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ORIGINAL ARTICLE

Han H. Aung · Lucy Dey · Sangeeta Mehendale
Jing-Tian Xie · Ji An Wu · Chun-Su Yuan

Scutellaria baicalensis extract decreases cisplatin-induced pica in rats

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Abstract *Purpose*: Nausea/vomiting are significant side effects associated with the use of chemotherapy in cancer patients. Treatment of nausea/vomiting caused by cisplatin, a potent chemotherapeutic agent and one of the most emetogenic stimuli, requires a combination of different antiemetic drugs. In this study, we investigated the effects of *Scutellaria baicalensis*, an antioxidant herbal medicine, on cisplatin-induced nausea using a rat model. *Methods*: Rats react to emetic/nausea-producing stimuli, such as cisplatin, with altered feeding habits, manifested by pica or increased consumption of kaolin (a type of clay). We measured pica in rats to quantify cisplatin-induced nausea, and to evaluate the antinausea effect of pretreatment with *S. baicalensis* extract (SbE) given intraperitoneally. *Results*: Cisplatin at 3 mg/kg induced significant pica accompanied by reduced food intake, suggesting the presence of nausea. Hence, this cisplatin dose was selected for testing the antinausea activity of SbE. Cisplatin-induced pica decreased significantly when animals were pretreated with SbE at doses of 1 mg/kg and 3 mg/kg ($P < 0.01$). At a higher SbE dose (10 mg/kg), kaolin consumption increased, rather than further decreased, and was significantly different from that in the groups treated with low SbE doses. *Conclusions*: SbE pretreatment decreased cisplatin-induced kaolin intake in the rat model of simulated nausea, suggesting that SbE and its active constituent(s) may play a therapeutic role in chemotherapy-induced emesis. Absence of therapeutic effect at the highest tested SbE dose could have been a result of prooxidant activity often associated with excess antioxidant concentration.

Keywords *Scutellaria baicalensis* · Herbal medicine · Cisplatin · Chemotherapy · Pica

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H. H. Aung · L. Dey · S. Mehendale · J.-T. Xie · J. A. Wu
C.-S. Yuan
Tang Center for Herbal Medicine Research,
Department of Anesthesia & Critical Care,
The Pritzker School of Medicine, University of Chicago,
Chicago, IL 60637, USA

C.-S. Yuan
Committee on Clinical Pharmacology and Pharmacogenomics,
The Pritzker School of Medicine, University of Chicago,
Chicago, IL 60637, USA

C.-S. Yuan (✉)
Department of Anesthesia & Critical Care,
The University of Chicago, 5841 S. Maryland Ave.,
MC 4028, Chicago, IL 60637, USA
E-mail: cyuan@airway.uchicago.edu
Tel.: +1-773-7021916
Fax: +1-773-8340601

Introduction

Nausea, vomiting and abdominal discomfort are common side effects associated with the use of chemotherapy in cancer patients, and adversely affect patients' quality of life [1, 2]. More importantly, these side effects may lead to dehydration, compromised patient compliance or refusal of potentially curative cycles of chemotherapy [1], and therefore need to be treated.

Cisplatin, a potent chemotherapeutic agent, is known to cause significant nausea/vomiting [1, 3]. A number of studies have shown that cisplatin, like other chemotherapeutic agents, generates free radicals and releases reactive oxygen species (ROS) [4, 5, 6, 7]. Such enhanced oxidant activity in the gastrointestinal tract could cause injury to enterochromaffin cells, as well as other cells, and result in serotonin (5-hydroxytyptamine, 5-HT) release. Ensuing stimulation of vagal afferent sensory nerves and the chemoreceptor trigger zone in the brain stem caused by the released 5-HT could ultimately result in emesis [8, 9]. Therefore it is postulated that antioxidants could attenuate cisplatin-induced oxidant gut injury and reduce nausea/vomiting.

Cancer patients undergoing treatment with chemotherapeutic agents, such as cisplatin, often prefer to treat

the medication side effects with alternative medical modalities as opposed to consuming additional drugs. An estimated 50% of cancer patients use complementary and alternative medicine, including herbal therapy, combined with conventional pharmacotherapy [10]. Since nausea/vomiting induced by cisplatin may be mediated by oxidants, we proposed to investigate the effectiveness of an antioxidant herb, *Scutellaria baicalensis* (a commonly used oriental herb) [11], in a cisplatin-treated rat model.

