

## ORIGINAL ARTICLE

Effects of *Pluchea lanceolata* Root Extract on Cisplatin--induced Nausea and Vomiting in Rat Pica ModelNAVEEN GOYAL<sup>1\*</sup>, SURENDRA KR. SHARMA<sup>2</sup>

For author affiliations, see end of text.

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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.

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°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*).

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129 referred as *MPL* (Methanolic extract of *Pluchea*

130 *lanceolata*).

131 **Kaolin preparation**

132 Kaolin was prepared based on earlier reported

133 method [21]. Briefly, pharmacological grade kaolin

134 (hydrated aluminum silicate) and gum acacia (Gum

135 Arabic) were mixed at a ratio of 99:1. A thick paste of

136 this mixture was prepared using distilled water. The

137 paste was rolled and cut into pieces similar to regular rat

138 chow pellets. The pellets were dried at room

139 temperature for 72 h.

140 **Experimental design**

141 The rats were randomly assigned to six groups of six

142 animals each. Group I and II treated with vehicle

143 (distilled water) was kept as normal and control group

144 respectively. Group III and IV were administered with

145 *MPL* (200 and 400 mg/kg body wt; p.o.) for 7 days.

146 Group V and VI were also administered with *MPL* (200

147 and 400 mg/kg body wt; p.o.) for 7 days. Group II, III

148 and IV were injected with a single dose of cisplatin (03

149 mg/kg body weight; i.p.) on day 4, to induce the pica

150 behavior. On each experimental day (next five

151 consecutive days), kaolin intake (g), food intake (g), and

152 body weight (g) were measured. To measure kaolin and

153 food intake, the remaining kaolin and food from the day

154 prior was collected including that spilled outside the

155 containers. The collected kaolin and food were dried for

156 72 h to obtain dry weight (g).

157 **Statistical analysis**

158 The statistical significance of differences among

159 values of individual parameters was evaluated by using

160 the Student's *t* test. All the values are expressed as mean

161  $\pm$  SD. The significance was set at  $p < 0.05$ .

## 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  $\pm$  1°C temperature, 45  $\pm$  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

## 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,

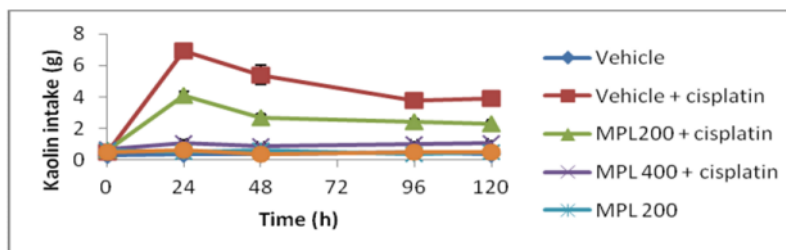


Fig 1. Effect of cisplatin (3 mg/kg) and cisplatin plus *MPL* (200 and 400 mg/kg) on kaolin intake. Values are expressed as mean  $\pm$  SD. <sup>a</sup> $p < 0.05$  with respect to normal, <sup>b</sup> $p < 0.05$  with respect to control.

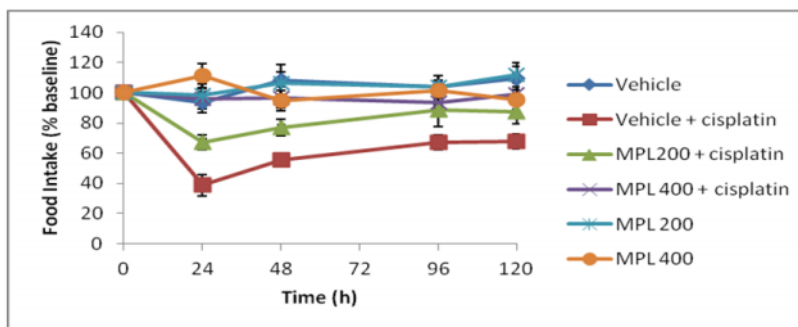


Fig 2. Effect of cisplatin (3 mg/kg) and cisplatin plus *MPL* (200 and 400 mg/kg) on reduced food intake (% baseline) induced by cisplatin in rats. Values are expressed as mean  $\pm$  SD. <sup>a</sup> $p < 0.05$  with respect to normal, <sup>b</sup> $p < 0.05$  with respect to control.

72, 96 and 120 h compared to normal animals of group I (97 baseline) compared to the group II ( $P < 0.05$ ). 168  
169 ( $p < 0.05$ ). The *MPL* (200 mg/kg) pretreatment 198 Additionally, after 48 h, reduction of food intake was  
170 significantly decreases the kaolin intake compared to 199 insignificant as compared to baseline, suggesting that  
171 the group II at 24, 48, 72 and 96 h ( $p < 0.05$ ). Kaolin 200 *MPL* significantly improved the reduction in food intake  
172 intake at 24 h ( $4.1 \pm 0.27$  g) was significantly lower in 201 induced by cisplatin at 24 and 48 h. Further, no  
173 *MPL* (200 mg/kg) pretreated animals than the animals 202 significant variation was found in food intake by the  
174 of group II ( $6.9 \pm 0.43$  g). However, kaolin intake was 203 animals of group I, V and VI, compared to its baseline  
175 still higher than normal baseline intake at 0 h ( $0.3 \pm 0.02$  204 (0 h).

