decreased the rate of diarrheal cases. After the withdrawal of 5-FU administration, the diarrheal cases started to disappear and no cases of diarrhea were found on days 12 and 13 of the experiment in Evodiamine 50 and 100 mg/kg and loperamide (3 mg/kg) treatment.

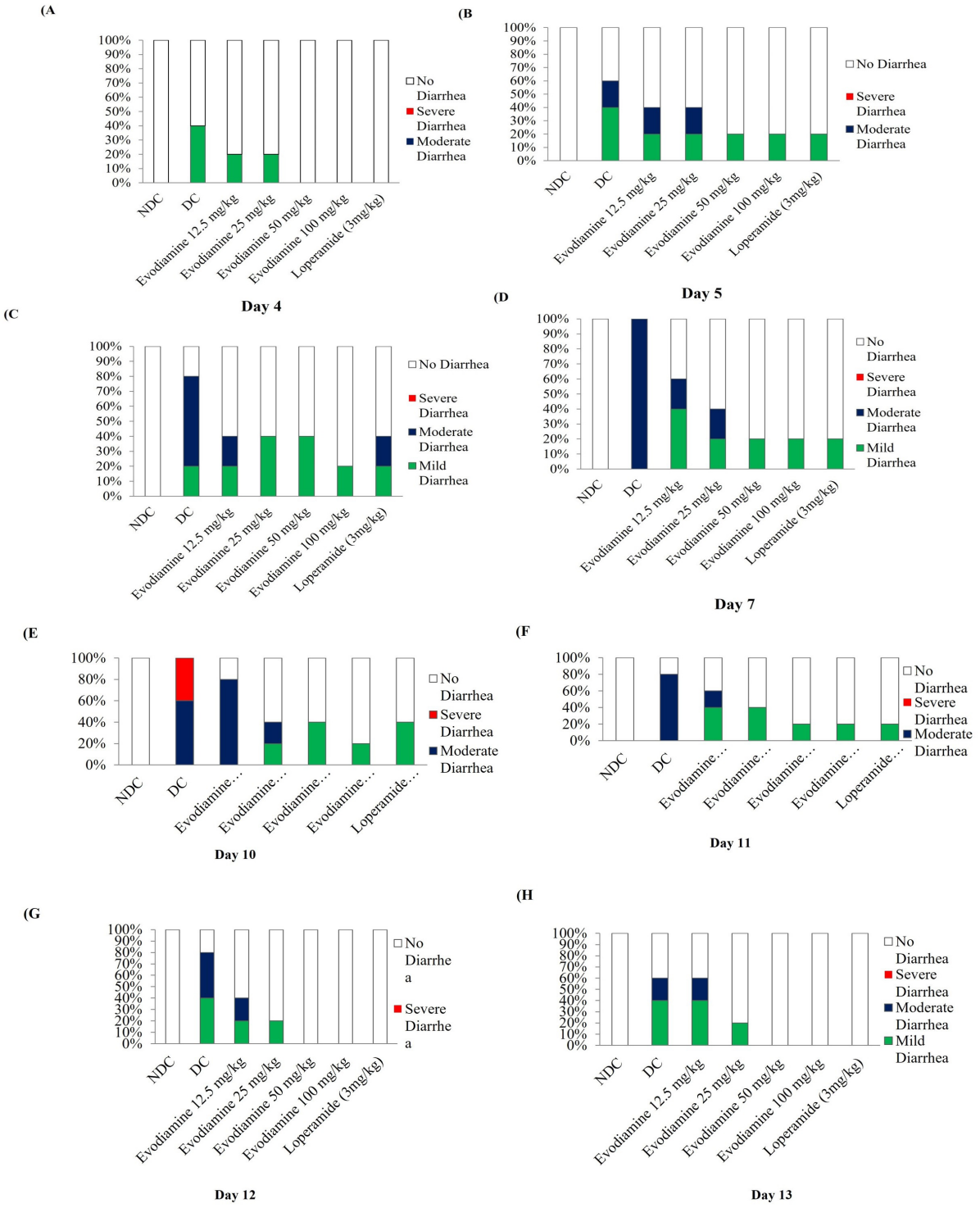

Figure 3: Effect of Evodiamine on the rate and intensity of chemotherapy (5-FU) induced diarrhea.

