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PHARMACOLOGICAL AND TOXICOLOGICAL EFFECTS OF GAS PLANT *(DICTAMNUS ALBUS L.)*

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Abstract

Purpose of the present study was to investigate pharmacological and toxicological effects of gas plant. Aqueous extracts prepared from its leaves and fruits were tested on the guinea-pig skin by comparing with 2,4-dinitrochlorobenzene. When histopathological examination was made on guinea-pig skin injected with the extracts, there was no change observed in mast cells, but acute exudative inflammation and infiltration of polymorphonuclear leukocytes were noticed in the hypodermis. Their edema forming activities were also tested in the rat paw experiment and their effects were compared to those induced by formalin. In vivo bronchial tone/blood pressure and isolated ileum experiments in guinea-pigs were performed. Aqueous extracts prepared from this plant were found to cause bronchoconstriction and hypotension, which were not dose-dependent. They also elicited concentration-dependent contractions of the isolated guinea-pig ileum, which were not abolished by chlorpheniramine, ketotifen and dexamethasone. D. albus extracts had no significant effect on the mouse pain threshold in "Tail-clip" experiments. Their effects on the central nervous system were examined by using swimming endurance test and observational screening on mice. In this case, a sedative activity was observed. It was concluded that aqueous macerates from leaves and fruits of D. albus causes an acute phase inflammatory response.

Key Words: *Gas plant; Dictamnus albus L.; histamine; edema; skin test; sedative effect*

Akgiritotu (Dictamnus albus L.)'nun Farmakolojik ve Toksikolojik Etkileri

Bu çalışmanın amacı Akgiritotu'nun farmakolojik ve toksikolojik etkilerini araştırmaktır. Yaprak ve meyvalarından hazırlanan sulu ekstreler kobay derisi üzerinde 2,4-dinitrobenzen ile karşılaştırmalı olarak test edilmiştir. Ekstrelerin injekte edildiği kobay derisi üzerinde histopatolojik inceleme yapıldığında mast hücrelerinde herhangi bir değişim gözlenmemiş, ancak hipodermiste eksudatif inflamasyon ve polimorfonükleer lökosit infiltrasyonu dikkat çekmiştir. Ayrıca ödem oluşturucu etkinlikleri sıçan pençe deneyinde de test edilmiş ve sözkonusu etkiler formalin ile oluşturulan etkiler ile karşılaştırılmıştır. Kobaylarda in vivo bronşiyal tonüs/kan basıncı ve izole ileum deneyleri gerçekleştirilmiştir. Sözkonusu bu bitkiden hazırlanan sulu ekstrelerin doza bağımlı olmayan bronkokonstriksiyon ve hipotansiyona neden olduğu bulunmuştur. Ekstreler izole kobay ileumunda klorpromazin, ketotifen ve deksametazon ile önlenemeyen ve konsantrasyona bağımlı olan kasılmalar oluşturmuşlardır. D. albus ekstrelerinin farelerde "Tail-Clip" deneylerinde ağrı eşiği üzerinde anlamlı bir etkisi olmamıştır. Ekstrelerin santral sinir sistemi üzerideki etkileri farelerde yüzme dayanıklılık testi ve gözlemsel tarama yardımı ile sınanmıştır. Burada sedatif etki gözlenmiştir. D. albus'tan hazırlanan sulu ekstrelerin akut fazlı inflamatuvar bir yanıta neden olduğu sonucuna varılmıştır.

Anahtar Sözcükler: *Akgiritotu; Dictamnus albus L.; histamin; ödem; deri testi; sedatif etki*

