Effects of *Pluchea lanceolata* Root Extract on Cisplatin--induced Nausea and Vomiting in Rat Pica Model

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**ABSTRACT**

Cisplatin is an effective chemotherapeutic against a wide range of cancers. However, it causes significant nausea and vomiting which limit its usefulness. In the present study, the effects of methanolic root extract of *Pluchea lanceolata* (DC.) C. B. Clarke, asteraceae (*MPL*) was investigated against cisplatin-induced nausea using a rat pica model. In rat pica model, rats react to cisplatin (emetic/nausea stimuli), with altered feeding habits, manifested by increased consumption of kaolin. The pica in rats was measured to quantify cisplatin-induced nausea, and to evaluate the protective effect of pretreatment with *MPL* given orally. Cisplatin at 3 mg/kg (i.p.) induced significant pica indicated by reduced food intake and increased kaolin consumption, suggesting the presence of nausea/emesis. Cisplatin-induced pica decreased significantly when animals were pretreated with *MPL* at doses of 400 mg/kg p.o. (*p* < 0.05). Cisplatin-induced pica was decreased significantly when animals were pretreated with *MPL* at doses of 400 mg/kg p.o. (*p* < 0.05). *MPL* pretreatment decreased cisplatin-induced kaolin intake in the rat model of simulated nausea, suggesting that *MPL* and/or its active constituent(s) may play a therapeutic role as protective against chemotherapy-induced emesis.

**Keywords:** Cisplatin, Pica, Pluchea lanceolata, Asteraceae

Chemotherapy regimens for the treatment of cancer are unfortunately better known for their toxicity than for their efficacy. Although some of the toxic effects may typically subside, only to recur and reach a second life-threatening, patients are often most fearful of the peak at approximately 48 to 72 hours after receipt of the nausea and emesis caused by chemotherapy, which are agent [5]. On the basis of the cisplatin model, emesis generally self-limited and seldom life-threatening [1]. occurring within the first 24 hours has been defined as Nausea and vomiting has been commonly reported by "acute", and emesis occurring more than 24 hours later patients ever since chemotherapeutic agents were first as "delayed" [6]. The incidence of "anticipatory emesis", used to treat cancer [2]. The severity and pattern of a third emetic syndrome, has decreased in recent years. chemotherapy-induced emesis depend on the specific "Anticipatory emesis" represents a learned response agents used, the dose, and the regimen. Cisplatin (cis-diaminedichloroplatinum), a platinum-containing emetic responses to chemotherapy [7]. As strategies for anticancer drug, is one of the most commonly used controlling emesis have improved, the frequency of cytotoxic agents in the treatment of a variety of solid malignant tumors [1] and is associated with profound [5]. Cisplatin-induced nausea and vomiting can be nausea and vomiting [3]. disruptive to a person's life in various ways. It can In the absence of effective antiemetic prophylaxis, negatively affect a patient's functional, nutritional, virtually all patients receiving cisplatin will have nausea psychological, social, physical and economical quality
of life. The pathophysiology of these symptoms has been partly attributed to oxidant injury to the intestinal epithelium. The mucosal injury results in excessive serotonin release from the enterochromaffin cells that could mediate the gastrointestinal adverse effects of chemotherapy and radiotherapy. Since, the plant material was further size reduced and oxidant injury to the gut may be the primary event stored until further use in an air tight container. The responsible for the gastrointestinal symptoms following powdered material (200 g) was extracted with chemotherapy or radiotherapy, we hypothesized that petroleum ether using a Soxhlet apparatus. The defatted pretreatment with an antioxidant should ameliorate material was air-dried, then extracted with 70% these symptoms. methanol using a Soxhlet apparatus. The extract was

Despite advances in antiemetic therapy, nausea and induced nausea/vomiting was evaluated using rat pica Kalon preparation. Kaolin was prepared based on earlier reported model of simulated emesis, where emetic stimuli is method. Briefly, pharmacological grade kaolin reflected by increasing consumption of non-nutritive hydrated aluminum silicate and gum acacia (Gum substances such as clay or kaolin. Cisplatin (Arabic) were mixed at a ratio of 99:1. A thick paste of induces significant nausea and vomiting in humans and this mixture was prepared using distilled water. The causes pica behavior in rats. In present study, paste was rolled and cut into pieces similar to regular rat effect of pretreatment with MPL on pica behavior was determined in cisplatin-treated rats.

