

SOME PSYCHOPHARMACOLOGICAL ACTIONS OF THE ESSENTIAL OIL OF LITSEA GLUTINOSA (LOUR.) C.B. ROBINS*

By

M.K. MENON, A. KAR AND C.S. CHAUHAN

Department of Pharmaceutical Sciences, University of Saugar, Saugar

Detailed pharmacological investigations of a large number of essential oils obtained from various medicinal plants were undertaken in this laboratory and these studies proved to be very fruitful. Thus essential oils possessing hypnotic, anorexiant, tranquillizing and analgesic properties were discovered (under publication) and the present study deals with the investigations made on the essential oil of *Litsea glutinosa* (Lour.) C.B. Robins.

L. glutinosa (Lour.) C. B. Robins. belongs to the natural order *Lauraceae*. It is distributed throughout the hotter parts of India. The bark is used as demulcent, astringent, aphrodisiac and antidysenteric (3). The oil from the berries is employed in rheumatism (3). The essential oil was obtained from the fresh shade-dried berries by steam-distillation in an yield of 1.5 to 2 per cent. It has a brownish orange colour with a characteristic odour and has a specific gravity of 0.9480 at 24°C.

Preliminary studies showed that the oil caused marked depression in experimental animals and a hypotensive effect of long duration in anaesthetized dogs. The present study deals with the central nervous effect of the oil.

MATERIALS AND METHODS

Preparation of solutions : The essential oil was employed in the form of an emulsion in 3 per cent polysorbate-80 solution. Solutions of other drugs were prepared in distilled water. All the injections were made intraperitoneally. Control experiments were performed simultaneously by administering equivalent quantities of the solvent. For all the experiments, male albino rats (Haffkine strain) weighing between 125 and 175 g were employed.

I. *Spontaneous motor activity (SMA) and ptosis* : Thirty rats were divided into three equal groups and were kept in individual cages. The first and the second groups were treated with the emulsion in doses of 150 mg/kg and 300 mg/kg respectively while the third group received the solvent. The animals were observed carefully and changes in their SMA and eyelids were scored 30 min after drug treatment and thereafter at hourly intervals for 4 hr.

II. *Rotarod performance* : A group of twenty trained rats were employed. The animals were so trained that they could remain for two min without falling from the top of a cylinder (15 cm diameter) rotating at the rate of 4 revolutions per min. The test was performed before

drug treatment, and then the drug emulsion (350 mg/kg) was administered to the animals. The test was repeated 30 min later and thereafter at hourly intervals for 4 hr. Animals which fell down during the two min period were immediately placed over the cylinder. The group treated with the solvent served as control.

III. *Rectal temperature* : The experiment was performed at room temperature ($21 \pm 1^\circ\text{C}$). Thirty rats, divided into three groups were kept in individual cages and the rectal temperature of each animal was measured by inserting the bulb of a clinical thermometer 1 cm into the rectum and keeping it there for a period of 1 min. Temperature was again measured 30 min after drug treatment (150 mg/kg and 300 mg/kg) and thereafter at hourly intervals for 4 hr.

IV. *Pentobarbitone-induced hypnosis* : Thirty rats were divided into three equal groups, the first group was treated with the solvent, and the second and third groups were treated with the oil emulsion in doses of 150 mg/kg and 300 mg/kg respectively. Fifteen min later all the three groups were treated with pentobarbitone sodium in a dose of 40 mg/kg. When the animals lost their righting reflex they were kept on their backs. The time when these animals regained their righting reflex and started moving about was noted.

V. *Analgesic effect* : Forty rats were divided into four groups and kept in individual cages. The pain threshold was measured by using a hot-wire analgesiometer (Techna Corporation, Lucknow, India). The temperature of the wire was so regulated that the normal reaction time as seen by the flicking of the tail of any individual rat did not exceed 5 sec. The normal reaction time for individual rats was measured before drug administration. The first and the second groups were treated with 150 mg/kg and 300 mg/kg of the drug; the third group was treated with morphine hydrochloride (4.5 mg/kg) and the fourth group treated with the polysorbate-80 solvent served as control. Pain threshold was measured 30 min after injection and thereafter at hourly intervals for 4 hr.

