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The Effect of *Rhazya stricta* Decne, a Traditional Medicinal Plant, on Spontaneous and Drug-Induced Alterations in Activity of Rats

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ALI, B. H., A. K. BASHIR AND M. O. M. TANIRA. *The effect of* Rhazya stricta (*Decne*), *a traditional medicinal plant, on spontaneous and drug-induced alterations in activity of rats.* PHARMACOL BIOCHEM BEHAV **64**(3) 455–459, 1999.—The effect of acute and chronic treatment of rats with a lyophilized extract of the leaves of the medicinal plant *Rhazya stricta* on total and ambulatory activity was studied. Given acutely at single oral doses of 1, 2, 4, and 8 g/kg, the extract produced dose-dependent decreases in total activity and ambulatory activity. Diazepam (20 mg/kg, orally) produced a decrease in rat activity comparable to that produced by a dose of 1 g/kg of the extract. When given daily at an oral dose of 2 g/kg for 21 consecutive days, the extract produced, on the last day of treatment, significant decrease in activity amounting to about 30% of control activity levels. Subcutaneous (SC) treatment of rats with caffeine (7.5, 15, and 30 mg/kg), dose-dependently and significantly increased total activity and ambulatory activity. These effects were dose-dependently attenuated when the extract was given concommittantly with caffeine at oral doses of 1, 2, and 4 mg/kg. Treatment of rats with zoxazolamine alone (10, 20, or 40 mg/kg, SC) or *R. Stricta* (1 and 4 g/kg orally) alone significantly decreased total and ambulatory activities. Concomittant treatment with zoxazolamine and *R. Stricta* decreased the rats activity to a greater degree than with either treatment given alone. © 1999 Elsevier Science Inc.

Locomotor activity Caffeine Dizaepam *Rhazya stricta* Zoxazolamine

RHAZYA stricta Decne (Family Apocynaceae) is a shrub with a smooth central stem and dense semierect branches (17): The plant grows commonly in the Arabian Peninsula, and is used in local folk medicine practices to treat diabetes mellitus, inflammatory conditions, and helminthiasis. Extensive phytochemical studies have been published on this plant [see (5), and references therein]. The plant leaves contain alkaloids with β-carboline nucleus, for example, akuammidine, rhaziminine, and tetrahydrosecamine (6). *R. Stricta* has also been shown to contain two flavonoids: isorhamnetin 3-(6-rhamnosylgalactoside)-7-rhamnoside, and 3-(6-rhamnosylgalactoside)-7-rhamnoside (Bashir, unpublished data). However, relatively little work has been reported on the pharmacological and toxicological properties of the plant (1,14,16). While testing the antihyperglycaemic effect of *R. Stricta*, a quiescent behavior in treated mice was noticed shortly after giving the plant extract, suggesting that it may have depressed the activity of the central nervous system (CNS). This possibility was tested and confirmed (1).

In this present study, we extended this work by investigating, in rats, the effect of *R. Stricta* extract on spontaneous activity, and on activity after treatment with a drug that increases motor activity (caffeine((7,8), and a drug that decreases activity (zoxazolamine) (12,13). Caffeine is a well-known psychomotor stimulant that acts by antagonizing adenosine and inhibiting phosphodiesterase (8). Zoxazolamine is in the centrally acting muscle relaxant class of drugs, which reportedly decreases CNS interneuronal activity, decreases dopaminergic turnover, and attenuates the induction of a pacemaker-like discharge pattern in dopaminergic neurons (12).

METHOD

Animals

Locally bred male Wistar rats of about 250 g were used. They were housed in groups of six animals, each at a temperature of 22 ± 2°C and 12 L:12 D cycle (lights on at 0700 h). The were given pelleted diet (Abu Dhabi Flour and Animal Feeds Factory) and tap water ad lib until the time they were put in the experimental cage. In all experiments each animal was used only once.

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Plant Material and Extraction Procedures

The plant was collected form Umm Gafa, Al-Ain district, in February 1994, and authenticated at the National Hebarium of the U.A.E. University, where a voucher specimen was deposited.

