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ORIGINAL ARTICLE

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 chemotherapeutics 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. ($p < 0.05$). *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 be life-threatening, patients are often most fearful of the nausea and emesis caused by chemotherapy, which are generally self-limited and seldom life-threatening [1]. Nausea and vomiting has been commonly reported by patients ever since chemotherapeutic agents were first used to treat cancer [2]. The severity and pattern of chemotherapy-induced emesis depend on the specific agents used, the dose, and the regimen. Cisplatin (cis-diaminedichloroplatinum), a platinum-containing anticancer drug, is one of the most commonly used cytotoxic agents in the treatment of a variety of solid malignant tumors [1] and is associated with profound nausea and vomiting [3].

In the absence of effective antiemetic prophylaxis, virtually all patients receiving cisplatin will have nausea and vomiting 1 to 2 hours after receiving chemotherapy [4]. At approximately 18 to 24 hours, the emesis typically subsides, only to recur and reach a second peak at approximately 48 to 72 hours after receipt of the agent [5]. On the basis of the cisplatin model, emesis occurring within the first 24 hours has been defined as 'acute', and emesis occurring more than 24 hours later as 'delayed' [6]. The incidence of 'anticipatory emesis', a third emetic syndrome, has decreased in recent years. 'Anticipatory emesis' represents a learned response conditioned by the severity and duration of previous emetic responses to chemotherapy [7]. As strategies for controlling emesis have improved, the frequency of anticipatory emesis has decreased.

Cisplatin-induced nausea and vomiting can be disruptive to a person's life in various ways. It can negatively affect a patient's functional, nutritional, psychological, social, physical and economical quality of life. The pathophysiology of these symptoms has been partly attributed to oxidant injury to the intestinal epithelium [8,9]. The mucosal injury results in excessive serotonin release from the enterochromaffin cells that could mediate the gastrointestinal adverse effects of chemotherapy and radiotherapy [10-14]. Since oxidant injury to the gut may be the primary event responsible for the gastrointestinal symptoms following chemotherapy or radiotherapy, we hypothesized that pretreatment with an antioxidant should ameliorate these symptoms.

Despite advances in antiemetic therapy, nausea and vomiting remain among the most feared adverse events associated with chemotherapy. Herbal medicines may represent an alternative new class of low-cost antiemetic agents for the treatment of chemotherapy-induced nausea/vomiting. In present paper, the efficacy of a methanolic extract of *Pluchea lanceolata* (DC.) C. B. Clarke, asteraceae, for protection against cisplatin-induced nausea/vomiting was evaluated using rat pica model of simulated emesis, where emetic stimuli is reflected by increasing consumption of non-nutritive substances such as clay or kaolin [15-18]. Cisplatin induces significant nausea and vomiting in humans and causes pica behavior in rats [19-20]. In present study, 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^{o}C temperature, 45 ± 5% humidity, 12-h light-dark cycle, and left to acclimatize 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 (India), 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 stored until further use in an air tight container. The powdered material (200 g) was extracted with petroleum ether using a Soxhlet apparatus. The defatted material was air-dried, then extracted with 70% methanol using a Soxhlet apparatus. The extract was filtered through Whatman No. 1 filter paper and the supernatant was evaporated using rotary evaporator at 45^{o}C and the final liquid suspension was lyophilized to get a reddish brown powder with 6.2% yield, hereafter referred as *MPL* (Methanolic extract of *Pluchea lanceolata*).

Kaolin preparation

Kaolin was prepared based on earlier reported method [21]. Briefly, pharmacological grade kaolin (hydrated aluminum silicate) and gum acacia (Gum Arabic) were mixed at a ratio of 99:1. A thick paste of this mixture was prepared using distilled water. The paste was rolled and cut into pieces similar to regular rat chow pellets. The pellets were dried at room temperature for 72 h.

Experimental design

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 $p < 0.05$.