Swiss albino female rats (8-12 weeks) were pre-treated with Evodiamine (12.5, 25, 50 and 100 mg/kg) or loperamide (3 mg/kg) for the first 3 days. Then 5-FU (50 mg/kg/day, i.p.) was injected to rats for 7 consecutive days starting from day 4 to day 10. At the end of 5-FU therapy, the rats were further treated with Evodiamine and loperamide for 3 more consecutive days up to day 13. The rate and intensity of diarrhea was measured as described in the Methodology section. Mild diarrhea: staining of anus; Moderate diarrhea: staining over top of legs and lower abdomen; Severe diarrhea: staining over legs and higher abdomen, often with continual anal leakage.

Table 1: Effect of Evodiamine on body weight of 5-FU induced diarrheal rats.

Sl. No.	Treatment group of animals	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13
1	NDC	185.67	186.33	187.33±4.05518	187.00	188.33	188.67	190.00	190.00	191.00	192.66±4.37163	192.67	193.33	194.33±4.25572
2	DC	192.00	193.33	194.33±3.17980	192.00	188.33	184.67	179.67	176.33	171.67	167.66±2.90593**	165.67	165.67	166.66±2.60342**
3	Evodiamine 12.5 mg/kg	183.67	184.67	185.33±5.36449	183.67	181.00	178.67	181.00	179.00	177.67	178.66±5.17472	178.00	179.67	181.88±5.69600
4	Evodiamine 25 mg/kg	185.00	186.00	186.66±4.05518	185.33	183.67	182.33	181.00	180.67	180.33	179.33±3.17980	180.00	182.00	184.00±2.30940
5	Evodiamine 50 mg/kg	191.67	192.67	193.66±4.33333	192.67	192.00	191.00	189.67	188.67	187.00	185.66±3.75648	186.00	187.00	188.33±3.75648
6	Evodiamine 100 mg/kg	194.33	195.33	196.66±4.66667	196.33	195.67	193.33	192.00	190.33	189.33	188.33±5.23974	189.67	191.67	193.33±5.23874
7	Loperamide (3 mg/kg)	188.33	189.33	190.66±8.98765	190.67	189.67	188.33	188.00	186.33	185.00	183.00±7.93725	182.33	184.00	186.00±7.57188

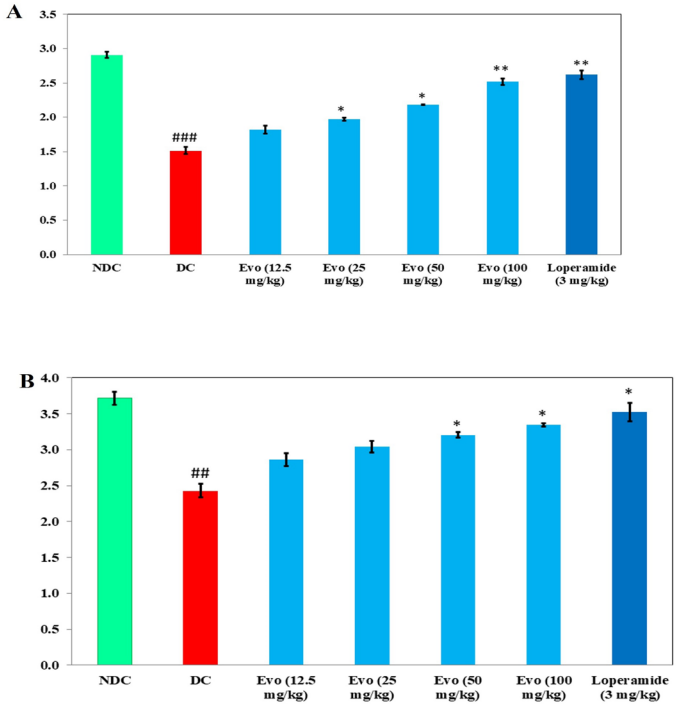

Figure 4: Effect of Evodiamine on the thymus and spleen index.

At the end of the experiment, the rats were sacrificed and thymus and spleen weights were measured to calculate the thymus (Figure 4a) and spleen index (Figure 4b) as mentioned in the Methodology section. The data are S.E.M. of five animals in each group. ## $p<0.01$ (Figure 4B), ### $p<0.001$ (Figure 4a) compared to Non-Diarrheal Control (NDC) group; *$p<0.05$, **$p<0.01$, ***$p<0.001$ compared to Diarrheal Control (DC) group. Evo: Evodiamine.