**Materials and Methods**

**Drugs and Chemicals**

Cisplatin injection (Cipla, Ltd., India), Kaolin and Methanol (SD Fine-Chem Ltd, India) and all other chemicals were of analytical grades.

**Animals**

Male Wistar strain rats (150-250 g, 3-4 months of age) were procured from the disease-free small animal house of CCS Haryana Agriculture University, Hisar, Haryana, India. The animals were housed at 24 ± 1°C temperature, 45 ± 5% humidity, 12-h light-dark cycle, and left to acclimate for 1 week before the experiments. Rats were allowed free access to water, standard laboratory rat chow and kaolin, placed in separated containers, continuously available throughout the experiment. Experiments were carried out between 09:00 and 17:00 h. The experimental protocol was approved by the Institutional Animal Ethics Committee, GJUS&T, Hisar, Haryana and the care of the laboratory animals was taken as per the guidelines of CPCSEA, Ministry of Forests and Environment, Government of India.

**Preparation of extracts of Pluchea lanceolata**

The shade dried roots of the plant *Pluchea lanceolata* (DC.) C. B. Clarke, asteraceae, was collected from waste land of Dist. Hisar and Sirsa, Haryana in October 2009 and authenticated by Raw Materials, Herbarium and Museum division of NISCAIR, New Delhi, India [Ref. no. NISCAIR/RHMD/Consult/2009-10/1290/93]. A voucher specimen (PP-569) was deposited in the Department of Pharmaceutical Science, Guru Jambheshwar University of Science and Technology, Hisar. The plant material was further size reduced and a thick paste was rolled and cut into pieces similar to regular rat chow pellets. The pellets were dried at room temperature for 72 h. Kaolin preparation

**Kalon preparation**

Kaolin was prepared based on earlier reported model of simulated emesis, where emetic stimuli is method. Briefly, pharmacological grade kaolin reflected by increasing consumption of non-nutritive hydrated aluminum silicate and gum acacia (Gum substances such as clay or kaolin. Cisplatin (Arabic) were mixed at a ratio of 99:1. A thick paste of induces significant nausea and vomiting in humans and this mixture was prepared using distilled water. The causes pica behavior in rats. In present study, paste was rolled and cut into pieces similar to regular rat effect of pretreatment with MPL on pica behavior was determined in cisplatin-treated rats.

The rats were randomly assigned to six groups of six animals each. Group I and II treated with vehicle (distilled water) was kept as normal and control group respectively. Group III and IV were administered with MPL (200 and 400 mg/kg body wt; p.o.) for 7 days. Group V and VI were also administered with MPL (200 and 400 mg/kg body wt; p.o.) for 7 days. Group II, III and IV were injected with a single dose of cisplatin (03 mg/kg body weight; i.p.) on day 4, to induce the pica behavior. On each experimental day (next five consecutive days), kaolin intake (g), food intake (g), and body weight (g) were measured. To measure kaolin and food intake, the remaining kaolin and food from the day prior was collected including that spilled outside the containers. The collected kaolin and food were dried for 72 h to obtain dry weight (g).

**Statistical analysis**

The statistical significance of differences among values of individual parameters was evaluated by using the Student’s t test. All the values are expressed as mean ± SD. The significance was set at p < 0.05.
72, 96 and 120 h compared to normal animals of group I (p < 0.05). The MPL (200 mg/kg) pretreatment significantly decreases the kaolin intake compared to group II at 24, 48, 72 and 96 h (p < 0.05). Kaolin intake at 24 h (4.1±0.27 g) was significantly lower in MPL (200 mg/kg) pretreated animals than the animals of group II (6.9±0.43 g). However, kaolin intake was still higher than normal baseline intake at 0 h (0.3 ±0.02 g). Pretreatment with MPL (400 mg/kg) significantly reduced kaolin intake compared to group II at 24, 48, 72, 96 and 120 h (p<0.05). Moreover, the kaolin consumption was near to the baseline intake at 0 h. Fig 1. Effect of cisplatin (3 mg/kg) and cisplatin plus MPL (200 and 400 mg/kg) on kaolin intake. Values are expressed as mean ± SD. *p < 0.05 with respect to normal, †p < 0.05 with respect to control.

