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NOTES

Pharmacological Effects of Paniculatin—a Glycoside Isolated from *Ipomoea digitata* Linn.

M. A. MATIN*, J. P. TEWARI, and D. K. KALANI†

Abstract □ A glycoside (paniculatin), m.p. 134°, $C_{30}H_{54}O_{13}$ has been isolated from the tubers of *Ipomoea digitata* Linn. It elevated the blood pressure, showed a stimulant effect on myocardium and respiration, a vasoconstrictor and bronchoconstrictor effect, a spasmogenic effect on smooth muscles of gut, and also an oxytocic activity. The LD_{50} (48 hr.), with 95% fiducial limits, was found to be 867.4 (755.3–985.1) mg./kg. (*SE* ± 1.03) intraperitoneally in mice.

Keyphrases □ Paniculatin—*Ipomoea digitata* glycoside □ Pharmacological screening—paniculatin □ LD_{50} value—paniculatin

The chemical examination of the tubers of *Ipomoea digitata* Linn. (syn. *Ipomoea paniculata*, R.Br.) revealed the presence of a β-sitosterol, neutral compound m.p. 72° (1), a glycoside and fixed oil (2), besides free reducing sugars and mucilage (3). A study of this common indigenous plant of India was undertaken as it has been described as tonic, aphrodisiac, galactogogue, and stimulant in the ancient literature (4–6). Aqueous and alcoholic extracts of the tubers of the plant revealed some interesting actions (7) that required further investigations. In this communication, the pharmacological effects of a glycoside (2, 3) isolated from the tubers of *Ipomoea digitata* have been reported.

EXPERIMENTAL

Authenticated samples of the tubers of *Ipomoea digitata* were extracted exhaustively with 95% ethanol. Recovery of the solvent and treatment of the residue with ether gave a glycoside (tentatively named paniculatin) as described earlier (2, 3). The glycoside, m.p. 134° (yield 0.02%).

Anal.—Calcd. for $C_{30}H_{54}O_{13}$: C, 57.87; H, 8.68; O, 33.45; mol. wt., 622. Found: C, 57.52; H, 8.98; O, 33.50; mol. wt., 618.

On acetylation in the usual way, it gave a tetraacetate, m.p. 65°.

Anal.—Calcd. for $C_{30}H_{54}O_{13}$ $(COCH_3)_4$: C, 57.72; H, 7.84; O, 34.44; mol. wt., 790; acetyl value % 21.77. Found: C, 57.51; H, 8.01; O, 34.48; mol. wt., 800; acetyl value % 22.21.

It was found to have three methoxyl groups, while C-methyl was found to be absent (methoxyl group found, 14.50, methoxyl group required 14.75 for three methoxyl groups). It gave a green color with ferric chloride solution and an aglycone on hydrolysis with H_2SO_4. It was found to be soluble in water, methanol, and ethanol and insoluble in ether, petroleum ether, chloroform, and carbon tetrachloride.

METHODS

The pharmacological effects of paniculatin were examined on different organ systems; it has been referred as drug in the following lines. In each case 10 experiments were performed to draw the inference.

Mongrel dogs (6–10 kg.) and cats (2–4 kg.) of either sex, were anesthetized with sodium pentabarbitol (40 mg./kg., intraperitoneally) and carotid blood pressure was recorded. Respiration was recorded by means of Marey's tambour connected to the trachea. Drugs were administered through the cannulated femoral vein. Experiments were repeated after the administration of atropine sulfate (2 mg./kg.), hexamethonium bromide (5 mg./kg.), tolazoline hydrochloride (10 mg./kg.), promethazine hydrochloride (7.5 mg./kg.), and also in bilaterally vagotomized dogs and spinal cats prepared according to the method of Burn (8). In order to study the effect of drug on carotid occlusion response, the common carotid arteries of both sides were exposed in the dog. Bulldog clips were applied on both the carotid arteries for 15 sec., at a point just below the bifurcation of the common carotid into external and internal carotid arteries; this brought about occlusion and a rise in blood pressure. In carotid occlusion studies in dogs the blood pressure was recorded from the femoral artery.

