Therapeutic effects of smecta or smectite powder on rats with paraquat toxication

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BACKGROUND: The plasma concentration of paraquat is closely related to the prognosis of patients with paraquat toxication, and the most common cause of death from paraquat poisoning is multiple organ failure (MOF). This study aimed to evaluate therapeutic effect of smecta on the plasma concentrations of paraquat and multi-organ injury induced by paraquat intoxication in rats.

METHODS: A total of 76 healthy adult SD rats were randomly divided into group A (control group, n=6), group B (poisoned group, n=30) and group C (smecta-treated group, n=30). Rats in groups B and C were treated intragastrically with PQ at 50 mg/kg, and rats in group A was treated intragastrically with saline (1 mL). Rats in group C were given intragastrically smecta at 400 mg/kg 10 minutes after administration of PQ, while rats in other two groups were treated intragastrically with 1 mL saline at the same time. Live rats in groups B and C were sacrificed at 2, 6, 24, 48, 72 hours after administration of PQ for the determination of paraquat plasma concentrations and for HE staining of the lung, stomach and jejunum. The rats were executed at the end of trial by the same way in group A.

RESULTS: The plasma concentration of paraquat (ng/mL) ranged from 440.314±49.776 to 4320.6150±413.947. Distinctive pathological changes were seen in the lung, stomach and jejunum in group B. Lung injuries deteriorated gradually, edema, leukocyte infiltration, pneumorrhagia, incrassated septa and lung consolidation were observed. Abruptio of mucosa, hyperemic gastric mucosa and leukocyte infiltration were obvious in the stomach. The hemorrhage of jejunal mucosa, the abruptio of villus, the gland damage with the addition of inflammatory cell infiltration were found. Compared to group B, the plasma concentration of paraquat reduced (P<0.01) and the pathological changes mentioned above were obviously alleviated in group C (P<0.05, P<0.01).

CONCLUSION: Smecta reduced the plasma concentration of paraquat and alleviated pathologic injury of rats with PQ poisoning.

KEY WORDS: Smecta; Paraquat; Pathological change; Therapeutic injury

INTRODUCTION

Paraquat (PQ) is a nonselective contact herbicide, and has been widely used in the world, especially in developing countries since the 1960s. However, PQ poisoning remains a major cause of death among patients with acute poisoning in Asia¹ and its mortality is as high as 80%.[²] PQ is absorbed mainly through the intestinal tract, its plasma level peaked within 4 hours after oral administration. PQ extensively accumulates in the whole body, but is mainly stored in the lung and stomach where it is retained even the blood concentration decreases, finally is excreted by the kidney.[¹]

A lot of animal experiments and clinical trials have proved that the toxicity of PQ usually lead to multiorgan injury.⁴⁻⁶ Because of the polyamine uptake system, the pulmonary concentration of PQ is 6–10 times higher than that in the plasma, so the lung is the target organ of PQ poisoning. The acute phase, in which lung injury
is characterized by pulmonary alveolitis, is followed by the proliferative phase defined by the occurrence of progressive fibrosis.[7] Kim et al[8] reported that the distinct change of pulmonary fibrosis in the high resolution computerized tomography (HRCT) was characterized by ground glass opacities (GGOs), and this suggested that the area of GGOs be a useful predictor of survival in acute PQ intoxication, especially in patients with a low plasma PQ level. With regard to poisoning symptoms, the digestive tract appeared at the soonest, such as stomachache, vomitus, and alimentary tract hemorrhage. Gastrointestinal dysfunction can speed up the absorption of poison or delay the excretion of poison, so it is necessary for physicians to take effective measures to reduce gastrointestinal damage resulting from PQ. Nevertheless, there are few studies on the protection of gastrointestinal structure.

So far, the treatment of PQ intoxication is still in the exploratory stage. A number of therapeutic methods for the treatment of PQ intoxication have shown poor efficacy,[9, 10] and only a few treatments revealed effectiveness.[11–13] Studies[14–16] focus mostly on gastric lavage, blood purification, glucocorticoid and cyclophosphamide, but there are different opinions on these methods. It was reported that to prevent the absorption of PQ by the gastrointestinal tract, patients were administered with activated charcoal in 250 mL magnesium citrate via a nasogastric tube,[14] suggesting that superactive adsorbent is beneficial to reduce blood concentration.