Rats react to emetic stimuli by altering their feeding habit, manifested as increased consumption of non-nutritive substances such as kaolin (a type of clay), a phenomenon known as pica [12, 13, 14, 15]. This rat model has been used previously to simulate nausea and vomiting and shows reduced pica in response to antiemetic drugs [13, 14]. In the current study, we measured pica to quantify nausea in cisplatin-treated rats, and evaluated the effects of *S. baicalensis* extract (SbE) on cisplatin-induced pica.

Materials and methods

Animals

The experimental protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of the University of Chicago. Male Wistar strain rats (Harlan Sprague Dawley, Indianapolis, Ind.), weighing between 150 and 300 g, were used in this study. Animals were housed in standard isolation cages (45×35×25 cm) under environmentally controlled conditions with 12-h light/12-h dark cycle. Rats were allowed free access to water, standard laboratory rat chow (Harlan-Teklad, Madison, Wis.) and kaolin (see below), which were placed in separated containers continuously available throughout the experiment.

Preparation *S. baicalensis* extract (SbE)

Plant root of *S. baicalensis* was obtained from the Shanghai Chinese Herbal Medicine Company (Shanghai, China). The roots were cut into small pieces and then soaked in cold water for 2 h. The mixture was heated to 95°C and stirred constantly for 1 h. The hot water-soluble fraction was filtered (0.1 μm filter), and then evaporated and lyophilized. Prior to the experiment, the dried powder was dissolved in distilled water for administration.

Analyzing constituents in the SbE

The constituents of SbE were identified by liquid chromatography/mass spectrometry (LC/MS; Hitachi M1000, Hitachi Denshi, Tokyo, Japan) with an atmospheric pressure chemical ionization interface. A 10-mg sample of extract was dissolved in 10 ml deionized water. The mobile phase consisted of 14 m*M* ammonium acetate in acetonitrile (v/v 1/99). The sample (150 µl solution) was injected and the flow rate was maintained at 0.8 ml/min. The system was calibrated with flavopiridol 402. As shown in Fig. 1, the extract contained the following flavones: wogonin (51.5%), baicalein (35.6%), skullcapflavone I (4.8%) and skullcapflavone II (8.3%).

To quantify the four flavones in the extract, baicalein (Sigma, St. Louis, Mo.) was used in the LC/MS analysis. Baicalein (1 mg/ml) was used as the standard, and the sample (150 µl solution) was injected. The height of the baicalein standard was equivalent to a 955-fold increase in baicalein in the extract. Thus, the concentration in 1 mg/ml extract consisted of 5.3 µ*M* wogonin, 3.9 µ*M* baicalein, 0.5 µ*M* skullcapflavone I, and 0.7 µ*M* skullcapflavone II. This result is similar to that found in previous analyses [11, 16, 17].

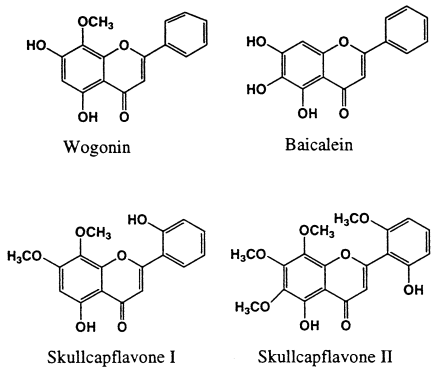

Fig. 1 Structure of constituents isolated from *S. baicalensis* roots

Kaolin preparation

Kaolin was prepared based on a method described previously [12, 13]. Briefly, pharmacological grade kaolin (or hydrated aluminum silicate; Fisher, Fair Lawn, N.J.) and acacia (or Gum Arabic; Fisher) were mixed at a ratio of 99:1. Distilled water was used to form a thick paste of this mixture. The paste was rolled and cut into pieces that resembled regular rat chow pellets. The pellets were dried at room temperature for 72 h.