To study the effect of drug on myocardium of different animals, perfusion of the frog's heart *in situ* and isolated frog's heart was

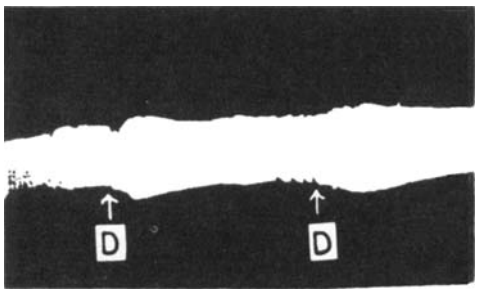

Figure 1—*Effect of paniculatin on frog heart in situ. Key: D, drug, 0.25 and 0.50 mg.*

carried out according to the method of Burn (8) and of isolated rabbit's heart by Langendorff's technique (8); auriculoventricular contractions of the dog were recorded according to the method of Jackson (9). The contractions were recorded on a slowly moving drum through a starling heart lever.

The effect of drug was observed on blood vessels of frog and rat hind limb preparation. Blood vessels of the frog were perfused with Ringer's[1] solution by introducing a cannula in the innominate artery and counting the drops of perfusate. Injections of the drug

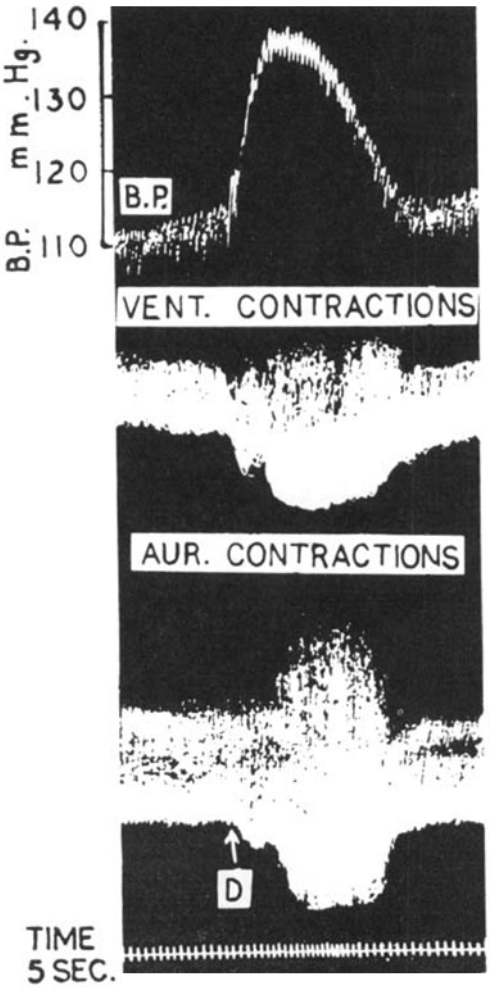

Figure 2—*Effect of paniculatin (D = drug, 5 mg./kg., intravenously) on carotid blood pressure of dog (♂; 6.2 kg.) and auriculo-ventricular contractions* in situ (*sodium pentabarbitol, 40 mg./kg., intraperitoneally was given for anesthesia.*)

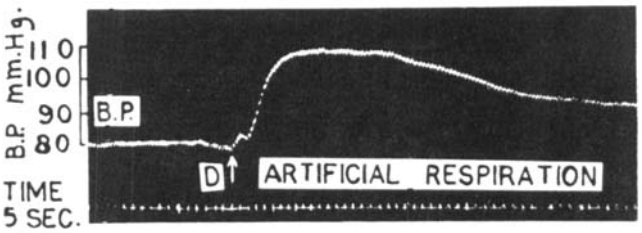

Figure 3—*Effect of paniculatin (D = drug, 5 mg./kg., intravenously) on carotid blood pressure of spinal cat (♀; 3.6 kg.) anesthetized with sodium pentobarbitol (40 mg./kg., intraperitoneally).*

were made in the ventral lymph sac. Blood vessels of the rat hind limb were perfused according to the method of Burn (8).