Smecta or smectite powder, a kind of natural aluminosilicate consisting of a double aluminium and magnesium silicate, is mainly made up of the octagonal montmorillonite particles which show the layer structure and heterogeneity charge distribution. One of the most remarkable pharmacological characteristics of smecta is its strong adsorption activity.[17] It not only adsorbs eight times its own weight of water, but also adsorbs toxins, bacteria, and rotavirus, keeping virulence factors from adhering to intestinal membranes.[18–20] In addition, with the ability to cover the mucosa and to combine with mucous glycoprotein, smecta strengthens the mucosal barrier.[21] Furthermore, smecta will not pass into the blood circulation after combination with morbid substances and barely decreases intestinal dynamics,[22] causing few side effects. As adsorbent, smecta has been widely used to treat various diseases,[23–25] including diarrhea, gastrointestinal bleeding, and peptic ulcer. A recent study[23] revealed that smecta at 6 g tid was well tolerated and reduced the time to recovery from acute watery diarrhoea episode. Even though the efficacy of Smecta in the treatment of digestive system diseases has been confirmed, the study on the use of smecta in PQ poisoning is rare.

Thus, this study aimed to testify whether smecta can reduce the plasma concentration determined by high-performance liquid chromatography (HPLC)[26,27] and improve pathological damage of the rats with PQ intoxication.

METHODS

Chemicals and instruments

Paraquat dichloride (HPLC) 99.9 area%, 0.1 g, was purchased from Sigma-Aldrich, USA. Acetonitrile (chromatographic pure), methyl alcohol (chromatographic pure), triethylamine (analytical pure), and thophosphoric acid (analytical pure) were purchased from Tianjin Guangfu Reagent Co., Ltd, China. Sodium 1-heptanesulfonate (analytical pure purity ≥98%, 20 g) was produced by BBI, Canada. Smecta was produced by Beauour Ipsen (Tianjin) Pharmaceutical Co., Ltd. Eclipse plus Chromographic Column (4.6×250 mm, 5 µm) was purchased from Agilent, USA. LC-20A High Performance Liquid Chromatograph, LC-20AT Pump, CBM-20A Controller, SPD-M20A Detector, SIL-20A Autosampler, CTO-10AS VP Column oven were all purchased from Shimadzu, Japan.

Animals

This study was performed using adult male SD rats (200±20 g) obtained from the Xinjiang Disease Prevention and Control Center. The rats were kept under standard laboratory conditions (12/12 h light/darkness, 22±2 ºC room temperature, 50%–60% humidity) for at least 1 week before the start of the experiment. The rats were allowed free access to tap water and rat chow ad libitum during the experiment.

Experimental protocol

A total of 66 healthy adult SD rats were randomly divided into group A (control group, n=6), group B (poisoned group, n=30), and group C (smecta treated group, n=30). Rats in groups B and C were treated intragastrically with a single dose of PQ (PQ, 50 mg/kg), and those in group A were treated intragastrically with 1 mL of saline. Rats in group C were given intragastrically smecta at 400 mg/kg 10 minutes after the administration of PQ, whereas rats in the other two groups were treated intragastrically with 1 mL of saline at the same time. Rats in groups B and C were sacrificed 2, 6, 24, 48, 72 hours after the administration of PQ, respectively. The rats were sacrificed, and their blood samples were taken. The serum
of the rats was separated immediately and stored at –72 °C for the determination of PQ plasma concentrations. The tissues of the lung, stomach and jejunum were taken for HE staining and pathological examination. The rats in group A were executed similarly.

**Determination of plasma PQ concentration**

PQ concentration was determined with the reported methods with minor modifications. Plasma samples were sent to Shihezi University College of Pharmacy for quantitative analysis using HPLC. Briefly, 35% perchloric acid (100 µL) was added to a test tube containing plasma supernatant (0.5 mL), and the mixed liquor of perchloric acid and plasma supernatant was centrifuged and the supernatant of the mixed liquor was analyzed with HPLC. Six blank control plasma samples (concentrations of samples was 20, 50, 100, 500, 1 000, 5 000 ng/mL, respectively) were prepared, then the peak area of these samples was detected. The regression equation of PQ plasma samples, which was used to calculate concentration of PQ, can be obtained according to peak area ($Y$) and concentration ($X$).