Experimental protocol

There was a 3-day adaptation period prior to study period (day 0). During this period, animals were placed in individual cages to allow access to both regular food and kaolin. Prior to testing the effects of SbE, three doses of cisplatin (Bedford Laboratories, Bedford, Ohio; available in aqueous form at 1 mg/ml), i.e. 3 mg/kg ($n=6$), 5 mg/kg ($n=3$) and 10 mg/kg ($n=3$), were given intraperitoneally (i.p.) to the animals. Based on the observation (see Results), cisplatin 3 mg/kg was selected for the evaluation of the effects of SbE pretreatment. We observed that one rat had mild diarrhea following administration of cisplatin at 10 mg/kg.

On Day 0, all five groups of rats received two i.p. injections at 2 P.M. and 2:30 P.M. Group 1 animals ($n=3$) received normal saline (vehicle) and normal saline (vehicle). Group 2 animals ($n=7$) received normal saline and cisplatin 3 mg/kg. Group 3 animals ($n=6$) received SbE 1 mg/kg and cisplatin 3 mg/kg. Group 4 animals ($n=6$) received SbE 3 mg/kg and cisplatin 3 mg/kg. Group 5 animals ($n=5$) received SbE 10 mg/kg and cisplatin 3 mg/kg.

At 3 P.M. on each experimental day, the animals' kaolin intake, food intake, and body weight were measured for five consecutive days. To measure kaolin and food intake, the remaining kaolin and food were collected including that spilled outside the containers. The collected kaolin and food were dried for 24 h to obtain dry weight values to the nearest 0.1 g.

No irritation, restlessness or other adverse effects (e.g., respiratory distress, abnormal locomotion, or catalepsy) were detected in rats following i.p. injection.

Statistical analysis

Data were analyzed using analysis of variance (ANOVA) followed by the Holm-Sidak test for multiple comparisons. Student's *t*-test was used for analysis of the area under the curves (AUC). In all cases, P values <0.05 were considered statistically significant.

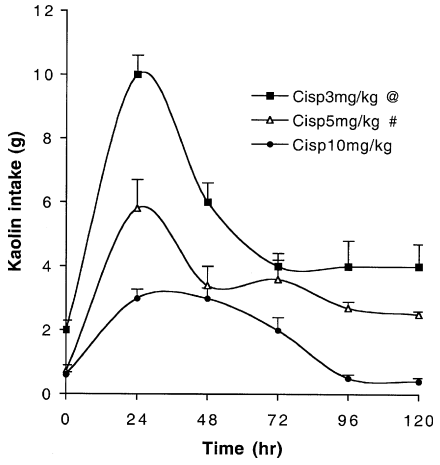

Fig. 2 Effect of three cisplatin doses on kaolin intake (*Cisp* cisplatin). $^{@}P<0.05$ 24, 48, 96 and 120 h vs baseline (0 h); $^{@}P<0.05$ 24 h vs 5 mg/kg and vs 10 mg/kg; $^{\#}P<0.01$ 24 h vs baseline

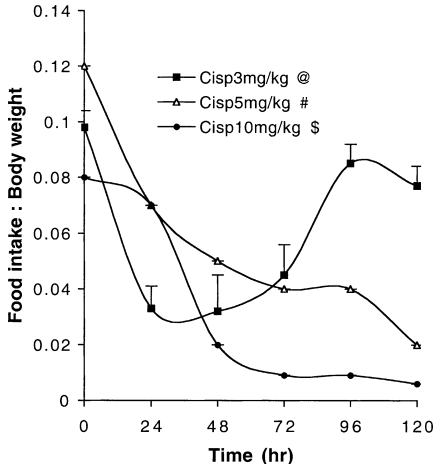

Fig. 3 Effect of three different cisplatin doses on food intake expressed as food intake:body weight ratio (g/g). $^{@}P<0.01$ 24, 48 and 72 h vs baseline; $^{\#}P<0.01$ 24, 48, 72, 96 and 120 h vs baseline; $^{\$}P<0.01$ 48, 72, 96, 120 h vs baseline

Results

Changes in kaolin intake following treatment with the three cisplatin doses (3, 5, and 10 mg/kg) are shown in Fig. 2. The greatest amount of pica/kaolin consumption was induced by 3 mg/kg cisplatin ($P<0.05$ compared to baseline). Although food intake reduced significantly after each of the three doses for 72 h, prolonged suppression of food intake was observed with 5 and 10 mg/kg cisplatin at 96 and 120 h (Fig. 3). Prolonged food suppression with the two high doses suggests toxic effects of cisplatin and hence those doses were not used in subsequent experiments. Since a dose of 3 mg/kg cisplatin caused the greatest effect on induction of pica with an acute and significant reduction in food intake, this dose was selected for the subsequent evaluation of the effect of SbE pretreatment on pica.

