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1 ORIGINAL ARTICLE

Effects of Pluchea lanceolata Root Extract on ^₃Cisplatin--induced Nausea and Vomiting in Rat Pica 4 Model

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9 ABSTRACT

10 Cisplatin is an effective chemotherapeutics against a wide range of cancers. However, it causes 11 significant nausea and vomiting which limit its usefulness. In the present study, the effects of methanolic 12 root extract of Pluchea lanceolata (DC.) C. B. Clarke, asteraceae (MPL) was investigated against 13 cisplatin-induced nausea using a rat pica model. In rat pica model, rats react to cisplatin (emetic/nausea 14 stimuli), with altered feeding habits, manifested by increased consumption of kaolin. The pica in rats was 15 measured to quantify cisplatin-induced nausea, and to evaluate the protective effect of pretreatment with 16 MPL given orally. Cisplatin at 3 mg/kg (i.p.) induced significant pica indicated by reduced food intake and 17 increased kaolin consumption, suggesting the presence of nausea/emesis. Cisplatin-induced pica 18 decreased significantly when animals were pretreated with MPL at doses of 400 mg/kg p.o. (p < 0.05). 19 MPL pretreatment decreased cisplatin-induced kaolin intake in the rat model of simulated nausea, 20 suggesting that MPL and/or its active constituent(s) may play a therapeutic role as protective against 21 chemotherapy-induced emesis.

22 Keywords: Cisplatin, Pica, Pluchea lanceolata, Asteraceae

Chemotherapy regimens for the treatment of cancer 41 and vomiting 1 to 2 hours after receiving chemotherapy 24 are unfortunately better known for their toxicity than for 42 [4]. At approximately 18 to 24 hours, the emesis 25 their efficacy. Although some of the toxic effects may 43 typically subsides, only to recur and reach a second 26 be life-threatening, patients are often most fearful of the 44 peak at approximately 48 to 72 hours after receipt of the 27 nausea and emesis caused by chemotherapy, which are 45 agent [5]. On the basis of the cisplatin model, emesis 28 generally self-limited and seldom life-threatening [1]. 46 occurring within the first 24 hours has been defined as 29 Nausea and vomiting has been commonly reported by 47 'acute', and emesis occurring more than 24 hours later Jused to treat cancer [2]. The severity and pattern of 49 a third emetic syndrome, has decreased in recent years. 32 chemotherapy-induced emesis depend on the specific 50 'Anticipatory emesis' represents a learned response 33 agents used, the dose, and the regimen. Cisplatin (cis- 51 conditioned by the severity and duration of previous 34 diaminedichloroplatinum), 35 anticancer drug, is one of the most commonly used 53 controlling emesis have improved, the frequency of 36 cytotoxic agents in the treatment of a variety of solid 54 anticipatory emesis has decreased. 37 malignant tumors [1] and is associated with profound 55 38 nausea and vomiting [3].

40 virtually all patients receiving cisplatin will have nausea 58 psychological, social, physical and economical quality

patients ever since chemotherapeutic agents were first 48 as 'delayed' [6]. The incidence of 'anticipatory emesis', a platinum-containing 52 emetic responses to chemotherapy [7]. As strategies for

Cisplatin-induced nausea and vomiting can be 56 disruptive to a person's life in various ways. It can In the absence of effective antiemetic prophylaxis, 57 negatively affect a patient's functional, nutritional,

59 of life. The pathophysiology of these symptoms has 114 NISCAIR, 60 been partly attributed to oxidant injury to the intestinal 115 NISCAIR/RHMD/Consult/-2009-10/1290/931. 61 epithelium [8,9]. The mucosal injury results in 116 voucher specimen (PP-569) was deposited in the 62 excessive serotonin release from the enterochromaffin 17 Department of Pharmaceutical 63 cells that could mediate the gastrointestinal adverse 118 Jambheshwar University of Science and Technology, 64 effects of chemotherapy and radiotherapy [10-14]. Since 119 Hisar. The plant material was further size reduced and 65 oxidant injury to the gut may be the primary event 120 stored until further use in an air tight container. The 66 responsible for the gastrointestinal symptoms following 121 powdered material (200 g) was extracted with 67 chemotherapy or radiotherapy, we hypothesized that 122 petroleum ether using a Soxhlet apparatus. The defatted 68 pretreatment with an antioxidant should ameliorate 123 material was air-dried, then extracted with 70% 69 these symptoms.