Evodiamine improved 5-FU induced diarrhea score in Swiss albino rats

The impact of Evodiamine on 5-FU induced diarrhea score has been presented in Table 3 and Figure 3. The rate and score of diarrheas have been recorded everyday with the onset of 5-FU treatment. As revealed in Table 3 and Figure 3a, 5-FU treatment on the 1st day of 5-FU treatment (4th day of the experiment) caused 40% cases of diarrhea in experimental rats with a score of 1 of each. Evodiamine at doses 12.5 and 25 mg/kg treatment groups were observed to have 20% cases of diarrhea with a score of 1 in both of the cases; whereas Evodiamine at 50 and 100 mg/kg treatment prevented the induction of diarrhea with a score of zero (0). Loperamide 3 mg/kg also exhibited a similar effect on rats with a diarrhea score of zero (0). The diarrhea score has continued to increase everyday with the 5-FU treatment group and on day 4 and 5 of 5-FU treatment (experiment day 7), 100% incidence of diarrhea was noted among the treated group with a diarrhea score of 2 for all the animals (Table 3, Figures 3d and 3e). On day 4th and 5th of 5-FU treatment, both of the Evodiamine at 50 and 100 mg/kg prevented the incidence of diarrhea to 20% with a diarrhea score of 1, similar to that of the loperamide treatment group. On day 6 and 7 of 5-FU treatment (experiment day 9 and 10), 100% incidence of diarrhea was observed among the animals of the 5-FU control group with a diarrhea score 2 (80%) and 3

Table 3: Effect of Evodiamine on 5-FU induced diarrhea score in Swiss albino rats.

Treatment group of animals	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13
NDC	0	0	0	0	0	0	0	0	0	0	0	0	0
DC	0	0	0	1, 1	1, 2, 1	2, 2, 2, 1	2, 2, 2, 2, 2	2, 2, 2, 2, 2	2, 2, 3, 2, 2	2, 2, 3, 3, 2	2, 2, 2, 2	2, 2, 1, 1	2, 1, 1
Evodiamine 12.5 mg/kg	0	0	0	1	1, 2	1, 2	1, 1, 2	2, 2, 1	2, 2, 2, 2	2, 2, 2, 2	2, 1, 1	1, 2	1
Evodiamine 25 mg/kg	0	0	0	1	1, 1	1, 1	1, 2	1, 1, 2	1, 1, 2	1, 2	1, 1	1	0
Evodiamine 50 mg/kg	0	0	0	0.00	1	1, 1	1	1	1, 1	1, 1	1	0	0
Evodiamine 100 mg/kg	0	0	0	0.00	1	1	1	1	1, 1	1	1	0	0
Loperamide (3 mg/kg)	0	0	0	0.00	1	1, 1	1	1	1	1, 1	1	0	0
Diarrhea score													

(20%) (Figures 3f and 3g and Table 3). Evodiamine at 50 mg/kg concentration prevented the incidence of diarrhea to 40% with a score of 1 on experiment day 9 and 10. Whereas, Evodiamine at 100 mg/kg concentration on the same days similarly but more potentially prevented the diarrhea incidence to 40% and 20%, respectively with a diarrhea score of 1 on both of the days. No case of diarrhea was noted in the case of experimental rats treated with Evodiamine 50 and 100 mg/kg one day after the withdrawal of 5-FU treatment (Figures 3i and j). Our investigation resulted in the dose-dependent improvement of the incidence and score of diarrheas similar to that of loperamide 3 mg/kg.

Evodiamine improved thymus and spleen indexes in 5-FU induced diarrheal rats

The effect of Evodiamine on thymus and spleen indexes has been presented in Figures 4a and b, respectively. The rats were pre-treated with Evodiamine for 3 days before, during and after the treatment of 5-FU (50 mg/kg) for 7 consecutive days. After completion of 13 days experiment period, the rats were euthanized and the thymus/spleen index was calculated as mentioned in the Methodology section. Our study resulted that treatment of rats with 5-FU significantly diminished the thymus (###p<0.001) and spleen indexes (##p<0.01) after 7 days of 5-FU treatment. However, treatment of rats with Evodiamine at 25 (*p<0.05), 50 (*p<0.05), 100 mg/kg (**p<0.01) concentrations and loperamide 3 mg/kg (**p <0.01) considerably elevated the thymus index (Figure 4a). Similarly, Evodiamine treatment at the 50 (*p<0.05), 100 (*p<0.05) concentrations and loperamide 3 mg/kg (*p <0.05) significantly enhanced spleen index (Figure 4b).