72, 96 and 120 h compared to normal animals of group I (baseline) compared to the group II (P<0.05). The MPL (200 mg/kg) pretreatment significantly decreases the kaolin intake compared to controls, suggesting that the group II at 24, 48, 72 and 96 h (p < 0.05). Kaolin intake at 24 h (4.1±0.27 g) was significantly lower in cisplatin induced by cisplatin at 24 and 48 h. Further, no significant variation was found in food intake by the group II (6.9± 0.43 g). However, kaolin intake was still higher than normal baseline intake at 0 h (0.3 ±0.02 g). Fig 2. Effect of cisplatin (3 mg/kg) and cisplatin plus MPL (200 and 400 mg/kg) on reduced food intake (% baseline) induced by cisplatin in rats. Values are expressed as mean ± SD. *p < 0.05 with respect to normal, †p < 0.05 with respect to control.

DISCUSSION

The present study inferred that methanolic extract from Pluchea lanceolata attenuated kaolin intake (pica) and cisplatin-induced nausea/vomiting in rats. Additionally, the antioxidant activity of MPL may be one of the mechanisms by which MPL attenuates cisplatin-induced nausea/emesis. The present study demonstrated that a single dose of MPL (200 mg/kg) significantly reduced food intake (% baseline) in cisplatin-treated rats. The increase in pica and reduced food intake at 24 h (38.6% of baseline) correspond to a nausea/emesis induced by cisplatin in baseline) and 48 h (35.7% of baseline) compared to the control group (p < 0.05). When pretreated with MPL, food intake was significantly improved at cisplatin-induced pica.

24 h as reduction in intake remained to 67.2% of baseline. The mechanism of cisplatin-induced nausea/vomiting is possibly mediated via cytotoxic damage to the enterochromaffin cells in the small intestine by ROS release and treatment with an antioxidant should reduce these side effects. Based on
these facts, the present investigation was done to evaluate the efficacy of *Pluchea lanceolata*, in cisplatin-induced pica. *In vitro* antioxidant activity of methanolic root extract of *Pluchea lanceolata* was already determined by DPPH free radical scavenging assay and hydrogen peroxide scavenging activity [26,27]. The results showed that MPL at dose of 200 mg/kg and 400 mg/kg reduced cisplatin-induced pica. This suggests that cisplatin-induced pica (nausea) could be treated with MPL. Although low doses of MPL caused reduced pica in cisplatin-treated rats, the improvement was still less as compared to normal kaolin intake.

These findings support the notion that herbal medications, such as MPL, could be an effective and inexpensive alternative for preventing chemotherapy-induced emesis without troublesome side effects.

Further, earlier studies also showed that herbal antioxidants may have a role in attenuating cisplatin-induced nausea and vomiting [28]. However, it is important to examine the interaction between the herbal extract and cisplatin, which could either hamper or augment the anticancer actions of cisplatin. As cisplatin acts by oxidative stress in tumor cells and treatment with antioxidants could detoxify ROS, the herb may prevent oxidative injury to tumor cells and sensitize the tumor cells to the anticancer effects of chemotherapy [29].

We conclude that herbal antioxidants potentially represent a new class of low-cost antiemetic agents for the treatment of chemotherapy-induced nausea/vomiting. Additional studies are required to further investigate the antiemetic actions of such herbal medications and the effects of interaction with the chemotherapeutic agents.

### REFERENCES

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**Pluchea Lanceolata and cisplatin-induced nausea/vomiting**

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