71 vomiting remain among the most feared adverse events 126 supernatant was evaporated using rotary evaporator at 72 associated with chemotherapy. Herbal medicines may 127 45°C and the final liquid suspension was lyophilized to 73 represent an alternative new class of low-cost antiemetic 128 get a reddish brown powder with 6.2% yield, hereafter 74 agents for the treatment of chemotherapy-induced 129 referred as MPL (Methanolic extract of Pluchea 75 nausea/vomiting. In present paper, the efficacy of a130 lanceolata). 76 methanolic extract of *Pluchea lanceolata* (DC.) C. B. 77 Clarke, asteraceae, for protection against cisplatin-78 induced nausea/vomiting was evaluated using rat pica₁₃₂ 79 model of simulated emesis, where emetic stimuli is 133 method [21]. Briefly, pharmacological grade kaolin 80 reflected by increasing consumption of non-nutritive 134 (hydrated aluminum silicate) and gum acacia (Gum 81 substances such as clay or kaolin [15-18]. Cisplatin 135 Arabic) were mixed at a ratio of 99:1. A thick paste of 82 induces significant nausea and vomiting in humans and 136 this mixture was prepared using distilled water. The 83 causes pica behavior in rats [19-20]. In present study,137 paste was rolled and cut into pieces similar to regular rat 84 effect of pretreatment with MPL on pica behavior was 138 chow pellets. The pellets were dried at room 85 determined in cisplatin-treated rats.

MATERIALS AND METHODS

87 Drugs and Chemicals

Cisplatin injection (Cipla, Ltd., India), Kaolin and 89 Methanol (SD Fine-Chem Ltd, India) and all other 90 chemicals were of analytical grades.

91 Animals

93 age) were procured from the disease-free small animal 94 house of CCS Haryana Agriculture University, Hisar, 95 Haryana, India. The animals were housed at $24 \pm 1^{\circ}$ C 96 temperature, $45 \pm 5\%$ humidity, 12-h light-dark cycle, 97 and left to acclimatize for 1 week before the 98 experiments. Rats were allowed free access to water, 99 standard laboratory rat chow and kaolin, placed in 100 separated containers continuously available throughout 101 the experiment. Experiments were carried out between 157 Statistical analysis 102 09:00 and 17:00 h. The experimental protocol was 158 103 approved by the Institutional Animal Ethics Committee, 159 values of individual parameters was evaluated by using 104 GJUS&T, Hisar, Haryana and the care of the laboratory 160 the Student's t test. All the values are expressed as mean 105 animals was taken as per the guidelines of CPCSEA, 160 the significance was set at p < 0.05. 106 Ministry of Forests and Environment, Government of 107 India.

108 Preparation of extracts of Pluchea lanceolata

The shade dried roots of the plant *Pluchea* 163 110 lanceolata (DC.) C. B. Clarke, asteraceae, was collected 164 groups under study. Fig 1 demonstrates that MPL 111 from waste land of Dist. Hisar and Sirsa, Haryana 165 pretreatment significantly reduced kaolin intake induced 112 (India), in October 2009 and authenticated by Raw166 by cisplatin. Cisplatin induced a significant increase in

New Delhi, India no. 124 methanol using a Soxhlet apparatus. The extract was Despite advances in antiemetic therapy, nausea and 125 filtered through Whatman No. 1 filter paper and the

31 Kaolin preparation

Kaolin was prepared based on earlier reported 139 temperature for 72 h.

140 Experimental design

The rats were randomly assigned to six groups of six 142 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. 46 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 Male Wistar strain rats (150-250 g, 3-4 months of 148 and IV were injected with a single dose of cisplatin (03 19 mg/kg body weight; i.p.) on day 4, to induce the pica 50 behavior. On each experimental day (next five 51 consecutive days), kaolin intake (g), food intake (g), and 2 body weight (g) were measured. To measure kaolin and 33 food intake, the remaining kaolin and food from the day 4 prior was collected including that spilled outside the 55 containers. The collected kaolin and food were dried for 6 72 h to obtain dry weight (g).