**Statistical analysis**

Statistical analysis was made using SPSS 13.0. All data were expressed as means±standard deviation. The survival rates of rats were compared using Fisher’s exact test for unordered categorical variables, pathological scores were compared with independent samples $t$ test, and PQ concentrations were compared using analysis of variance (ANOVA) followed by LSD multiple comparison test. A $P$ value less than 0.05 was considered statistically significant.

**RESULTS**

**Behavioral changes of rats**

Two hours after PQ poisoning, symptoms including rapid shallow respiration, dyspnea, loss of appetite, piloerection, and hemorrhage in the nostril and angulus oris, were observed in rats of group B as compared with normal rats. After the thoracic cavity and abdominal cavity of rats in group B were open, pulmonary edema, pulmonary congestion, gastric distention, intestinal tympanites, and intestinal obstruction were seen. These

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**Figure 1.** HPLC chromatogram of blank control plasma sample in the control group (PQ concentration, 1000 ng/mL).

**Figure 2.** HPLC chromatogram of plasma sample in group B (2 hours after PQ administration).

**Figure 3.** HPLC chromatogram of plasma sample in group C (2 hours after PQ administration).

**Figure 4.** Comparison of PQ concentrations between groups B and C. $P$ value at 2, 6, 24, 48, 72 hours after PQ administration was 0.000, 0.001, 0.017, 0.001, and 0.000, respectively.
symptoms were less marked in group C. Seventy-two hours after treatment, the survival rate of rats in the control group was 100%, whereas it was 90% in group B and 97% in group C, respectively. There were no changes in group A.

**Linear correlation and concentration of paraquat**

The regression equation of plasma PQ: \( Y = 98.8210X + 5707.5407 \). The PQ concentration varied from 20 ng/mL to 5000 ng/mL, and the minimum detection limit was 20 ng/mL. Partial HPLC chromatograms are shown in Figures 1–3.

In groups B and C, the plasma concentration of PQ lowered with the time, peaked at 2 hours after PQ administration, and kept at a higher level within 6 hours after intoxication. After that, the plasma concentration of PQ started to decrease, and reached the minimum level 72 hours after PQ administration (Figure 4). Compared to group B, the plasma concentration of PQ in group C reduced rapidly, but there was no significant difference between the two groups (\( P < 0.05 \) or \( P < 0.01 \)).

**Pathological injury**

There were marked pathological changes in the lung, stomach and jejunum in group B. Lung injuries deteriorated with time. Congestion, edema, and slight leukocyte infiltration were the early pathologic changes of the lung. Twenty-four hours after PQ poisoning, pneumorrhagia, incrassated septa, and consolidation of the lung were observed (Figure 5).

Marked pathologic changes were observed in

![Figure 5. Comparison of lung injury among the three groups 72 hours after PQ poisoning (HE, original magnification×100).](image5)

![Figure 6. Comparison of stomach injury among the three groups 2 hours after PQ poisoning (HE, original magnification×100).](image6)

![Figure 7. Comparison of jejunum injury among the three groups 2 hours after PQ poisoning (HE, original magnification×100).](image7)
stomach tissue such as abrasion of mucosa, hyperemic
gastric mucosa and gastrorrhagia within 24 hours after
PQ poisoning. Leukocyte infiltration and impairment of
gastric glands were also found. Thus the repair of
stomach tissue was followed (Figure 6).

The jejunum injuries of rats were characterized by
hemorrhage of mucosa, abrasion of villus, gland damage,
and inflammatory cell infiltration within 24 hours after PQ
poisoning. Then, the hemorrhage of mucosa was alleviated
and gland damage aggravated (Figure 7). These pathological
changes were markedly alleviated in group C compared
with group B (\( P<0.05, \) \( P<0.01 \)) (Figures 5–7, Table 1). In
group B, no marked pathological changes were seen in the
lung, stomach and jejunum (Figures 5–7).