The effect of drug was observed on isolated preparations of rabbit's and guinea pig's ileum. The animals were sacrificed by exsanguination. The freshly removed segments were suspended in a 50-ml. isolated organ bath, containing Tyrode[2] solution maintained at 37 ± 1° and freely oxygenated. The effect of the drug, given 0.5 min. before or simultaneously with acetylcholine chloride (0.1 mcg./ml.), 5-hydroxytryptamine creatinine sulfate (0.01 mcg./ml.), and histamine diphosphate (0.2 mcg./ml.) was also observed on rabbit's and guinea pig's ileum *in vitro*. Intestinal movements *in situ* in dogs were recorded through Jackson's enterograph. To study the effect of drug on smooth muscles of bronchi, perfusion of the isolated guinea pig lung preparation was carried out according to the method of Burn (8).

The effect was also observed on isolated uterus of the nongravid albino rat. One of the uterine horns was suspended in a 10-ml. bath containing oxygenated DeJalon's solution (10) maintained at 32 ± 1°. The effect of a single dose was recorded for 60 sec. and an interval of 5 min. was allowed between the successive doses.

The effect of drug was also studied on electrically induced contractions (preganglionic stimulation) of the cat's nictitating membrane.

Effect on central nervous system and acute toxicity were observed in mice. Albino mice of either sex, weighing 18–20 g., were randomly distributed with respect to treatment and cage assignments (eight mice per cage). The animals were kept in an air conditioned room at 22–25°. Food and water were allowed *ad libitum*. The dose levels used were 100, 200, 400, 800, and 1,600 mg./kg. The drug was administered intraperitoneally (single injection) in 0.5 ml. of normal saline. Control animals received the normal saline only. Eight animals were used for each dose. Deaths were recorded daily. LD_{50} (48 hr.) was determined according to the method of probit analysis (11).

RESULTS

The drug in graded doses caused an increase in the rate and amplitude of the frog's heart (Fig. 1) *in situ*, isolated frog heart and rabbit heart. It also increased the rate and amplitudes of auriculoventricular contractions *in situ* in dogs (Fig. 2). It also showed a vasoconstrictor effect on blood vessels of frog and rat hind limb in a concentration of 25 mcg./ml.

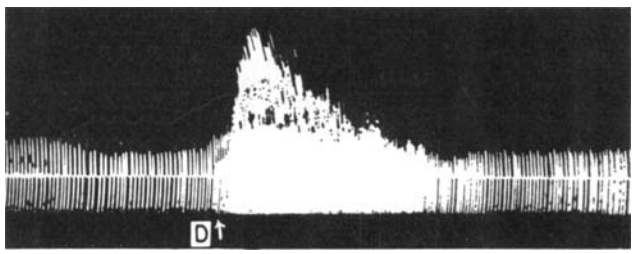

Figure 4—*Effect of paniculatin (D = drug, 5 mg./kg., intravenously) on respiration of dog (♂; 6.0 kg.) anesthetized with sodium nembutal (40 mg./kg., intraperitoneally).*

[1] NaCl, 6.5 g.; KCl, 0.14 g.; $CaCl_2$, 0.12 g.; $NaHCO_3$, 0.2 g.; Na_2HPO_4, 0.01 g.; glucose, 1 g.; distilled water, 1 l.

[2] NaCl, 8.0 g.; KCl, 0.2 g.; $MgCl_2$, 0.1 g.; $NaHCO_3$, 1.0 g.; $CaCl_2$, 0.2 g.; Na_2HPO_4, 0.1 g.; glucose, 1.0 g.; distilled water, 1 l.

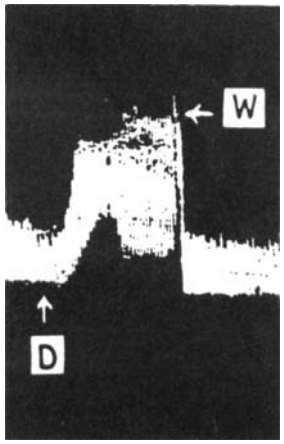

Figure 5—*Effect of paniculatin (D = drug, 25 mcg./ml.) on isolated rabbit ileum* in vitro.