DISCUSSION

Chemotherapy-induced diarrhea is one of the major difficulties in the treatment of cancers which retards the effective treatment regimen, hindrances to reduce the chemotherapy dose below the therapeutic level and ultimately causes failure of chemotherapeutic treatment.

Loperamide is an agonist on the opioid receptor in the GI tract which decreases peristalsis movement and increases fluid reabsorption.[56] High dose loperamide (a synthetic opiate derivative) ameliorates diarrhea connected with chemotherapy. However, loperamide is utilized as the primary therapy to treat chemotherapy-induced diarrhea despite but exerts several adverse-effects like constipation, stomach pain, dizziness, dry mouth, rashes, drowsiness, dizziness, bloating, nausea and vomiting.[57] High-dose loperamide usage should be accompanied by regular monitoring due to the potential risk of paralytic ileus.[58,59] Besides, the effectiveness of loperamide as monotherapy for severe diarrhea is limited.[60,61] Scientists worldwide are actively seeking new compounds, particularly phytomedicines, to cure chemotherapy-induced diarrhea and other issues. This is due to the significant adverse effects associated with current pharmacological treatments.

Recently, TCM has attracted more interests of medical professionals to mitigate cancer-related adverse effects and to reduce the chemotherapy-connected complications. Evodiamine is an indoloquinazoline alkaloid is a major bioactive compound extracted from fruits of *E. rutaecarpa* Benth under the Rutaceae family. Evodiamine and its derivatives have been scientifically investigated and established for its different pharmacological activities.[41] However, the therapeutic potential of Evodiamine

against chemotherapy-induced diarrhea has not been assessed by any researcher.

The current work evaluated the preventive and treatment potential of Evodiamine (the bioactive compound from the fruit of *E. turaecarpa* Benth) against CID. Our investigation resulted that Evodiamine dose-dependently prevented and improved the conditions of 5-FU (50/kg) induced diarrhea with the reduction of diarrhea rate and score in Swiss albino rats (Tables 2 and 3, as well as Figure 3). Besides, Evodiamine treatment significantly improved chemotherapy-induced body weight and thymus and spleen indexes in rats (Figures 2 and 4). Evodiamine thus prevented and improved the rate and intensity of diarrhea as well as diarrhea-related other factors such as loss of body weight and organ weight (thymus and spleen). 5-FU stimulates bowel wall inflammation, consequently inducing increased accretion of fluid and electrolytes into the intestinal lumen which substantially disrupting the osmotic gradient in the GI tract and ultimately leads to the elevated production of fluid into the stool.[60,62] The probable mechanism of action of antidiarrheal effect of Evodiamine is that by acting at m-opioid receptor in the intestine, Evodiamine slows down the intestinal peristalsis movement. Besides, Evodiamine demonstrates anti-secretory properties of intestine by the Thromboxane A2 (TXA2) inhibition, which is produced by activated platelets.[63]

Experimental evidences showed that 5-FU triggers apoptosis in mouse thymocytes and spleen via stimulation of CD95 (APO-1/Fas) system. Apoptosis in thymocytes and spleen at 18 hr after 5-FU treatment. Apoptosis reduced the organ weight and thymus and spleen cell numbers by nearly 40%. The apoptotic cell numbers found to correlate with the organ and body weight loss.[64] The probable mechanism for the prevention of the reduction of spleen and thymus weight by preventing the apoptosis of thymocytes and splenocytes by blocking the CD95(APO-1/Fas) system.

Chemotherapy-induced diarrhea can be categorized into two groups: uncomplicated (grade 1-2 without any complications) or complicated (grade 3-4 with one or more complicating signs or symptoms). It can also be classified as early onset (within 24 hr after treatment) or late-onset (more than 24 hr after treatment). Additionally, it can be further divided into persistent (lasting for more than 4 weeks) or non-persistent (lasting for less than 4 weeks) based on The National Cancer Institute's Common Terminology Criteria for Adverse Effects grading system.[2,31] Simple cases of CID can be treated by adjusting the diet and giving regular anti-diarrheal medication, but severe cases of diarrhea require strong doses of anti-diarrheal medicines and hospitalization.[2]