**DISCUSSION**

The first case of paraquat mortality was published in
1966,\(^{[31]}\) followed by a large number reports. PQ poisoning
as a medical problem has become a social burden and
attracted much attention. Ingestion of over 20 mL of
PQ is likely to cause death due to multi-organ failure,
and 10–20 mL may result in irreversible lung fibrosis
leading to death within several weeks.\(^{[32]}\) Suntres\(^{[33]}\)
made a large sample analysis showing that the oral lethal
dose of PQ for adults was 30–40 mg/kg. There was a
close relationship between PQ plasma concentration and
mortality.\(^{[34]}\) Current treatment of PQ poisoning focuses on
reducing the absorption of PQ from the gastrointestinal
tract and increasing its elimination.\(^{[35]}\) Even though
activated charcoal was used to treat PQ toxification,\(^{[14]}\)
evidence was not enough to confirm that charcoal can
improve the prognosis of patients. Since the therapeutic
effect of smecta on rats with PQ toxification has rarely
been studied, we tried to explore whether smecta can
reduce the PQ plasma concentration and improve the
pathological changes of rats after PQ poisoning.

The pharmacokinetics of PQ is different in people
and animals. The peak plasma concentration of patients
occurs within 2–4 hours after ingestion of PQ and then
decreases.\(^{[35]}\) The initial decrease, which is called the
distribution phase, is faster and has a half life of about 5
hours, while the volume of distribution is about 1.2–1.6
L/kg. The half life in the subsequent elimination phase is
about 84 hours. On the other hand, the peak plasma
concentration occurs in dogs about 60–90 minutes after
ingestion of PQ and disruption of the gastric mucosal
barrier.\(^{[36,37]}\) PQ distribution can be described as a
three-compartment model: 1) plasma compartment; 2)
compartment with rapid uptake and removal such as the
kidney; 3) slow uptake compartment such as the lung,
reaching a maximum concentration 4–5 hours after
ingestion of PQ regardless of the plasma PQ level. This
model explains the unique changes in plasma PQ level.
However, the dynamics of PQ in rats has been rarely
investigated. Studies\(^{[38,39]}\) revealed that plasma paraquat
concentration of rats maintained high within 24 hours
after PQ poisoning and vanished within 72 hours, which
can be detected in the lungs, stomach and intestine 10
days after administration of PQ.

In our study, the dead rats were eliminated. The plasma
concentrations of PQ in rats with intoxication
decreased with time, and the peak concentration
occurred at 2 hours after PQ administration and it was
kept at a higher level within 6 hours after intoxication.
After that, the plasma concentration of PQ started to
decrease and reached the minimum level 72 hours after
administration of PQ (Figure 4). At the same time, the
plasma concentration of PQ was lower in the smecta-
treated group than in the poisoned group (\( P<0.05 \) or
\( P<0.01 \)). This finding indicates that smecta is useful
to reduce the plasma concentration of PQ in rats. The
conspicuous effect of smecta on the plasma concentration
of PQ is ascribed to its ability to adsorb toxicant, and
combination of PQ and smeta completely excreted
through the intestinal tract. Tiwary et al\(^{[40]}\) observed the
adsorption capacity of different adsorbents including
Kaolin, smecta (montmorillonite powder) and activated
charcoal, and found that smecta is effective to reduce the
PQ concentration in patient's urine.

The acute toxic effects of PQ on human and rats
included a series of symptoms, multiple organ dysfunction

**Table 1. Pathological scores of rats (mean±SD)**

| Groups | Lung       | Stomach   | Jejunum  |
|--------|------------|-----------|----------|
| A      | 0.500±0.632| 0.333±0.516| 0.555±0.403|
| B      |            |           |          |
| 2 h    | 2.000±0.447**| 4.000±1.788**| 2.444±0.455**|
| 6 h    | 2.916±0.801**| 7.000±0.894**| 1.944±0.389**|
| 24 h   | 4.500±0.707**| 6.000±0.894**| 2.445±0.455**|
| 48 h   | 5.250±0.861**| 4.000±0.894**| 2.444±0.455**|
| 72 h   | 7.833±1.032**| 3.833±0.752**| 1.778±0.621**|
| C      |            |           |          |
| 2 h    | 1.500±0.447**| 2.000±0.894**| 1.777±0.621**|
| 6 h    | 1.917±0.585**| 3.000±0.895**| 1.333±0.298**|
| 24 h   | 3.500±0.447**| 4.333±1.862**| 1.389±0.389**|
| 48 h   | 4.083±0.917**| 3.667±1.633**| 1.333±0.471**|
| 72 h   | 5.583±0.585**| 2.833±1.169**| 1.000±0.298**|