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INTRODUCTION

Gas plant (*Dictamnus albus* L.) is a quite common plant in the world (1-3). *D. albus* L. is found as a wild plant in certain localities of Turkey, especially in the north Anatolian part. The genus *Dictamnus* L. (Rutaceae) is represented in the flora of Turkey by a single species, *D. albus* L. (3). The plant is rich in flavonoids (4), quinoline alkaloids (5), psoralens as coumarins (6) and essential oils (7). The main psoralens in *D. albus* are 5-methoxypsoralen and 8-methoxypsoralen (6), whereas the main components in the essential oil are dictagymnin, feniculin, methylchavicol and *trans*-anethol (7). In Indian folk medicine, *Dictamnus albus* has been used as an emmenagogue and abortive agent (8,9). This abortive action seems to be closely related to its mutagenic and embryotoxic effects (10,11). Jaundice and skin disorders like psoriasis have been cured by this plant in folk medicine (10). Its flowering branches are used in Turkey as a folk remedy for its stomachic, tonic, stimulant and antipyretic activities (12). However, it is well known that *D. albus* causes contact photodermatitis in man (6,13,14). It has long been known that aerial parts of Gas plant may cause skin irritations due to photosensitization. As a result of the irritation, skin rash may occur within 24 hours following the first contact with the plant (13,14). Although *D. albus* has been investigated extensively in terms of clinical aspects of photodermatitis, there is only a limited data is available on its effects in animal models. Hence, primary purpose of the present study was to investigate its pharmacological and toxicological effects on experimental animals.

EXPERIMENTAL

Animals.

Male guinea-pigs (300-400 g), Wistar rats (250-350 g) and albino mice (about 30 g) were used. They were housed in well ventilated rooms with a temperature of 23±3ºC. All rats and mice were fed with standard pellets and water *ad libitum*. In addition, fresh vegetables were given to guinea-pigs.

Drugs

2,4-Dinitrochlorobenzene (DNCB), compound 48/80, histamine phosphate, eosin B disodium, desipramine hydrochloride and urethane were purchased from Sigma, St.-Louis, USA. Heparin (Liquemin), dexamethasone phosphate disodium, ketotifen fumarate, chlorpheniramine maleate were gifts from Roche, Deva, Sandoz and Doğu Drug Companies, Istanbul, Turkey, respectively. Hematoxyllin was obtained from Merck, Darmstadt, Germany. All chemicals, except DNCB, were dissolved in distilled water and used freshly by preparing appropriate dilutions. DNCB was dissolved in absolute ethanol (95% v/v) and used freshly. Doses and concentrations of the drugs used in the present study were chosen on the basis of literature data.

Plant material

Plant material was collected from the wild flora and authenticated by an authority. Aerial parts of *Dictamnus albus* were collected in July from Çakıllı region, Ankara to Samsun (35 km). A voucher specimen of this plant (ESSE 10045) has been deposited in the Herbarium of the Faculty of Pharmacy, Anadolu University. 200 g of fresh leaves were then cut into very small pieces with a scissors and macerated with 2.0 L of distilled water for 48 h (Ex1). Relative moistures in leaves and fruits were determined as 75% and 55%, respectively. In a same manner, fresh fruits were macerated with distilled water for 48 h to prepare 10% w/v extract. Aqueous macerate of fruits was coded by Ex2. Small portions of Ex1 and Ex2 was stored in deep freeze at -70°C and diluted with physiological saline (0.9%) immediately before the pharmacological experiments mentioned below. A portion of both macerates was evaporated under vacuum to obtain dry macerates and calculate the yield of maceration process. Yields for Ex1 and Ex2 were 0.8 % and 0.75 %, respectively. Using these yield values, doses given to animals were expressed mg/kg body weight. Effective doses and concentrations of Ex1 and Ex2 were determined by pilot experiments in which dose (concentration) scanning experiments were performed for each pharmacological test system.

Measurements of bronchial tone and blood pressure in guinea-pigs

Measurements of bronchial tone and blood pressure were made as described previously (15). Briefly, guinea-pigs were anaesthetized by 1.0-1.25 g/kg urethane i.p. Further urethane was given (i.p.) when necessary to maintain suppression of spontaneous respiratory movements. The trachea was immediately cannulated and inflated by a respiration pump (Ugo Basile, No.7025, Varese, Italy) with 5-10 mL stroke volume, generally at 72 strokes per min. The tracheal cannula was connected to a brochospasm transducer (Ugo Basile, No. 7020, Varese, Italy) by means of side arm, which permitted some air to escape through a water valve in the transducer, offering a resistance of 10 cm water. The changes due to bronchoconstriction were recorded on a two-channel "Gemini" recorder (Ugo Basile, No.7070, Varese, Italy) connected to the bronchospasm transducer. Meanwhile, the venous cannula (1.5 mm external diameter drawn out to 0.25-0.5 mm) was inserted in an external jugular vein for the administration of plant extracts or histamine. To prevent clots, heparin (250-500 units) was injected intravenously through the cannula and washed with 0.5 mL saline. Then, the left or right carotid artery was isolated and a clamp was attached. A plastic cannula, slightly larger than the venous cannula, was connected to a blood pressure transducer (Ugo Basile, No.52591, Varese, Italy) coupled to the recording microdynamometer. The cannula was inserted into the carotid artery and the arterial clamp was removed after testing the unit for leaks. The experiments were started 30 min after setting up, and 1-2 mL saline was given to substitute fluid loss. After this period, histamine and plant extracts were given at the following doses through the venous cannula histamine 0.5 μg/kg, Ex1: 4, 8 and 16 mg/kg; Ex2: 3.75, 7.5 and 15 mg/kg.