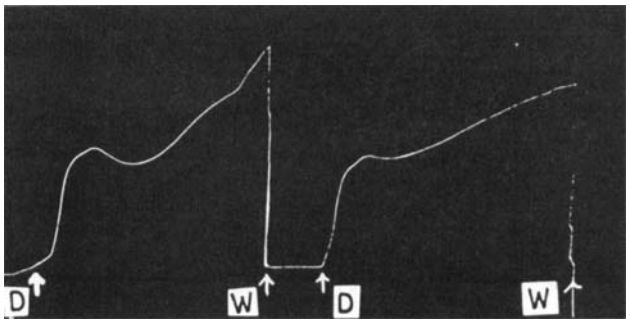

Figure 6—*Effect of paniculatin (D = drug, 25 mcg./ml.) on rat uterus* in vitro.

The drug (2–10 mg./kg. intravenously) produced a rise in blood pressure (Fig. 2). Smaller doses either had no effect or occasionally produced a slight rise; prior administration of atropine, tolazoline, hexamethonium, promethazine, as well as bilateral cervical vagotomy did not modify the pressor response which was also observed in spinal cats (Fig. 3); further the drug had no effect on the carotid occlusion response in anesthetized animals. The drug had a stimulatory effect on respiration (Fig. 4) which was not modified by prior administration of atropine.

The drug (25 mcg./ml.) stimulated the movements in segments of ileum from freshly killed guinea pigs and rabbits (Fig. 5); the action was not modified by atropine or anthihistamines; further the drug neither synergized nor antagonized the actions of acetylcholine, histamine, and 5-hydroxytryptamine when given half a minute before or simultaneously with spasmogens. The drug (5 mg./kg.) also increased the tone and peristaltic movements of the gut *in situ* in anesthetised animals. It also produced bronchoconstriction, by guinea pig lung perfusion experiments, in a concentration of 25 mcg./ml. The drug (25 mcg./ml.) caused the contraction of isolated nongravid rat uterus (Fig. 6) but had no effect on the electrically induced contractions of the cat's nictitating membrane.

No specific central nervous system stimulant or depressant effects were observed in mice in doses up to 600 mg./kg. intraperitoneally. Higher doses, however, caused tremors, ataxia, and respiratory embarassment. LD_{50} (48 hr.), with 95% fiducial limits, was found to be 867.4 (755.3–985.1) mg./kg. ($SE \pm 1.03$), intraperitoneally in mice.

DISCUSSION

Paniculatin, a glycoside isolated from the tubers of *Ipomoea digitata* Linn., was found to be water-soluble and thermostable. It showed a pressor response on intravenous administration in normotensive anesthetized animals along with a stimulant effect on the heart. The pressor effect was also observed in spinal animals; it was not modified by adrenergic, cholinergic, or ganglion blockade; prior administration of antihistaminic drugs or bilateral cervical vagotomy. The pressor response appears to be due to peripheral vasoconstriction as evidenced by blood vessel perfusion experiments and also the myocardial stimulant property of paniculatin as observed in different animals. It further showed, besides the vasoconstrictor effect, a spasmogenic effect on the smooth muscles of gut, a bronchoconstrictor effect, and an oxytocic activity on rat uterus. The LD_{50} was found to be 867.4 (755.3–985.1) mg./kg. ($SE \pm 1.03$) intraperitoneally in mice which showed it to be a safe drug.

An alcoholic fraction of *Ipomoea digitata* Linn. was reported to have stimulant as well as depressant pharmacological effects on different organ systems of experimental animals (7). However, paniculatin was found to have only stimulatory effects and was devoid of inhibitory or relaxant effects on different organ systems. It appears that the stimulant effects observed with the crude alcoholic fraction (7) were due to paniculatin isolated from the tubers of *Ipomoea digitata* Linn., while the relaxant effects may be due to certain unidentified factor in the tubers of the plant.

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