Compared with group A, \( P<0.05, \) \( P<0.01 \); compared with group B,
\( P<0.05, \) \( P<0.01 \).
associated with pathological injury provoked by superoxide anion together with inflammatory activation. Because of a polyamine uptake system, the lung is a primary target organ of PQ toxicity. In the current study, the lung injury of rats in the poisoned group was concordant with the results of a previous study.\[41\] Pulmonary alveolitis, pneumorrhagia, and lung consolidation were serious and supported by such symptoms as rapid shallow respiration, cyanosis, hemorrhage in the nostril. The damage induced by PQ to the stomach and jejunum was also found. This damage was characterized by hemorrhage of mucosa, abruption of mucosa, gland damage and inflammatory cell infiltration. It is reasonable to determine that apparent abruption of mucosa, gland damage and inflammatory damage was characterized by hemorrhage of mucosa, cyanosis, hemorrhage in the nostril. The damage induced changes. The toxic symptoms were ameliorated and injury of rats in the poisoned group was concordant with target organ of PQ toxicity. In the current study, the lung associated with pathological injury provoked by superoxide of a polyamine uptake system, the lung is a primary anion together with inflammatory activation. Because of a polyamine uptake system, the lung is a primary target organ of PQ toxicity. In the current study, the lung injury of rats in the poisoned group was concordant with the results of a previous study.\[41\] Pulmonary alveolitis, pneumorrhagia, and lung consolidation were serious and supported by such symptoms as rapid shallow respiration, cyanosis, hemorrhage in the nostril. The damage induced by PQ to the stomach and jejunum was also found. This damage was characterized by hemorrhage of mucosa, abruption of mucosa, gland damage and inflammatory cell infiltration. It is reasonable to determine that apparent abruption of mucosa, gland damage and inflammatory damage was characterized by hemorrhage of mucosa, cyanosis, hemorrhage in the nostril. The damage induced changes. The toxic symptoms were ameliorated and injury of rats in the poisoned group was concordant with target organ of PQ toxicity. In the current study, the lung associated with pathological injury provoked by superoxide of a polyamine uptake system, the lung is a primary anion together with inflammatory activation. Because of a polyamine uptake system, the lung is a primary target organ of PQ toxicity. In the current study, the lung injury of rats in the poisoned group was concordant with the results of a previous study.\[41\] Pulmonary alveolitis, pneumorrhagia, and lung consolidation were serious and supported by such symptoms as rapid shallow respiration, cyanosis, hemorrhage in the nostril. The damage induced by PQ to the stomach and jejunum was also found. This damage was characterized by hemorrhage of mucosa, abruption of mucosa, gland damage and inflammatory cell infiltration. It is reasonable to determine that apparent abruption of mucosa, gland damage and inflammatory damage was characterized by hemorrhage of mucosa, cyanosis, hemorrhage in the nostril. The damage induced changes. The toxic symptoms were ameliorated and injury of rats in the poisoned group was concordant with target organ of PQ toxicity. In the current study, the lung associated with pathological injury provoked by superoxide of a polyamine uptake system, the lung is a primary anion together with inflammatory activation.