Isolated guinea-pig ileum

Experiments on the isolated guinea-pig ileum were performed as described previously (16). Briefly, male guinea-pigs were killed by a blow on the head and terminal ileum pieces of 2 cm long were suspended in a 10 mL organ bath containing Krebs solution (at 37ºC and aerated with a mixture of 95 % O_2 and 5 % CO_2. The suspended ilea were maintained under a resting tension of 1.0 g for a stabilization period of 1 h, while the tissues were washed out every 10 min. For recording of contractions, tissues were connected to an isotonic transducer (Ugo Basile, No.7006, Varese, Italy) coupled to a two-channel "Gemini" recorder (Ugo Basile, No.7070, Varese, Italy) with a 5-fold magnification. Three doses of Ex1 ($8x10^{-5}$, $1.6x10^{-4}$ and $3.2x10^{-4}$ g/mL) and Ex2 ($7.5x10^{-5}$, $1.5x10^{-4}$ and $3x10^{-4}$ g/mL) were added into the organ bath and non-cumulative concentration-response relationships were obtained both in the absence and presence of antagonists. The antagonists were chlorpheniramine, ketotifen and dexamethasone with an incubation period of 30 min in bathing medium. Non-cumulative concentration-response relationships were also obtained for histamine in the absence and presence of antagonists. To obtain non-cumulative concentration-rseponse relationships, the dose cyles for histamine and plant extracts were 5 min with a 45 s of contact time. To investigate the involvement of histamine release, compound 48/80 ($3x10^{-5}$ g/mL) was added into the organ bath in some experiments. All contractions obtained in the present study were expressed as a percentage of maximum contraction of histamine.

Rat paw edema

Paw edema was induced by injecting formalin (2 and 3.5%) and plant extracts into the subplantar region of hind paw of the rats (17). Plant extracts were also injected in combination with formalin. Control rats received saline only. In each case, the injection volume was 0.1 mL. The edema formation in the rat hind paw was determined by the increase in paw volume as measured by a plethysmometer (Ugo Basile, No.7150, Varese, Italy). Rat paw volumes were expressed in mL. Measurements of the rat paw volume were repeated 60, 90 min and 6 h, 24 h after the injections.

Tail-Clip experiments on mice

Possible nociceptive and antinociceptive activities of aqueous macerates of *D. albus* were measured by application of mechanical tail-clip as described previously elsewhere (18). Briefly, three groups of five animals each were used. A control response (2-4 s) was determined by an i.p. injection of 0.1 mL 0.9% physiological saline solution. Mice belonging to second and third group were injected with Ex1 and Ex2 at the dose of 130 and 126 mg/kg i.p., respectively. Test latencies were assessed 30 min after drug administration to mice for all test substances and control group. To avoid irreversible damage in tail structures of mice, a maximum latency of 10 sec was imposed if no response occurred within that time.

Swimming endurance test

The method for swimming endurance test in mice was described earlier (19). Briefly, four groups of five mice each were used. One group served as control and mice in the second, third and fourth groups received i.p. injections of Ex1 (130 mg/kg), Ex2 (126 mg/kg) and desipramine (30 mg/kg), respectively. Desipramine and plant extracts were dissolved in physiological saline solution 1 h before the experiment. Injection volume did not exceed 0.2 mL in each case. Control mice were given the same volume of saline 1 h before the experiment. The mice were allowed to swim until exhaustion in a separate plastic jar (30x15x30 cm) containing 15 cm water maintained 24-26^{o}C. The end point was taken when the animals drowned for 10 s and swimming time for each animal was noted. The mean swimming time for each group was calculated.