The leaves were air-dried in the shade and coarsely pulverized, and the resultant powder (200 g) was macerated with distilled water (3 l) for 16 h at room temperature, with occasional shaking. The extract was filtered and the filtrate obtained was lyophilized using a freeze dryer. The final lyophilized product constituted about 18.3% of the original material. Aqueous solutions were freshly prepared from the same lyophilized product and used in all tests. The aqueous extract was always administered orally in a volume of 2 ml/kg body weight. An HPLC fingerprinting of the plant extract has been documented in this laboratory (Ali et al., submitted).

Treatments

Spontaneous activity. 1) *Acute treatment*: six groups were used. The first group was given distilled water (2 ml/kg) orally. The second, third, fourth, and fifth groups were treated orally by gavage with *R. Stricta* extract at single doses of 1, 2, 4, and 8 g/kg, respectively. The last group was given diazepam (Stesolid®, Dumex) at an oral dose of 20 mg/kg. 2) *Chronic treatment*: two groups were used. The first (control) group was given distilled water (2 ml/kg) orally by gavage for 21 days, and the second was given *R. Stricta* extract (2 g/kg) by the same route for 21 consecutive days.

In all experiments rats were habituated to the activity meter cages for 1 h a day before the start of the experiment.

Drug-induced alterations in activity. 1) *Caffeine*: the effect of acute treatment with *R. Stricta* on caffeine-induced hypermotility (7) was evaluated. In this experiment 13 groups (n = 6 rats each) were used and were treated as follows: *Group 1* was given distilled water orally at a dose of 2 ml/kg (three rats) and 0.9% w/v NaCl at the same dose SC (three rats). The activity in rats given either treatment was similar; therefore, the two groups were combined. *Groups 2, 3, and 4* were injected SC with caffeine at doses of 7.5, 15, and 30 mg/kg, respectively. *Groups 5, 6, and 7* were injected SC with caffeine (7.5 mg/kg) and were concomittantly given *R. Stricta* orally at doses of 1, 2, and 4 g/kg, respectively. *Groups 8, 9, and 10* were injected SC with caffeine (15 mg/kg) and were concomit-

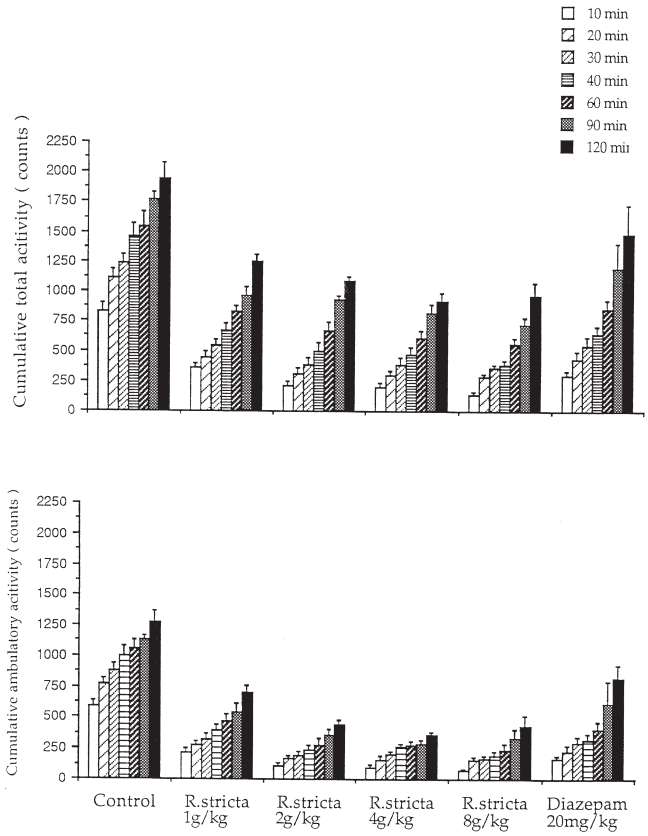

FIG. 1. The effect, in rats, of acute administration of *Rhazya stricta* extract or diazepam on the cumulative total (upper panel) and ambulatory (lower panel) activity. Each rat was treated with the plant extract, vehicle, or diazepam, and immediately singly placed in the cage of the activity meter, and 5 min thereafter measurements were started (zero time). Counts were taken 10, 20, 30, 40, 60, 90, and 120 min. Each column and vertical bar represents mean ± SEM (n = 6 per group). All treatments produced significant ($p > 0.05$) reduction in total and ambulatory activity in all the time points.

