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 typically subside, only to recur and reach a second peak at approximately 48 to 72 hours after receipt of the agent, these are often most fearful of the nausea and emesis caused by chemotherapy, which are general self-limited and seldom life-threatening. Nausea and vomiting has commonly reported by patients since chemotherapy agents were first used to treat cancer. The severity and pattern of nausea/emesis depend on the specific agents used, the dose, and the regimen. Cisplatin (cis-diaminedichloroplatinum), a platinum-containing antineoplastic drug, is one of the most commonly used cytotoxic agents in the treatment of a variety of solid tumors and is associated with profound nausea and vomiting. In the absence of effective antiemetic prophylaxis, emetic responses to chemotherapy negatively affect a patient's functional, nutritional, and psychological, social, physical and economical quality of life. It can virtually all patients receiving cisplatin will have nausea and vomiting 1 to 2 hours after receiving chemotherapy, and emesis 1 to 2 hours after chemotherapy treatment decreased 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.
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 methanol 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.

Despite advances in antiemetic therapy, nausea and induced nausea/vomiting was evaluated using rat pica. 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 substances such as clay or kaolin [15-18]. Cisplatin (Arabic) were mixed at a ratio of 99:1. A thick paste of this mixture was prepared using distilled water. The causes pica behavior in rats [19-20]. 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, India, in October 2009 and authenticated by Rawla, Ministry, 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 defatted 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 referred as MPL (Methanolic extract of *Pluchea lanceolata*).

**Kaolin preparation**

Kaolin was prepared based on earlier reported method [21]. Briefly, pharmacological grade kaolin reflected by increasing consumption of non-nutritive substances such as clay or kaolin [15-18]. Cisplatin (Arabic) were mixed at a ratio of 99:1. A thick paste of this mixture was prepared using distilled water. The causes pica behavior in rats [19-20]. 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.

**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 from waste land of Dist. Hisar and Sirsa, Haryana, India, in October 2009 and authenticated by Rawla, Ministry, 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 defatted 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 referred as MPL (Methanolic extract of *Pluchea lanceolata*).

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72, 96 and 120 h compared to normal animals of group I (baseline) compared to the group II (P<0.05).

(p < 0.05). The MPL (200 mg/kg) pretreatment significantly decreases the 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 inferred that methanolic extract from Pluchea lanceolata attenuated kaolin intake (pica) consumption was near to the baseline intake at 0 h. This suggests that MPL at 400 mg/kg reduced the pica for a longer time compared to MPL at 200 mg/kg. The group I, V and VI did not show any 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 significantly reduced in food intake at 24 h (38.6% of baseline) compared to the control group (p < 0.05). When pretreated with MPL extract of Pluchea lanceolata, effectively attenuated 200 mg/kg, 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 [23-25] and treatment with an antioxidant should reduce these side effects. Based on

**DISCUSSION**

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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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