Open patch skin test in guinea-pigs

The method for the open patch skin test in guinea-pig was similar to that described earlier (20). Briefly, after removal of dorsal hair with an electric clipper, single intradermal injections of 0.1 mL plant macerates or DNCB were made into the skin of right or left sacrum. One hour after the injections, all guinea-pigs were exposed to the sun light for one hour (between 12.$\underline{30}$ to 13.$\underline{30}$). After the exposure to sun light, animals were kept in normal housing condition and the changes on the skin were observed at 12th, 24th and 48th hours. Changes in the skin were scored by comparing with those induced by DNCB as follows: No change (0), slight erythema (+), dense erythema (++), slight edema (+++), dense edema (++++) and dense edema with necrotic foci (+++++).

Histopathological examination of the guine-pig skin

After removing dorsal hair of the guinea-pigs, single intradermal injections (0.1 mL) of Ex1 and Ex2 were made into the skin of right or left sacrum. Two groups of 5 animals served as controls, which were injected, with saline and ethanol (95% v/v). 24 h and 48 h after the intradermal injections, skin specimens for histopathological examination were taken by biopsy under light ether anesthesia. After the fixation with neutral buffered formalin solution (10% v/v) for 2 days, specimens were embedded in paraffin wax, sectioned at 5 μm and stained with haematoxylin and eosin B (21).

Acute lethal toxicity in mice

Acute lethal toxicities of *Dictamnus albus* extracts in mice were determined according to the method of Lorke (22). The advantages of this method are a saving in experimental animals, swiftness of the experimental procedure and relevance for the assessment of acute toxicity of natural products. Mice were divided into three groups of five mice each. Three subcutaneous doses of Ex1 (1.30, 13.0 and 130 mg/kg) and Ex2 (1.26, 12.6 and 126 mg/kg) were given to mice. Injection volume did not exceed 0.05 mL in each case. Where any animals died at the time of day was noted, during the first day in hours and observed thereafter in 5 days.

General behaviour

Animals injected with plant extracts were observed for 1 h before the swimming endurance test and for 30 before the tail-clip experiments and any lethality that occurred in the animal groups 24 h after all the experimental procedures was recorded (23).

Statistical analysis

All the data given represent the mean values ± standard error of mean (SEM). The data obtained were evaluated by Student's *t*-test. Dose-dependency of the effect of drugs and extracts on the guinea-pig ileum was tested by the application of linear regression procedure (24). All calculations were made by using a computer program executed in an IBM 300GL computer (25).

Table 1. Results of open patch skin test in guinea-pigs. For the details of scoring see Materials and Methods section.

Groups	**Animals**			**Average**
	I	**II**	**III**	
Ethanol (96 % v/v)	+	++	+	+
Saline	0	+	0	0
DNCB	+++++	+	++	+++
Ex1	0	+	++	+
Ex2	++++	++	+	++

Table 2. Results of rat paw edema (Mean±SEM; n=6 in each case).

	Volume of rat paw (mL)				
Groups	0 min	60 min	90 min	6 h	24 h
Saline	2.71±0.08	2.84±0.09	2.82±0.07	2.68±0.14	2.78±0.15
Formalin (2%)	2.56±0.14	2.39±0.17	2.53±0.10	2.64±0.06	2.87±0.08[a]
Formalin (3.5%)	2.47±0.41	3.82±0.39[b]	3.63±0.22[a]	4.21±0.28[d]	4.04±0.17[c]
Ex1	2.75±0.18	3.27±0.14[b]	3.23±0.12[b]	3.31±0.19[a]	3.28±0.19[a]
Ex2	2.61±0.21	2.95±0.28	2.98±0.17	3.15±0.20[a]	2.83±0.19
Formalin 2% (+Saline)	2.45±0.13	2.78±0.13[a]	2.44±0.12	2.71±0.13	2.62±0.12
Formalin 3.5% (+Saline)	2.90±0.50	4.32±0.52[d]	3.96±0.25[c]	4.02±0.28[c]	3.96±0.22[c]
Formalin 2% (+Ex1)	3.18±0.15	3.61±0.18[b]	3.88±0.22[c]	3.72±0.21[c]	3.02±0.27
Formalin 2% (+Ex2)	2.63±0.18	2.67±0.18	3.36±0.27[b]	3.49±0.23[c]	3.41±0.21[c]