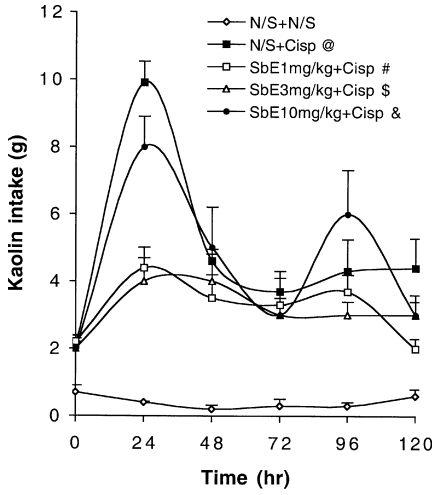

Fig. 4 Effect of cisplatin and SbE on kaolin intake. The increase in kaolin intake induced by cisplatin at 3 mg/kg was decreased by administration of SbE at 1 mg/kg and 3 mg/kg (*N*/*S* normal saline, *Cisp* cisplatin 3 mg/kg, *SbE S. baicalensis* extract). $^{@}P<0.05$ 24, 48, 96 and 120 h vs baseline; $^{@}P<0.05$ 24 h vs all SbE-treated groups; $^{\#}P<0.01$ 24 h vs baseline; $^{\$}P<0.01$ 24 h vs baseline; $^{\&}P<0.01$ 24, 48 and 96 h vs baseline; $^{\&}P<0.05$ 24 and 96 h vs SbE 1 mg/kg + Cisp and SbE 3 mg/kg + Cisp

After injection 3 mg/kg cisplatin (group 2), kaolin intake increased significantly compared to baseline at 24, 48, 96 and 120 h ($P<0.05$; Fig. 4). Cisplatin-induced kaolin intake was also reduced by pretreatment with SbE at 1 mg/kg (group 3) and 3 mg/kg (group 4) ($P<0.01$; Fig. 4). Kaolin intake was not significantly different between groups at 0 h. The AUCs for kaolin intake from 0 to 48 h for group 1, group 2, group 3, group 4, and group 5 were 44, 624, 408, 396, and 588 g·h, respectively. Kaolin intake was unaffected after saline injection in group 1. There was a significant decrease in kaolin intake from 624 g·h in group 2, to 408 g·h in group 3 ($P<0.01$), and to 396 g·h in group 4 ($P<0.01$). The reductions in AUC of kaolin intake between group 2 and group 3, group 2 and group 4, and group 2 and group 5 were 35%, 37%, and 6%, respectively. Increasing the dose of SbE to 10 mg/kg did not further decrease pica (group 5).

Figure 5 shows changes in food intake (expressed as food intake:body weight ratio). There was a significant reduction in food intake after cisplatin injection compared to baseline ($P<0.01$). The group pretreated with 3 mg/kg SbE (group 4) was significantly different from cisplatin-treated groups at 72 h ($P<0.05$), suggesting a tendency towards faster recovery to baseline.

Figure 6 shows the effects of cisplatin and SbE administration on body weight. Body weight increased gradually in the vehicle-treated group during the five observation days since the animals were in the growth stage. During this period, compared to the vehicle group, all groups treated with cisplatin lost weight irrespective of the pretreatment with SbE, as suggested by a significant group effect (effect of cisplatin, $P<0.05$).