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**REFERENCES**

1. Gunnell D, Eddleston M, Phillips MR, Konradsen F. The global distribution of fatal pesticide self-poisoning: systematic review. BMC Public Health 2007; 7: 357.
2. Lin JL, Lin DT, Chen KH, Huang WH. Repeated pulse of methylprednisolone and cyclophosphamide with continuous dexamethasone therapy for patients with severe paraquat poisoning. Crit Care Med 2006; 34: 368–373.
3. Kang MS, Gil HW, Yang JO, Lee EY, Hong SY. Comparision between kidney and hemoperfusion for paraquat elimination. Korean Med Sci 2009; 24: S156–160.
4. Roberts DM, Wilks MF, Roberts MS, Swaminathan R, Mohamed F, Dawson AH, et al. Changes in the concentrations of creatinine, cystatin C and NGAL in patients with acute paraquat self-poisoning. Toxicol Lett 2011; 202: 69–74.
5. Gupta SP, Patel S, Yadav S, Singh AK, Singh S, Singh MP. Involvement of nitric oxide in maneb- and paraquat-induced Parkinson’s disease phenotype in mouse: is there any link with lipid peroxidation? Neurochem Res 2010; 35: 1206–1213.
6. Tung JN, Lang YD, Wang LF, Chen CM. Paraquat increases connective tissue growth factor and collagen expression via angiotensin signaling pathway in human lung fibroblasts, Toxicology in Vitro 2010; 24: 803–808.
7. Petry TW, Wolfgang GH, Jolly RA, Ochoa R, Donarski WJ. Antioxidant-dependent inhibition of diquat-induced toxicity in vivo. Toxicology 1992; 74: 33–43.
8. Kim YT, Jou SS, Lee HS, Gil HW, Yang JO, Lee EY, et al. The area of ground glass opacities of the lungs as a predictive factor in acute paraquat intoxication. J Korean Med Sci 2009; 24: 636–640.
9. Vale JA, Meredith TJ, Buckly BM. Paraquat poisoning: clinical features and immediate general management. Hum Toxicol 1987; 6: 41–47.
10. Lin JL, Liu L, Leu ML. Recovery of respiratory function in survivors with paraquat intoxication. Arch Environ Health 1986; 50:432–439.
11. Chen GH, Lin JL, Huang YK. Combined methylprednisolone and dexamethasone therapy for paraquat poisoning. Crit Care Med 2002; 30: 2584–2587.
12. Lin NC, Lin JL, Lin DT, Yu CC. Combined initial cyclophosphamide with repeated methylprednisolone pulse therapy for severe paraquat poisoning from dermal exposure. J Toxicol Clin Toxicol 2003; 41: 877–881.
13. Lin JL, Lin DT, Chen KH, HuangWH. Repeated pulse of methylprednisolone and cyclophosphamide with continuous dexamethasone therapy for patients with severe paraquat poisoning. CritCare Med 2006; 34: 368–373.
14. Lin JL, Lin-Tan DT, Chen KH, Huang WH, Hsu CW, Hsu HH, et al. Improved survival in severe paraquat poisoning with repeated pulse therapy of cyclophosphamide and steroids. Intensive Care Med 2011; 37: 1006–1013.
15. Dinis-Oliveira RJ, Duarte JA, Sánchez-Navarro A, Remião F, Bastos ML, Carvalho F. Paraquat poisonings: mechanisms of lung toxicity, clinical features, and treatment. Crit Rev Toxicol 2008; 38: 13–71.
16. Suzuki K, Takasu N, Okabe T, Ishimatsu S, Ueda A, Tanaka S, et al. Effect of aggressive haemoperfusion on the clinical course of patients with paraquat poisoning. Hum Exp Toxicol 1993; 12: 323–327.
17. Zheng CD, Duan YQ, Gao JM, Ruan ZG. Screening for anti-lipase properties of 37 traditional Chinese medicinal herbs. J Ethnopharmacol 2003; 83: 203–209.
18. Salazar-Lindo E, et al. Oral diosmectite reduces stool output and diarrhea duration in children with acute watery diarrhea. Clin Gastroenterol Hepatol 2009; 7: 456–462.
20 Kuge T, Shibata T, Willett MS. Multicenter, double-blind, randomized comparison of wood creosote, the principal active ingredient of Seirogan, an herbal antidiarrheal medication, and loperamide in adults with acute nonspecific diarrhea. Clin Ther 2004; 26: 1644–1651.

21 Allen A, Leonard A. Mucus structure. Gastroenterol Clin Biol 1985; 9: 9215.

22 Khediri F, Mrad AI, Azzouz M, Doughi H, Najjar T, Mathiex-Fortunet H, et al. Efficacy of diosmectite (smecta) in the treatment of acute watery diarrhoea in adults: a multicentre, randomized, double-blind, placebo-controlled, parallel group study. Gastroenterol Res Pract 2011; 2011: 783196.