[a]$p<0.05$, [b]$p<0.025$, [c]$p<0.01$ and [d]$p<0.005$ relative to 0 min values

RESULTS

When compared to DNCB, aqueous macerate of leaves (Ex1) and fruits (Ex2) caused only slight and moderate skin lesions in guinea-pigs, respectively (Table 1). Histopathological examination of the guinea-pig skin indicated no change in the dermis and epidermis. Ex1 did not cause a significant change in the microscopic morphology of guinea-pig skin. In contrast, local injection Ex2 was found to be ineffective on mast cells in the guinea-pig skin, while acute exudative inflammation and infiltration of polymorphonuclear leukocytes were noticed in the hypodermis. Inflammatory effect of *Dictamnus albus* was confirmed with rat paw edema experiments. Extracts prepared from this plant increased formalin-induced rat paw edema. Intraplantar injections of Ex1 and Ex2 alone caused edema in rat paws and the magnitude of these edema formations were comparable to that caused by formalin (Table 2). Aqueous macerates from *Dictamnus albus* was found to cause bronchospasms in guinea-pigs. However, these bronchospasms were not dose-dependent and their magnitudes were considerably smaller than those obtained by the intravenous administration of 0.5 μg/kg Hist. Ex1 and Ex2 were also ineffective on the blood pressure of guinea-pigs, while histamine (0.5 μg/kg i.v.) caused a significant fall in the blood pressure. Ex1 and Ex2 caused concentration-dependent contractions in the guinea-pig ileum (Fig. 1a). When compared to Hist, these contractions were small in magnitude. Both effects of *D. albus* extracts and histamine were antagonized by chlorpheniramine at the concentration of 10^{-8} g/l (Fig. 1b-d). However, the inhibitory activity of chlorpheniramine against Ex1 and Ex2 was weaker than that against Hist. At a concentration range between $3.09x10^{-4}$ and $3.09x10^{-6}$ g/l, ketotifen was found to inhibit histamine, Ex1 and Ex2-induced contractions of guinea-pig ileum (Fig. 1e-g). Dexamethasone ($2.41x10^{-5}$ g/L) did not inhibit histamine, Ex1 and Ex2-induced contractions of the ileum (Table 3). Compound 48/80 was also ineffective against histamine, Ex1 and Ex2-induced contractions of the ileum.

Both Ex1 and Ex2 were found to be ineffective on "Tail-Clip" latencies of mice, whereas both macerates and desipramine caused a significant decrease in their swimming time (Table 4). Observational screening of mice also revealed an obvious sedation and a decrease in their spontaneous motor activities. In the acute toxicity experiments, only one animal died after the injection of Ex2 at the dose of 126 mg/kg i.p. Ex1 did not cause any lethality in mice, even at the dose as much as 130 mg/kg.

Table 3. Effect of dexamethasone ($2.41x10^{-5}$ g/L) on the contractile effects of histamine, Ex1 and Ex2 (Mean±SEM, n=6 in each case).

	Percent Contractile Responses		Statistical Significance
Contracting agent (Doses g/l)	Controls	+Dexamethasone	
Histamine			
$2.00x10^{-9}$	14.56 ± 2.62	8.77 ± 3.32	$p > 0.1$
$3.00x10^{-8}$	64.98 ± 5.00	76.24 ± 13.87	$p > 0.1$
$6.00x10^{-8}$	88.02 ± 6.78	87.33 ± 8.11	$p > 0.1$
$1.20x10^{-7}$	95.24 ± 6.42	92.88 ± 10.59	$p > 0.1$
$2.50x10^{-7}$	97.82 ± 3.59	90.56 ± 6.81	$p > 0.1$
$5.00x10^{-7}$	100.00 ± 2.03	83.17 ± 5.45	$p < 0.005$
Ex1			
$1.60x10^{-1}$	25.88 ± 4.77	29.80 ± 4.46	$p > 0.1$
$3.10x10^{-1}$	41.59 ± 6.29	50.83 ± 8.29	$p > 0.1$
$6.10x10^{-1}$	53.83 ± 6.29	52.68 ± 7.40	$p > 0.1$
Ex2			
$1.50x10^{-1}$	25.48 ± 3.17	27.96 ± 6.28	$p > 0.1$
$3.00x10^{-1}$	40.69 ± 5.59	45.98 ± 9.63	$p > 0.1$
$6.00x10^{-1}$	59.79 ± 7.74	73.93 ± 8.46	$p > 0.1$