RESULTS

Kaolin intake (pica) was measured in rats of various groups under study. Fig 1 demonstrates that *MPL* pretreatment significantly reduced kaolin intake induced by cisplatin. Cisplatin induced a significant increase in kaolin consumption in the animals of group II at 24, 48,

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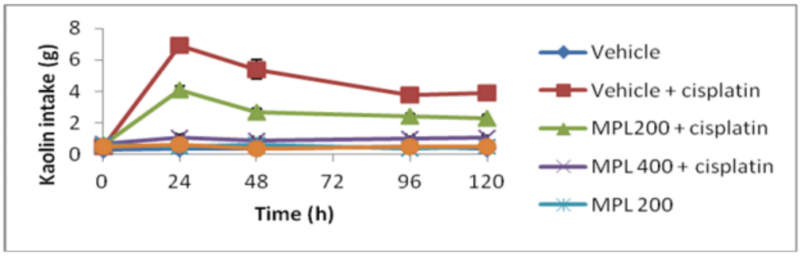

Fig 1. Effect of cisplatin (3 mg/kg) and cisplatin plus *MPL* (200 and 400 mg/kg) on kaolin intake. Values are expressed as mean ± SD. $^{a}p < 0.05$ with respect to normal, $^{b}p < 0.05$ with respect to control.

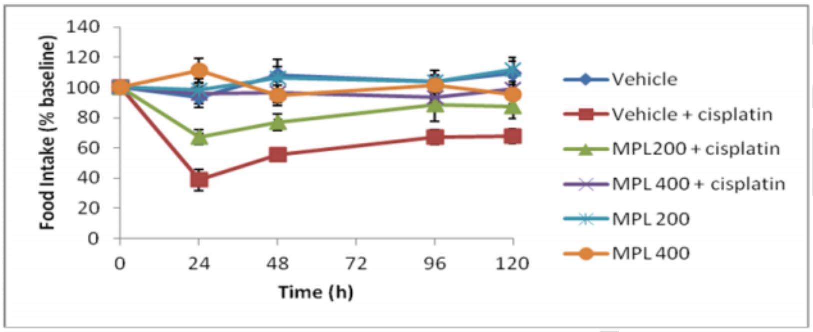

Fig 2. Effect of cisplatin (3 mg/kg) and cisplatin plus *MPL* (200 and 400 mg/kg) on reduced food intake (% baseline) induced by cisplatin in rats. Values are expressed as mean ± SD. $^{a}p < 0.05$ with respect to normal, $^{b}p < 0.05$ with respect to control.

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 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 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, and 72, 96 and 120 h ($p < 0.05$). Moreover, the kaolin consumption was near to the baseline intake at 0 h. This suggests that *MPL* at 400 mg/kg reduced the pica for longer and to a greater magnitude compared to *MPL* at 200 mg/kg. The group I, V and VI did not show any significant variation in kaolin intake during the experiment when compared to its baseline (0 h). Fig 2 shows the effect of pretreatment with *MPL* on food intake following cisplatin administration.

Treatment with cisplatin in the group II resulted in a significant reduction in food intake at 24 h (38.6% of baseline) and 48 h (55.7% of baseline) compared to the control group I ($p < 0.05$). When pretreated with *MPL* 200 mg/kg, food intake was significantly improved at 24 h as reduction in intake remained to 67.2% of baseline. However, the food intake was still less, compared to the control group ($p < 0.05$). The treatment with *MPL* 400 mg/kg, food intake improved significantly at 24 h (reduction in intake; 95.9% of baseline) compared to the group II (P<0.05). Additionally, after 48 h, reduction of food intake was insignificant as compared to baseline, suggesting that *MPL* significantly improved the reduction in food intake induced by cisplatin at 24 and 48 h. Further, no significant variation was found in food intake by the animals of group I, V and VI, compared to its baseline (0 h).

Discussion

The present study inferred that methanolic extract from *Pluchea lanceolata* attenuated kaolin intake (pica) in cisplatin-treated 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 cisplatin (3 mg/kg; i.p.) induced an alteration in food habit, indicated by increased kaolin consumption and reduced food intake in rats. The increase in pica corresponds to a nausea/emesis induced by cisplatin in humans [22]. The study also showed that methanolic extract of *Pluchea lanceolata*, effectively attenuated cisplatin-induced pica.

The mechanism of cisplatin-induced nausea/vomiting is possibly mediated via cytotoxic damage to the enterochromaffin cells in the small intestine by ROS release [23-25] and treatment with an antioxidant should reduce these side effects. Based on

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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 act by oxidative stress in tumor cells and treatment with antioxidants could detoxify ROS, the herb may prevent oxidant 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.

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