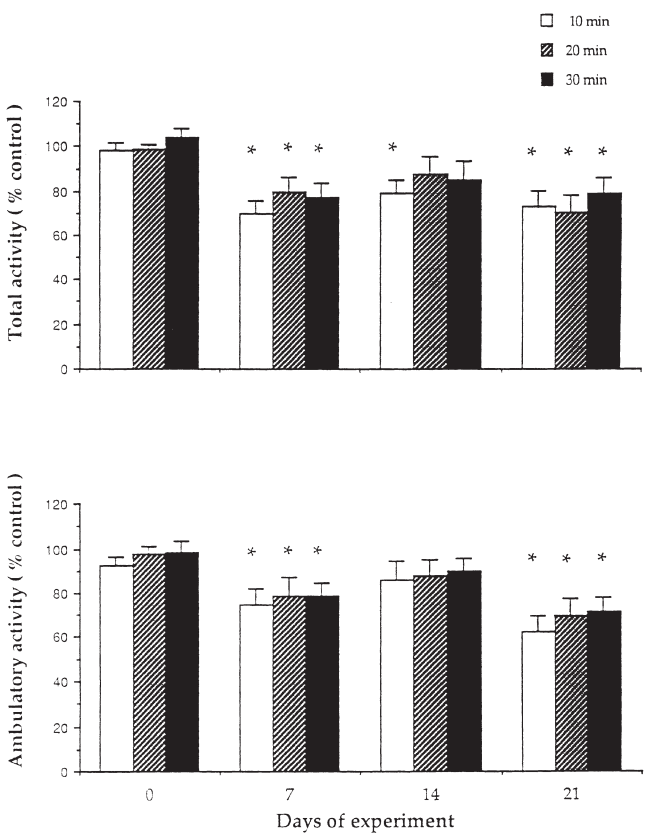

FIG. 2. The effect of oral treatment of rats with extract of *Rhazya stricta* (2 g/kg/day for 21 days) on total and ambulatory activity. Results are expressed as percentage of the activity of control rats (treated orally with distilled water at a dose of 2 ml/kg/day for 21 days). Each column and vertical bar represent mean ± SEM (n = 6). Asterisks denote significant differences from the respective control (on day 0). Rats were placed singly in the cage of an activity meter and left for 5 min prior to the start of measurement. Thereafter, activity counts were recorded after 10, 20, and 30 min.

tantly given *R. Stricta* orally at doses of 1, 2, and 4 g/kg, respectively. *Groups 11, 12, and 13* were injected SC with caffeine (30 mg/kg) and were concomittantly given *R. Stricta* orally at doses of 1, 2, and 4 g/kg, respectively.

Immediately following the treatments rats were gently put in the cage of the activity meter, and after 5 min measurement started. Activity was measured at 10, 20, 30, 40, and 60 min.

2) *Zoxazolamine:* zoxazolamine produces paralysis in rats when given (SC) at a dose of 100 mg/kg (13). From several preliminary experiments we found that the administration of the drug at doses of 10–40 mg/kg SC produced significant decreases in total and ambulatory activities of rats without causing paralysis. In this experiment, 60 rats were divided randomly into 10 equal groups.

The first, second, and third groups were treated with zoxozolamine (SC) at single doses of 10, 20, and 40 mg/kg, respectively. The fourth and fifth groups were treated with zoxazolamine (10 mg/kg), together with *R. stricta* at oral doses of 1 and 4 g/kg, respectively. The sixth and seventh groups were treated with zoxazolamine (20 mg/kg) together with *R. stricta* at oral doses of 1 and 4 g/kg, respectively. The eight and ninth groups were treated with zoxazolamine (40 mg/kg), together with *R. stricta* at oral doses of 1 and 4 g/kg, respectively. The last (10th) group was treated with the vehicle of zoxazolamine (0.9% w/v NaCl to which a few drops of 1 N HCl was added). Activity was measured as previously described for up to 60 min.