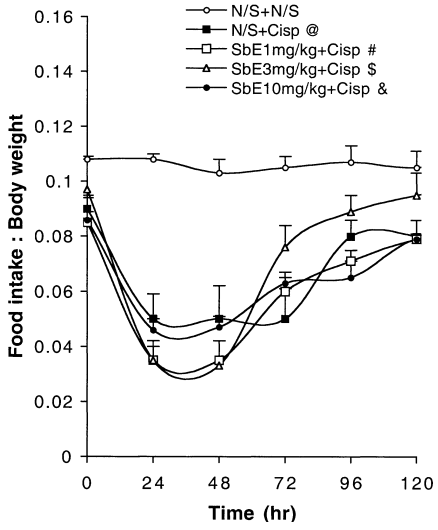

Fig. 5 Effect of cisplatin and SbE on food intake expressed as food intake:body weight ratio (g/g). There was a significant reduction in food intake following cisplatin treatment with or without coadministration of SbE extract (*N/S* normal saline, *Cisp* cisplatin 3 mg/kg, *SbE S. baicalensis* extract). $^{@}P < 0.01$ 24, 48 and 72 h vs baseline; $^{@}P < 0.05$ 72 h vs N/S + Cisp and SbE 3 mg/kg + Cisp; $^{\#}P < 0.01$ 24, 48 and 72 h vs baseline; $^{\$}P < 0.01$ 24, 48 and 72 h vs baseline; $^{\&}P < 0.01$ 24, 48 and 72 h vs baseline

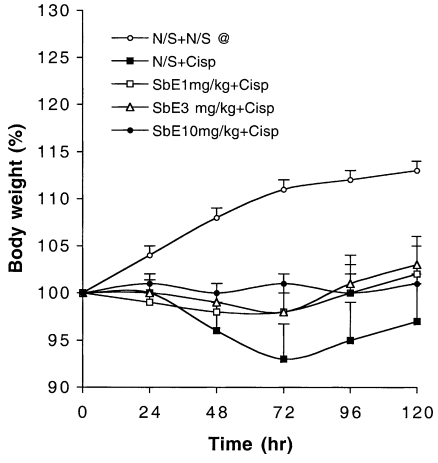

Fig. 6 Effect of cisplatin and SbE administration on body weight. The body weight of each group on day 0 was normalized to 100% and change in body weight is expressed as percentage change from time 0 (*N/S* normal saline, *Cisp* cisplatin 3 mg/kg, *SbE S. baicalensis* extract). $^{@}P < 0.05$ vs all cisplatin-treated groups

In the cisplatin-only group (group 2), the body weight appeared to decrease the most.

Discussion

We demonstrated that a single dose of cisplatin induced an alteration in food habit, characterized by prolonged increased kaolin consumption (up to and at 120 h) and reduced food intake (for 72 h) in rats. The prolonged increase in pica corresponds to a prolonged and delayed emetic response to cisplatin in humans [2]. We also demonstrated that pretreatment with SbE, an antioxidant herb, effectively attenuated cisplatin-induced kaolin intake.

Cisplatin-induced nausea/vomiting is possibly mediated via cytotoxic damage to the enterochromaffin cells in the small intestine [18, 19, 20]. The resultant 5-HT release could cause the emesis and nausea associated with cisplatin treatment [18, 19, 21]. Since chemotherapeutic agents are known to release ROS [4], it is possible that cisplatin could induce oxidant injury to enterochromaffin cells that results in 5-HT release, stimulation of 5-HT_3 receptors located on the vagal afferents, and initiation of the emetic reflex in the brain stem [22, 23, 24, 25]. ROS release by cisplatin has been confirmed in other studies [6, 8]. If ROS cause cisplatin-induced nausea/vomiting, then treatment with an antioxidant should reduce these side effects. This supposition has been confirmed in a study in which cisplatin-induced emesis was effectively prevented by preadministration of the antioxidant *N*-(2-mercaptopropionyl)-glycine [7]. Additionally, cisplatin-induced emesis is exaggerated by ferric chloride, which is known to catalyze the production of cytotoxic oxygen radicals, and is ameliorated by deferoxamine, an iron chelator [23]. Based on these facts, we proposed to investigate the efficacy of an antioxidant herb, SbE, in treating cisplatin-induced pica or simulated nausea.

Scutellaria baicalensis is a widely used herb in traditional medical systems of China and Japan [17, 26]. The dried root has been used clinically to treat allergies, inflammatory diseases, hyperlipidemia, and arteriosclerosis [17]. The major constituents of *S. baicalensis* are flavonoids, a group of polyhydroxy phenols [16]. These flavonoids, including baicalein, baicalin and wogonin, are known to possess antioxidant and other pharmacological effects. The effects of SbE may result in part from its constituent flavones, which can attenuate oxidant stress and protect cells from lethal oxidant damage. We have confirmed the antioxidant effects of SbE, which result in protection of cardiomyocytes from oxidant injury [11]. We therefore sought to determine whether the antioxidant, SbE, could be used to treat cisplatin-induced symptoms mediated through putative oxidant mechanisms.