Our result showed that before inducing diarrhea with 5-FU, Evodiamine had no negative impact on bodyweight, rather a gradual increase of weight has been marked. However, 5-FU treatment resulted in the decrease of bodyweight in the 5-FU control when compared between before and after 5-FU treatments (**p<0.01) (Figure 2, Table 1). Evodiamine ameliorated the 5-Fu-triggered body weight reduction in rats, demonstrating regulations in food intake in addition to the loss of intestinal contents due to decrease of cases and severity of diarrhea. Chemotherapy-induced diarrhea may be linked to changes in gut movement, which can hinder the absorption of fluids and disrupt the balance of microorganisms in the intestines. Hemorrhage is typically accompanied by diarrhea in people receiving chemotherapy.[17] We have observed that fecal blood has come out in grade 3 diarrhea in rats challenged with 5-FU at days 6 and 7 (Figures 3f and g) and Evodiamine treatment at 25, 50 and 100 mg/kg concentrations prevented the stool bleeding. These outcomes highlight that Evodiamine has the efficacy of decreasing the ulcerative wounds in the gastrointestinal tract.

Prior study demonstrated that the administration of 5-FU resulted in a considerable diminution in both food uptake and bodyweight.[65] Cancer patients have a decrease in their consumption of food and weight due to feelings of nausea and discomfort caused by chemotherapy treatment.[66] In our study, the Evodiamine to 5-FU treated rats significantly protected the loss of body weight and maintained the bodyweight nearly the normal level (Table 1 and Figure 2).

5FU is frequently used as a potential chemotherapeutic agent. Whereas, nearly 80% of patients receiving 5FU develop chemotherapyinduced mucositis including diarrhea.[67] This unpleasant effect can exacerbate the QOL in people receiving chemotherapy and may result in premature termination of chemotherapy. Hence, there is a need for efficient preventive and therapeutic drugs to combat chemotherapy related diarrhea.

All the rats in this investigation had the clinical manifestations of diarrhea. Additionally, we observed a substantial drop in the thymus and spleen indexes of the model rats as compared to those of the control. The levels of thymus and spleen indices, which are influenced by the degree of lymphocyte proliferation, can be utilized as indicators to partially assess the immunological function of the host.[68] The findings demonstrated that the administration of 5-Fu chemotherapy had an impact on the immune system of the experimental group.

CONCLUSION

Our study demonstrated that Evodiamine prevented and potentially ameliorated the incidence and severity of 5-FU-induced diarrhea in an experimental model. Treatment of chemotherapy-induced rats with Evodiamine also significantly prevented and retarded the loss of body weight and thymus and spleen weight indexes as well. This is the first report of Evodiamine for the effect on chemotherapy-induced diarrhea. From our findings, we can conclude that Evodiamine can be a talented salutary agent to prevent and treat of chemotherapy-induced

diarrhea. However, as this is a preliminary report, further investigations are encouraged.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

BJH conceptualized, designed, monitored, carried out experiments and supervised the whole study. KS contributed in the design of the study and carried out experiments. BJH, MMW, GYZ and HW carried out experiments and involved in manuscript preparation and data analysis. BJH and KS wrote the manuscript draft and they contributed equally in planning, designing of the study, performing experiments and writing manuscript draft. All authors read the manuscript and agreed to be accountable for all aspects of the work and approved the final manuscript.

STATEMENT OF HUMAN AND ANIMAL RIGHTS

All the assays involving animals were performed as per the Experimental Animal Care and Use Protocol by the Animal Ethics Committee of Northwest University First Hospital and as per the Guidelines for Care and Use of Laboratory Animals published by the US National Institutes of Health. The Federation of European Laboratory Animal Science Associations (FELASA) guidelines were adopted to mitigate the pain of the experimental rats.

ETHICAL APPROVAL

The animal ethical approval was obtained from the Animal Ethics Committee of Northwest University First Hospital (Approval Number: 20230211).

ABBREVIATIONS

FELASA: Federation of European Laboratory Animal Science Associations; **TXA2:** Thromboxane A2; **CID:** chemotherapy-induced diarrhea; **QOL:** Quality-Of-Life; **5- FU:** 5-Fluorouracil.

SUMMARY

Traditional Chinese medicine has a long history of use to treat different types of ailments for more than 3000 years back. Treatment of chemotherapy-induced rats with Evodiamine also significantly prevented and retarded the loss of body weight and thymus and spleen weight indexes as well. This is the first report of Evodiamine for the effect on chemotherapy-induced diarrhea. From our findings, we can conclude that Evodiamine can be a talented candidate to prevent and treat chemotherapy-induced diarrhea.

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