Measurement of Motor Activity

Locomotor (ambulatory) and behavioral (total) activity (11) was measured using a computerized animal activity meter (Opto Varimex Columbus Instruments, Columbus, OH). Total activity included the ambulatory (actual relocation) activity score and the activity confined to a small space, that is, repeated crossing of a single photocell. An array of 15 infrared emitter/detector pairs, spaced at 2.5-cm intervals, measured the animal activity along a single axis of motion. The counts of photo interruptions were displayed on the front panel meters as ambulatory activity and total activity. Immediately after acute treatment, each rat was placed in the transparent plastic cage (43 m × 43 m 22 cm) of the activity meter. After a 5-min habituation period in the cage, the activity meter was zeroed and counts were then taken after 10, 20, 30, 40, 60, 90, and 120 min. The measurements were taken between 0800 and 1200 h. In the chronic experiment, the activity of the animals was tested for 30 min weekly for 3 consecutive weeks. On the day of the test, the extract was given after the activity was measured.

Drugs and Chemicals

Caffeine and zoxazolamine (2-amino-5-chlorobenzoxzole) were purchased from Sigma Chemical Company (St. Louis, MO) Diazepam (Stesolid emulsion) was from Dumex, Denmark.

TABLE 1

THE EFFECT OF TREATMENT OF RATS WITH CAFFEINE AND *RHAZYA STRICTA* ON CUMULATIVE TOTAL (T) AND AMBULATORY (A) ACTIVITY

		10 min	20 min	30 min	40 min	60 min
Control	T	1013.8 ± 98.8	1296.5 ± 87.4	1620.2 ± 101.9	1874.8 ± 83.7	2229.3 ± 110.8
	A	707.5 ± 41.1	898.5 ± 72.4	1073.8 ± 89.1	1248.3 ± 108.1	1454.2 ± 113.2
Caffeine (7 mg/kg)	T	1584.3 ± 114.8	1844.5 ± 119.8	2093.5 ± 112.4	2325.8 ± 132.4	2546.0 ± 156.2
	A	747.7 ± 42.7*	909.0 ± 40.2*	1083.0 ± 38.3*	1250.5 ± 66.9*	1465.7 ± 46.7*
Caffeine (15 mg/kg)	T	1731.2 ± 112.9	2211.0 ± 148.0	2657.3 ± 142.6	2959.2 ± 148.3	3358.7 ± 207.1
	A	1057.8 ± 94.8	1341.1 ± 92.4	1562.0 ± 90.1	1734.0 ± 86.8	1928.2 ± 84.4
Caffeine (30 mg/kg)	T	2502.3 ± 198.5	3067.3 ± 168.1	3680.5 ± 1	3979.3 ± 234.2	4488.7 ± 198.5
	A	1267.5 ± 42.2	1494.0 ± 37.5	1782.8 ± 39.96	2095.4 ± 88.5	2338 ± 56.15
Caffeine (7.5 mg/kg) and	T	1214 ± 69.4	1463.3 ± 72.2	1707.2 ± 42.3	1919.2 ± 58.8	2125.7 ± 51.1
R. stricta (1 g/kg)	A	574.2 ± 41.8	640.3 ± 38.8	851.0 ± 39.8	1112.8 ± 40.1	1292.8 ± 46.0
Caffeine (7.5 mg/kg) and	T	1064.3 ± 50.11	1355 ± 67.5	1574.8 ± 69.7	1840.3 ± 82.06	2025.3 ± 52.3
R. stricta (2 g/kg)	A	527.7 ± 26.9	568.0 ± 22.1	640 ± 24.2	831.3 ± 36.4	943.2 ± 43.7
Caffeine (7.5 mg/kg) and	T	729.7 ± 68.2	984.5 ± 62.9	1170.0 ± 69.8	1388.7 ± 72.5	1602.0 ± 65.2
R. stricta (4 g/kg)	A	453.0 ± 20.1	526.7 ± 22.0	567.8 ± 17.1	629.2 ± 17.1	724.0 ± 37.5