RESULTS

Kaolin intake (pica) was measured in rats of various 113 Materials, Herbarium and Museum division of 167 kaolin consumption in the animals of group II at 24, 48,

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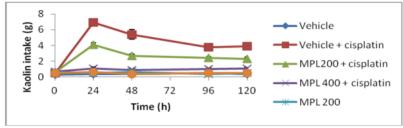


Fig 1. Effect of cisplatin (3 mg/kg) and cisplatin plus MPL (200 and 400 mg/kg) on kaolin intake. Values are expressed as mean ± SD. ^ap < 0.05 with respect to normal, ${}^{b}p < 0.05$ with respect to control.

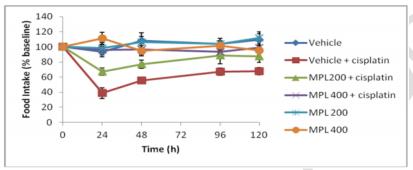


Fig 2. Effect of cisplatin (3 mg/kg) and cisplatin plus MPL (200 and 400 mg/kg) on reduced food intake (% baseline) induced by cisplatin in rats. Values are expressed as mean \pm SD. $^{a}p < 0.05$ with respect to normal, $^{b}p < 0.05$ with respect to control.

 $_{169}(p < 0.05)$. The MPL (200 mg/kg) pretreatment 98 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). Kaolin200 MPL significantly improved the reduction in food intake 172 intake at 24 h (4.1±0.27 g) was significantly lower in201 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± 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 0.02204 (0 h). 176 g). Pretreatment with MPL (400 mg/kg) significantly

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

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 any209 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 2211 The present study demonstrated that a single dose of 185 shows the effect of pretreatment with MPL on food212 cisplatin (3 mg/kg; i.p.) induced an alteration in food 186 intake following cisplatin administration.

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 MPL217 extract of Pluchea lanceolata, effectively attenuated 191200 mg/kg, food intake was significantly improved at218 cisplatin-induced pica. 192 24 h as reduction in intake remained to 67.2% of 219 193 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

168 72, 96 and 120 h compared to normal animals of group I₁₉₇ baseline) compared to the group II (P<0.05).

DISCUSSION

The present study inferred that methanolic extract 213 habit, indicated by increased kaolin consumption and Treatment with cisplatin in the group II resulted in a214 reduced food intake in rats. The increase in pica

The mechanism cisplatin-induced 196 significantly at 24 h (reduction in intake; 95.9% of 223 antioxidant should reduce these side effects. Based on

320 21.

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
227 root extract of *Pluchea lanceolata* was already 284 10.
228 determined by DPPH free radical scavenging assay and 286
229 hydrogen peroxide scavenging activity [26,27]. The 287 11.
230 results showed that *MPL* at dose of 200 mg/kg and 400 288
231 mg/kg reduced cisplatin-induced pica. This suggests 289 12.
232 that cisplatin-induced pica (nausea) could be treated 290
233 with *MPL*. Although low doses of *MPL* caused reduced 291
234 pica in cisplatin-treated rats, the improvement was still 292
235 less as compared to normal kaolin intake.
293 13.

These findings support the notion that herbal 294 295 medications, such as *MPL*, could be an effective and 238 inexpensive alternative for preventing chemotherapy-296 14. 239 induced emesis without troublesome side effects. 298 240 Further, earlier studies also showed that herbal 299 241 antioxidants may have a role in attenuating cisplatin-300 242 induced nausea and vomiting [28]. However, it is 301 15. 243 important to examine the interaction between the herbal 302 244 extract and cisplatin, which could either hamper or 303 16. 245 augment the anticancer actions of cisplatin. As cisplatin 304 246 act by oxidative stress in tumor cells and treatment with 305 247 antioxidants could detoxify ROS, the herb may prevent 306 17. 248 oxidant injury to tumor cells and sensitize the tumor 308 249 cells to the anticancer effects of chemotherapy [29].

We conclude that herbal antioxidants potentially 310 251 represent a new class of low-cost antiemetic agents for 311 252 the treatment of chemotherapy-induced 312 313 nausea/vomiting. Additional studies are required to 313 254 further investigate the antiemetic actions of such herbal 315 medications and the effects of interaction with the 256 chemotherapeutic agents.

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