Data from the present study showed that SbE at both 1 mg/kg and 3 mg/kg reduced cisplatin-induced pica. This suggests that cisplatin-induced pica (nausea) could be treated with SbE. The mechanism of the antinausea effect could be mediated by the antioxidant properties of SbE [11]. Additionally, SbE has been demonstrated to bind 5-HT_{1A} receptors, which could contribute to its antinausea effect [27, 28]. In a dose-response evaluation, when the SbE dose was increased to 10 mg/kg, there was no further decrease in pica, demonstrating a saturation of the response. On the contrary, the anti-pica effect was substantially reversed. It is possible that higher doses of antioxidants could result in prooxidant activity rather than antioxidant activity, which may potentiate

cisplatin-induced injury. We have recently observed that grapeseed proanthocyanidin extract (GSPE), a commonly used antioxidant, demonstrates antioxidant activity at low concentrations in cultured cardiomyocytes exposed to oxidant stress. However, at higher doses, GSPE becomes a prooxidant, and rather than protecting cells from oxidants causes cell death [29]. Whether the reversal of the therapeutic effect following a higher SbE dose was due to its prooxidant activity remains to be investigated in future studies. These findings support the notion that herbal medications, which contain multiple active constituents, may be therapeutic only at certain doses and that the consumption of large uncontrolled quantities of antioxidant dietary supplements in an effort to achieve higher efficacy could be detrimental.

Although low doses of SbE caused reduced pica in cisplatin-treated rats, there was no improvement in the food intake with SbE. Similar findings have been observed when cisplatin-induced pica is treated with dexamethasone [15]. The reduced food intake was attributed to the metabolic effects of dexamethasone. In the current study, the reason for poor recovery of reduced food intake is not known. Further studies are required to determine whether SbE independently affects food intake in rats.

Clinically, cisplatin-induced nausea/vomiting has been described as a biphasic phenomenon, with each phase responding to distinct antiemetic drugs [18]. Overall, conventional antiemetics such as dopamine antagonists, antihistamines, anticholinergics, and glucocorticoids have a modest efficacy against chemotherapy-induced emesis, either when administered alone or in combination. A newer class of antiemetics, that is the 5-HT_3 receptor antagonists such as granisetron and ondansetron, have improved the therapy of chemotherapy-induced emesis. However, these drugs, in addition to their high cost, appear not to be effective against the delayed emetic response to cisplatin [18, 30]. Neurokinin receptor antagonists have demonstrated better efficacy in treating the delayed emetic phase [31, 32]. Thus patients who are treated with cisplatin chemotherapy have to consume additional multiple drugs to treat severe side effects, which in turn leads to additional side effects such as extrapyramidal effects, constipation etc [33, 34, 35, 36]. A herbal medicine, such as SbE and its flavonoids, could be an effective and inexpensive alternative to preventing chemotherapy-induced emesis without troublesome side effects. Our results suggest that SbE at a dose of 3 mg/kg attenuated kaolin consumption in both phases. The mechanism involved in the attenuation of acute pica could by the antioxidant effects of SbE, but the mechanism involved in the reduction in pica in the later phase is not clear.

It is important to examine the pharmacokinetic and pharmacodynamic interaction between the antioxidant herb and cisplatin, which could either hamper or augment the anticancer actions of cisplatin. Antineoplastic agents result in oxidative stress in cells that may interfere with their antineoplastic activity. Treatment with antioxidants could detoxify ROS, prevent oxidant injury to tumor cells and sensitize the tumor cells to the anticancer effects of chemotherapy [4]. Thus concomitant antioxidant use may potentiate cisplatin activity. A recent study by Cipak et al. has indicated that flavonoid antioxidants either potentiate or inhibit cisplatin-induced apoptosis depending on the specific flavonoid [37]. The effect of flavonoids in SbE on cisplatin activity has not been studied previously and further studies are needed to confirm that SbE administration does not adversely alter the pharmacological parameters of cisplatin.

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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