Caffeine (15 mg/kg) and	T	1476.7 ± 99.8	1645.7 ± 129.7	1963.7 ± 117.4	2252.7 ± 118.1	2597.7 ± 82.4
R. stricta (1 g/kg)	A	871.0 ± 33.5	1027.5 ± 75.4	1299.0 ± 63.2	1494.0 ± 80.5	1675.2 ± 91.7
Caffeine (15 mg/kg) and	T	1119.2 ± 54.9	1318.5 ± 66.8	1903.7 ± 64.8	1719.5 ± 69.2	1948.0 ± 81.8
R. stricta (2 g/kg)	A	733.0 ± 40.1	896.3 ± 33.4	1043.0 ± 39.0	1204.2 ± 47.4	1300.7 ± 56.5
Caffeine (15 mg/kg) and	T	991.5 ± 82.7	1165.3 ± 63.6	1350.8 ± 70.2	1548.0 ± 66.4	1702.5 ± 66.9
R. stricta (4 g/kg)	A	659.5 ± 34.2	769.7 ± 47.8	895.7 ± 34.2	1052.0 ± 38.9	1179.0 ± 42.5
Caffeine (30 mg/kg) and	T	1462.5 ± 41.4	1683.0 ± 60.1	1962.0 ± 62.5	2298.7 ± 111.9	2521.2 ± 107.7
R. stricta (1 g/kg)	A	881.1 ± 18.2	1078.3 ± 32.4	1235.8 ± 55.7	1430.7 ± 52.9	1618.0 ± 64.6
Caffeine (30 mg/kg) and	T	1386.1 ± 31.7	1504.7 ± 43.3	1698.0 ± 44.2	1960.3 ± 45.2	2177.0 ± 57.3
R. stricta (2 g/kg)	A	767.3 ± 37.4	876.0 ± 47.5	1074.8 ± 52.6	1239.0 ± 64.9	1404.5 ± 75.03
Caffeine (30 mg/kf) and	T	843 ± 38.6	908.2 ± 35.7	1024.5 ± 39.4	1296.0 ± 127.9	1464.0 ± 125.1
R. stricta (4 g/kg)	A	521.7 ± 26.3	600.0 ± 8.3	666.0 ± 19.3	714.8 ± 17.7	762.8 ± 17.03

Values are means ± SEM (n = 6).
All values from treated rats are significantly lower than that of control except where marked (†).

Statistical Analysis

Values reported are means ± SEM (number of observations). Differences between mean groups were assessed using a one-way analysis of variance, followed by Scheffe's or Dunnet's test using a computer program (Statview 5).

p-Values less than 0.05 were considered significant.

RESULTS

Acute Treatment With R. stricta

Acute administration of single graded doses of *R. stricta* extract (1–8 g/kg) caused significant and dose-dependent decreases in ambulatory activity and total activity of treated rats ($p < 0.05$). Diazepam (20 mg/kg) produced significant decreases in activity comparable to that produced by the plant extract when given at a dose of 1 g/kg, $F(5, 72) = 25.9$, $p < 0.0001$, for measurement of total activity at 30 min, and $F(5, 72) = 22.7$, $p < 0.0001$ for ambulatory activity at 30 min (Fig. 1).

Chronic Treatment with R. stricta

The results of this experiment are shown in Fig. 2. Measurements of activity during chronic administration of *R. stricta* (2 g/kg) showed that total activity and ambulatory activity decreased with time in the first week of treatment. The decrease amounted to about 20% on day 7. Activity incompletely recovered on day 14, and on day 21 it was decreased by about 30%, $F(5, 72) = 20.1$, $p < 0.05$, for measurement of total activity at 30 min; and $F(5, 72) = 19.7$, $p < 0.05$, for ambulatory activity at 30 min.