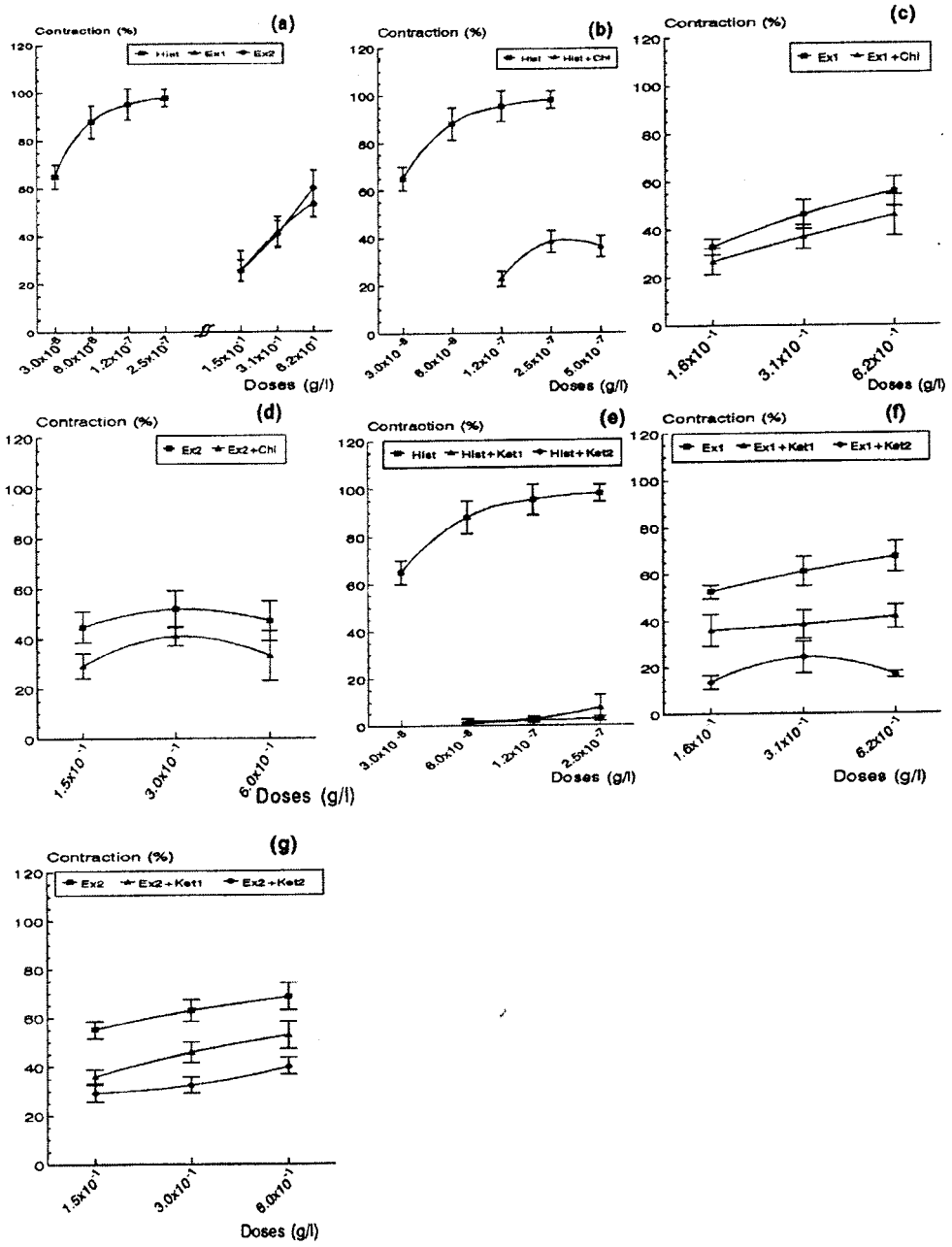

Figure 1. Effect of histamine (Hist), aqueous extracts of the leaves (Ex1) and fruits (Ex2) of *Dictamnus albus* L. on the guinea-pig ileum (a). Effect of $1.0x10^{-8}$ g/l chlorpheniramine (Chl) on the contractile activity of Histamine (b), Ex1 (c) and Ex2 (d) on the guinea-pig ileum. Effect of ketotifen (Ket1: $3.09x10^{-6}$ g/mL and Ket2: $3.09x10^{-4}$ g/mL) on the contractile activity of histamine (e), Ex1 (f) and Ex2 (g) on the guinea-pig ileum. Vertical bars depict the standard error of mean (n=5 in each case).