176 g). Pretreatment with *MPL* (400 mg/kg) significantly 177  
177 reduced kaolin intake compared to group II at 24, 48, 205  
178 and 72, 96 and 120 h ( $p < 0.05$ ). Moreover, the kaolin

179 consumption was near to the baseline intake at 0 h. This 206 The present study inferred that methanolic extract  
180 suggests that *MPL* at 400 mg/kg reduced the pica for 207 from *Pluchea lanceolata* attenuated kaolin intake (pica)  
181 longer and to a greater magnitude compared to *MPL* at 208 in cisplatin-treated rats. Additionally, the antioxidant  
182 200 mg/kg. The group I, V and VI did not show any 209 activity of *MPL* may be one of the mechanisms by  
183 significant variation in kaolin intake during the 210 which *MPL* attenuates cisplatin-induced nausea/emesis.  
184 experiment when compared to its baseline (0 h). Fig 2 211 The present study demonstrated that a single dose of  
185 shows the effect of pretreatment with *MPL* on food 212 cisplatin (3 mg/kg; i.p.) induced an alteration in food  
186 intake following cisplatin administration. 213 habit, indicated by increased kaolin consumption and

187 Treatment with cisplatin in the group II resulted in a 214 reduced food intake in rats. The increase in pica  
188 significant reduction in food intake at 24 h (38.6% of 215 corresponds to a nausea/emesis induced by cisplatin in  
189 baseline) and 48 h (55.7% of baseline) compared to the 216 humans [22]. The study also showed that methanolic  
190 control group I ( $p < 0.05$ ). When pretreated with *MPL* 217 extract of *Pluchea lanceolata*, effectively attenuated  
191 200 mg/kg, food intake was significantly improved at 218 cisplatin-induced pica.

192 24 h as reduction in intake remained to 67.2% of 219 The mechanism of cisplatin-induced  
193 baseline. However, the food intake was still less, 220 nausea/vomiting is possibly mediated via cytotoxic  
194 compared to the control group ( $p < 0.05$ ). The treatment 221 damage to the enterochromaffin cells in the small  
195 with *MPL* 400 mg/kg, food intake improved 222 intestine by ROS release [23-25] and treatment with an  
196 significantly at 24 h (reduction in intake; 95.9% of 223 antioxidant should reduce these side effects. Based on

## DISCUSSION

- 224 these facts, the present investigation was done to 281 9.  
 225 evaluate the efficacy of *Pluchea lanceolata*, in cisplatin- 282  
 226 induced pica. *In vitro* antioxidant activity of methanolic 283  
 227 root extract of *Pluchea lanceolata* was already 284 10.  
 228 determined by DPPH free radical scavenging assay and 285  
 229 hydrogen peroxide scavenging activity [26,27]. The 286  
 230 results showed that *MPL* at dose of 200 mg/kg and 400 287 11.  
 231 mg/kg reduced cisplatin-induced pica. This suggests 288  
 232 that cisplatin-induced pica (nausea) could be treated 289 12.  
 233 with *MPL*. Although low doses of *MPL* caused reduced 290  
 234 pica in cisplatin-treated rats, the improvement was still 291  
 235 less as compared to normal kaolin intake. 292  
 236 These findings support the notion that herbal 293 13.  
 237 medications, such as *MPL*, could be an effective and 294  
 238 inexpensive alternative for preventing chemotherapy- 295  
 239 induced emesis without troublesome side effects. 296 14.  
 240 Further, earlier studies also showed that herbal 297  
 241 antioxidants may have a role in attenuating cisplatin- 298  
 242 induced nausea and vomiting [28]. However, it is 299  
 243 important to examine the interaction between the herbal 300  
 244 extract and cisplatin, which could either hamper or 301 15.  
 245 augment the anticancer actions of cisplatin. As cisplatin 302  
 246 act by oxidative stress in tumor cells and treatment with 303 16.  
 247 antioxidants could detoxify ROS, the herb may prevent 304  
 248 oxidant injury to tumor cells and sensitize the tumor 305  
 249 cells to the anticancer effects of chemotherapy [29]. 306 17.  
 250 We conclude that herbal antioxidants potentially 307  
 251 represent a new class of low-cost antiemetic agents for 308  
 252 the treatment of chemotherapy-induced 309 18.  
 253 nausea/vomiting. Additional studies are required to 310  
 254 further investigate the antiemetic actions of such herbal 311  
 255 medications and the effects of interaction with the 312  
 256 chemotherapeutic agents. 313
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345 **CURRENT AUTHOR ADDRESSES**

346 Naveen Goyal, Roorkee College of Pharmacy, Roorkee-247667,  
347 Haridwar, Uttarakhand, India. E-mail: hsmaveen@yahoo.co.in  
348 (Corresponding author)

349 Surendra Kr. Sharma, Department of Pharmaceutical Sciences, Guru  
350 Jambheshwar University of Science and Technology, Hisar-  
351 125001, Haryana, India.

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