Caffeine Treatment

Caffeine administration, at doses of 7.5, 15, and 30 mg/kg, produced dose-dependent and significant increases in ambulatory activity and total activity of rats (Table 1). Concomittant oral treatment with *R. stricta* (1 and 4 g/kg) significantly reduced, in a dose-dependent fashion, the caffeine-induced increase in activity levels ($p < 0.05$).

Zoxazolamine Treatment

The results of this experiment are shown in Table 2. Zoxazolamine administration (SC) at doses of 10, 20, and 40 mg/kg, produced significant decreases in the ambulatory activity and total activity of rats ($p < 0.05$). Concomittant treatment of zoxazolamine and *R. stricta* at the doses of 1, 2, and 4 g/kg decreased activity further ($p < 0.05$).

DISCUSSION

The present results showed that the extract of *R. stricta* decreased spontaneous total and ambulatory activity and decreased caffeine-induced hyperactivity. Concomittant treatment with *R. stricta* and zoxazolamine decreased the rats' activity to a greater degree than either treatment administered alone. These findings corroborate our previous results (1) which indicated that *R. stricta* possesses CNS depressant (mainly sedative) properties that bear some resemblance to those produced by diazepam (2). The exact mechanism by which *R. stricta* produces these effects is not certain. However, we hypothesize that it may have acted through a benzodiazepine (BDZ) mechanism.

The behavioral suppression observed in this and a previous study (1) is considered a direct effect and not due to any indi-

TABLE 2

THE EFFECT OF TREATMENT OF RATS WITH ZOXAZOLAMINE (ZOX) AND *RHAZYA STRICTA* ON CUMULATIVE TOTAL (T) AND AMBULATORY (A) ACTIVITY OF RATS

		10 min	20 min	30 min	40 min	60 min
Control (0.9%) w/v NaCI)	T	994.8 ± 76.4	1102.2 ± 80.3	1320 ± 69	1664.5 ± 105.3	1912.7 ± 97.0
	A	567.8 ± 41.6	786.8 ± 41.0	956 ± 45.6	1119.0 ± 51.3	1343.4 ± 50.1
ZOX 10 mg/kg	T	857 ± 5.1	962.3 ± 62.9	1077.3 ± 41.8	1276.3 ± 46.6	1513.3 ± 54.6
	A	439.7 ± 16.2	621 ± 27.3	803.8 ± 31.1	1037 ± 81.8	1202.8 ± 65.4
ZOX 20 mg/kg	T	644.3 ± 32.8	713.2 ± 33.6	819.3 ± 45.2	932.5 ± 44.6	1176.8 ± 72.97
	A	363.7 ± 19.9	424 ± 24.7	609 ± 26.0	807 ± 16	940.5 ± 27.1
ZOX 40 mg/kg	T	526.8 ± 26.3	659.8 ± 24.1	767.7 ± 43.9	912.7 ± 41.5	1007.5 ± 51.3
	A	294.2 ± 25.1	352.8 ± 17.7	416.8 ± 22.3	496.7 ± 27.7	637.3 ± 23.6
ZOX (10 mg/kg) and	T	728.8 ± 46.5	817.8 ± 53.5	906.5 ± 42.2	1015 ± 52.3	1253 ± 44.5
R. stricta (1 g/kg)	A	359.6 ± 13.9	500.8 ± 22.86	661.5 ± 25.6	826.2 ± 65.8	966.7 ± 57.4
ZOX (10 mg/kg) and	T	652.5 ± 43.5	733.7 ± 48.8	808.8 ± 40.5	904 ± 47.1	1120.0 ± 41.5
R. stricta (4 g/kg)	A	318.5 ± 10.2	445.2 ± 21.8	584.5 ± 24.1	740.7 ± 60	840.8 ± 58.0
ZOX (20 mg/kg) and	T	582.3 ± 33.0	627.3 ± 28.8	735.8 ± 37.9	809.2 ± 43.3	1016.7 ± 65.1
R. stricta (1 g/kg)	A	307.7 ± 19.7	413.5 ± 45.3	535.8 ± 28.8	709.7 ± 13.7	816.3 ± 20
ZOX (20 mg/kg) and	T	426.3 ± 71.5	550.0 ± 26.9	644.5 ± 33.7	702.7 ± 37.5	886.3 ± 62.1
R. stricta (4 g/kg)	A	278.8 ± 20.5	320.2 ± 21.1	454.5 ± 28.1	621.5 ± 12.2	710.5 ± 16.2
ZOX (40 mg/kg) and	T	464.3 ± 24.2	578.2 ± 27.1	681.5 ± 39.5	810.7 ± 71.7	871.3 ± 44.9
R. stricta (1 g/kg)	A	265 ± 21.4	313 ± 15.2	357.0 ± 21.8	434.3 ± 22.5	553.0 ± 23
ZOX (40 mg/kg) and	T	466 ± 26.6	578.5 ± 19.6	673 ± 37.2	798.2 ± 31.8	895.8 ± 47.2
R. stricta (4 g/kg)	A	252.2 ± 22	314 ± 14.8	365.8 ± 20.4	429.2 ± 25.5	563.7 ± 20.9