23 Chang FY, Lu CL, Chen CY, Luo JC. Efficacy of dioctahedral smectite in treating patients of diarrhea-predominant irritable bowel syndrome. J Gastroenterol Hepatol 2007; 22: 2266–2272. Epub 2007 Jun 7.

24 Duffour J, Gourgou S, Seitz JF, Castéra D, et al. Efficacy of prophylactic anti-diarrhoeal treatment in patients receiving Campto for advanced colorectal cancer. Anticancer Res 2002; 22: 3727–3731.

25 Degtiareva II, Opanasiuk ND, Golota OV. The use of Smecta for the treatment of the basic digestive tract diseases. Lik Sprava 1994; 9–12: 88–92.

26 Fuke C, Arao T, Morinaga Y, Takaesu H, Ameno K, Miyazaki T. Analysis of paraquat, diquat and two diquat metabolites in biological materials by high-performance liquid chromatography. Leg Med (Tokyo) 2002; 4: 156–163.

27 Fuke C, Ameno K, Ameno S, Kiritu T, Shinohara T, Sogo K, et al. A rapid, simultaneous determination of paraquat and diquat in serum and urine using second-derivative spectroscopy. J Anal Toxicol 1992; 16: 214–216.

28 Mikawa K, Nishina K, Takao Y, Obara H. ONO-1714, a nitric oxide synthase inhibitor, attenuates endo-toxin-induced acute lung injury in rabbits. Anesth Analg 2003; 97: 1751–1755.

29 Bustos SP, Reithmeier RA. Structure and stability of hereditary spherocytosis mutants of the cystolic domain of the erythrocyte anion exchanger 1 protein. Biochemistry 2006; 45: 1026–1034.

30 Caplan MS, Jilling T. Neonatal Necrotizing enterocolitis: possible role of probiotic supplementation. J Pediatr Gastroenterol Nutr 2000; 30: S18–22.

31 Bullivant CM. Accidental poisoning by paraquat: a report of two cases in man. Br Med J 1966; 1: 1272–1273.

32 Lock EA, Wilks MF. Paraquat. In: Handbook of Pesticide Toxicology, 2nd edn. San Diego, Academic Press, 2001: 1559–1603.

33 Suntres ZE. Role of antioxidants in paraquat toxicity. Toxicology 2002; 180: 65–77.

34 Koo JR, Yoon JW, Han SI, Choi MJ, Park II, Lee YK, et al. Rapid analysis of plasma paraquat using sodium dithionite as a predictor of outcome in acute paraquat poisoning. Am J Med Sci 2009; 338: 373–377.

35 Houze P, Baud FJ, Mouy R, Bismuth C, Bourdon R, Schermann JM. Toxicokinetics of paraquat in humans. Hum Exp Toxicol 1990; 9: 5–12.

36 Hawkesworth GH, Bennett PN, Davies DS. Kinetics of paraquat elimination in the dog. Toxicol Appl Pharmacol 1981; 57: 139–145.

37 Bennett PN, Davies DS, Hawkesworth GM. In vivo absorption studies with paraquat and diquat in the dog. Br J Pharmacol 1976; 58: 284.

38 Ma YT, Tian YP, Shi HW, Ly CH, Liu JH, Sun ZP. Effects of high dose ambroxol on lung injury induced by paraquat in rats. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi 2007; 25: 523–526.

39 Nagao M, Zhang WD, Itakura Y, Kobayashi M, Yamada Y, Yagi K, et al. Immunohistochemical localization and dynamics of paraquat in the stomach and esophagus of rats. Int J Leg Med 1993; 106: 142–144.

40 Tiwary AK, Poppenga RH, Puschnier B. In vitro study of the effectiveness of three commercial adsorbents for binding oleander toxins. Clin Toxicol (Phila) 2009; 47: 213–218.

41 Amany AA. Protective effect of montelukast on paraquat-induced lung toxicity in rats. Biosci Trends 2009; 3: 63–72.