Table 4. Results of swimming endurance test in mice (Mean ± SEM values, n=5 for each group).

Groups	Swimming Time (min)	Significances relative to controls
Controls	250 ± 25	
Desipramine	183 ± 16	$p<0.05$
Ex1	106 ± 50	$p<0.005$
Ex2	79 ± 27	$p<0.005$

DISCUSSION

Gas plant (*Dictamnus albus* L.) is a good example of plants, which cause phytophotodermatitis (6,13,14). The photodermatitis caused by Gas plant is due to its psoralen content (6). Although therapeutic implications and phototoxicities of psoralens have been investigated extensively, the mechanism of their action in the skin has not been established yet (26-28). One possible explanation for the mechanism of their phototoxic actions is the formation of reactive oxygen species, and consequent damage of DNA leading cell death or mutagenesis (28). In the present study, open patch skin tests in guinea-pigs confirmed previous reports on the photodermatitis caused by Gas plant (*Dictamnus albus*) in human subjects (13,14). After exposure to sunlight, the contact dermatitis caused by its aqueous extracts is slightly weaker than that induced by DNCB (Table 1). Since there was no sign of histamine release from mast cells of guinea-pig skin, the dermatitis caused by these plant extracts seems to be non-allergic in nature. There were, however, acute exudative inflammation and infiltration of polymorphonuclear leukocytes in the hypodermis of guinea-pig due to the intradermal injection of plant extracts, which suggest an acute phase inflammatory response. Infiltration of leukocytes due to increase in capillary permeability is one of the characteristics of acute phase inflammatory response (29). Rat paw edema experiments also confirmed the acute phase inflammatory responses induced by the extracts from *D. albus* which caused edema in a similar magnitude with that induced by formalin (Table 2). The findings obtained in the organ bath experiments clearly showed that the release of histamine and prostanoids is not involved in the effect of Gas plant, since compound 48/80, ketotifen and dexamethasone did not abolish contractile effects of aqueous extracts of *D. albus*. From these findings, it may be suggested that the contractile effect of Gas plant on guinea-pig ileum is a direct one and is not mediated by histamine and prostanoids.

On the basis of findings obtained in the present study, aqueous extracts of *Dictamnus albus* exhibits effects on CNS. Extracts of *D. albus* were found to be ineffective in "Tail-Clip" experiments suggesting that they have no algesic and analgesic properties at the dose applied. In contrast, they caused a significant decrease in the swimming time of mice suggesting a depressant activity on the CNS. This observation was also confirmed in our general behaviour screening

experiments which indicated an obvious sedative activity and decrease in the spontaneous activities of mice following plant extracts. In a previous study, decreased motor activity in mice due to the CNS has been reported upon administration of alcoholic extract of *Dictamnus albus* (30). These effects on the CNS may be due to psoralen contents of the plant extracts. Psoralens have been reported to stimulate melatonin secretion and increases plasma melatonin concentrations (31). It is well documented that melatonin has sedative properties and plays an important role in circadian sleeping period of mammalian species (32). Therefore, melatonin may play a role in the depressant activity of *D. albus* on CNS. However, this possibility will require further investigations. Acute lethal toxicity experiments indicated the moderate toxicity of aqueous extracts of *Dictamnus albus*. However, toxicity assessment in the present study is only limited with the determination of lethality upon systemic administration and with the observation of photodermatitis upon it topical application. Mutagenicity and teratogenicity of *D. albus* reported in previous studies (10,11,28) are beyond of the scope of this study. In conclusion, our findings strongly suggested that *D. albus* may have not only therapeutic implications as in the case of other psoralen containing plants but also toxicological interest.

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