Values are means ± SEM (n = 6)

All values from treated rats were significantly lower than that of control.

rect effects such as malaise resulting from, to the oral intake of, the relatively high dose of the plant extract. We have recently obtained reproducible evidence that the plant extract dose dependently modifies the concentration of brain tribulin, which is an endogenous monoamine oxidase (MAO) inhibitor and a BDZ receptor ligand. (Ali et al., in preparation). This lends support to our hypothesis that the plant extract has a BDZ-like effect. The presence of β-carboine alkaloids in *R. stricta* extract (5,6) gives another indication of the similarity of actions of the extract to BDZ, as it has been shown previously that some β-carbolines possess pharmacological properties similar to those of BDZ agonists (15). A study of the possible antagonism of the effect of the extract by the BDZ antagonist flumazenil seems warranted, and may more directly delineate whether the actions of *R. stricta* are mediated via BDZ receptors. Also, it is conceivable that the CNS-depressant properties of the extract were preceeded or accompanied by neurochemical changes. However, we have found that acute and chronic treatment of rats with the extract does not seem to significantly affect the concentration of amino acids in various areas of the brain (Ali et al., unpublished data). Currently, a study of the effect of the plant extract on brain amines and their metabolites is in progress.

The extract attenuated caffeine-induced hypermotility in rats. Similar results were reported before in humans, where by administration of aminophylline (a methylxanthine similar to caffeine) antagonized diazepam sedation (3). In addition, the alkaloids isolated from *R. Stricta* extract are structurally similar to mitragynine isolated form the well-known psychoactive plant *Mitraagyna speciosa* (10). Both plants are known to contain alkaloids with a β-carboline nucleus. Therefore, it can be hypothesized that the action of the *R. stricta* extract may be due to its alkaloid constituents. Caffeine has anixogenic-like activity in rats (9), which may involve, at least partially, BZD antagonism (4). The suppression by *R. stricta* of caffeine-induced hypermotility is probably due to pharmacological antagonism, and suggests that the plant extract may have an anxiolytic action.

The attenutation by the plant extract of the motor response to caffeine, and the subadditivity to the effect of zoxazolamine support our findings with acutely administered plant extract, and illustrate the reproducibility of *R. stricta's* pharmacological effects.

It is of interest to note that daily administration of the extract at the same dose (2 g/kg) for 21 days apparently caused no tolerance or dependence, although on day 14 a decrease in the activity of the treated rats was noted. No plausible explanation for this could be given, and on the last day of treatment (day 21), no sign of recovery to previous activity levels was evident. Also, there was no evidence of spontaneous signs of withdrawal following chronic treatment with the plant extract. It is also interesting to note that although there does not appear to be any difference in the time course of the effects of 2 and 4 g/kg of *R. stricta* (Fig. 1), the higher dose seems to have a greater time-dependent effect than the lower dose in the presence of caffeine.

The present results were obtained with a lyophilized preparation from a crude extract. The relatively high doses used here might reflect the low concentration of the active compounds present in the extract. Studies with purified fractions of the extract will be conducted for further pharmacological characterization.

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REFERENCES

1. Ali, B. H.; Bashir, A. K.; Banna, N.; Tanira, M. O. M.: Central nervous system activity of *Rhazya stricta* in mice. Clin. Exp. Pharmacol. Physiol. 22:248–253; 1995.
2. Angelis, L.: Animal techniques for evaluating benzodiazepine drugs. Methods Find. Exp. Pharmacol.1:129–155; 1979.
3. Arvidson, S. B.; Ekstrom-Jodal, B.; Martinelli, S. A. G.; Niemand, D.: Aminophylline antagonizes diazepam sedation. Lancet 2:1467; 1982.
4. Baldwin, H. A.; File, S. E.: Caffeine-induced anxiogenesis: Role of adenosine, benzodiazepine and noradrenergic receptors. Pharmacol. Biochem. Behav. 32:181–186; 1989.
5. Bashir, A. K.; Abdalla A. A.; Hassan, E. S.; Wasfi, I. A.; Amiri, M. H.; Crabb, T. A.: Alkaloids with antimicrobial activity from the root of *Rhazya stricta* Decne, growing in the United Arab Emirates. Arab Gulf J. Sci. Res. 12:119–131; 1994.
6. Bashir, A. K.; Abdalla, A. A.; Wasfi, I. A.; Hassan, E. S.; Amiri, M. H.; Crabb, T. A.: Phytochemical and antimicrobial studies on the leaves of *Rhazya stricta* growing in United Arab Emirates. Fitotrepia. LXV:84–85; 1994.
7. Dews, P. B.: The measurement of the influence of drugs on voluntary activity in mice. Br. J. Pharmacol. 8:46-48; 1953.
8. Dews, P. B.: Caffeine. Berlin: Springer; 1984.
9. Jain, N.; Kemp, N.; Adeyemo, O.; Buchanan, P.; Stone, T. W.: Anxolytic activity of adenosine receptor activation in mice. Br. J. Pharmacol. 116:2127–2133; 1995.
10. Jansen, K. L. R.; Prast, C. J.: Psychoactive properties of Mitragynine (Kratom). J. Psychoactive Drugs 20:455–457; 1988.
11. Kulkarni, S. K.; Sharma, A.: Reversal of diazepam withdrawal induced hyperactivity in mice by BR 16-A (Mentat®), a herbal preparation. Indian J. Exp. Biol. 32:886–888; 1994.
12. McMillen, B. A.; Williams, H. L.; Lehmann, H.; Shepard, P. D.: On central muscle relaxants, strychnine-insensitive glycine receptors and two old drugs: Zoxazolamine and HA-966. J. Neural. Transm. 89:11–25; 1992.
13. Sasaki, N.: Effects of furazolidone on duration of righting reflex loss induced with hexobarbital and zoxazolamine. J. Vet. Med. Sci. 56:667–670; 1994.
14. Tanira, M. O. M.; Ali, B. H.; Bashir, A. K.; Chandarnath, S. I.: Some pharmacological and toxicological studies on *Rhazya stricta* Decne in rats, mice and rabbits. Gen. Pharmacol. 27:1261–1267; 1996.
15. Turski, L.; Stephens, D. N.: Effect of the β-carboline abecarnil on spinal reflexes in mice and on muscle tone in genetically spastic rats: A comparison with diazepam. J. Pharmacol. Exp. Ther. 267:3721–3723; 1993.
16. Wasfi, I. A.; Bashir, A. K.; Amiri, M. H.; Abdalla, A. A.: The effect of *Rhazya stricta* on glucose homeostasis in normal and streptozotocin diabetic rats. J. Ethnopharmacol. 43:141–147; 1994.
17. Western, A. R.: *Rhazya stricta* Decne. In: The flora of the United Arab Emirates, an introduction. Al-Ain: United Arab Emirates University; 1989: 111.