VI. *Conditioned avoidance response (CAR) of trained rats* : The animals were so trained that they climbed a pole on hearing a bell sound in order to avoid an electric shock passed through the grid floor 10 sec later. Further training led to the development of secondary conditioned response (SCR) in these animals as shown by Maffi (10) where the animals climbed the pole immediately after being placed in the cage and before hearing the bell sound. The trained rats were tested before drug treatment and only those which showed SCR were selected. After administering 300 mg/kg of the drug, the animals were again tested 15 and 30 min later and thereafter at hourly intervals for 4 hr. Chlorpromazine hydrochloride (5 mg/kg) was given to another group of trained rats and they were tested 15 and 30 min later and thereafter at hourly intervals for 4 hr.

VII. *Interaction with mescaline, iproniazid and d-amphetamine* : For each of the above experiments 12 animals divided into two equal groups were employed. The rectal temperature of individual animal was measured using a clinical thermometer as mentioned before. One

of the groups was treated with the essential oil in a dose of 300 mg/kg, whereas the other group received the solvent. Fifteen min later both the groups were treated with one of the central stimulants, namely mescaline hydrochloride (80 mg/kg) or d-amphetamine sulphate (5 mg/kg) or iproniazid phosphate (100 mg/kg in two doses, first dose given 24 hr before and the second dose 6 hr before treatment with oil emulsion). The animals were kept in individual cages and the rectal temperature was taken 30 min after drug treatment, and thereafter at hourly intervals for 4 hr. In addition the degree of central stimulation and lethality, if any, were also noted.

VIII. *Acute Toxicity* : A preliminary study on the toxicity of the drug was made.

RESULTS

I. *Sedative effect of the drug* : Treatment of the animals with the oil caused marked reduction in their SMA and many of the rats were often seen lying on their sides during the first hr. When they moved about in the cage, their gait was normal. The oil was quite effective in decreasing the SMA of the animals. With the higher dose the effect lasted for a longer time (Table I). Though many of the animals showed closure of the eyelids, complete closure was present only in a negligibly small number of animals. In many of the animals which showed reduction in SMA, ptosis was not present. (Table II).

TABLE I
Effect of the essential oil on the spontaneous motor activity in rats

Drug and dose	Number of animals in which spontaneous activity was affected															
	30 min			60 min			120 min			240 min						
	0	—	±	0	—	±	0	—	±	0	—	±				
Control 3 per cent polysorbate-80 (10)	0	1	9	0	0	10	0	1	9	0	2	8				
Oil/150 mg/kg (12)	7	3	2	1	5	6	2	2	8	2	1	9				
Oil/300 mg/kg (10)	5	3	2	6	2	2	2	7	1	1	0	9				

0 indicates no spontaneous activity; - indicates reduction of spontaneous activity;
± indicates no effect on spontaneous activity

Figures in parentheses indicate the number of animals employed in each group.

TABLE II
Effect of the essential oil on the degree of closure of eyelids in rats

Drug and Dose	Number of animals showing closure of eyelids															
	30 min				60 min				120 min				240 min			
	++++	+++	++	±	++++	+++	++	±	++++	+++	++	±	++++	+++	++	±
Control poly-sorbate-80 (12)	0	0	0	12	0	0	1	11	0	0	2	10	0	0	2	10
Oil 150 mg/kg (12)	0	1	5	6	0	0	6	6	0	0	0	12	0	0	0	12
Oil 300 mg/kg (12)	0	0	7	3	1	2	4	3	0	2	4	4	0	0	2	8

++++ indicates complete closure; +++ indicates 3/4th closure; ++ indicates 1/2 closure; ± indicates 3 normal.
Figures in parentheses indicate the number of animals.

II. *Rotarod performance* : Before drug treatment no trained animal fell down from the rotating drum during the two min test period. Thirty min after drug treatment, no statistically significant effect was seen, but the average number of times, the animals fell rose to 2.4 ± 1.1 (\pm S. E.) because two animals fell down 16 times and 7 times respectively. After 1 hr all the animals showed normal response.

III. *Effect on the rectal temperature of rats* : The oil produced slight hypothermic effect in rats. With the lower dose of the drug, the effect started within 30 min and a maximum fall of 1°C was observed at 1 hr. A dose of 300 mg/kg produced a maximum fall of 1.2°C at 30 min and this effect lasted for 1-2 hr only.

IV. *Pentobarbitone-induced hypnosis* : In the solvent treated control animals, the mean sleeping time was 116 ± 12.9 min. Pretreatment of the animals with 150 mg/kg of the oil caused an increase in the sleeping time (194 ± 13.2 min, $P < 0.001$). A dose of 300 mg/kg of the oil caused a further enhancement in the barbiturate-induced hypnosis (235 ± 16.2 min, $P < 0.001$).

V. *Analgesic effect* : The results obtained are shown in Table III. It can be seen that in a dose of 300 mg/kg the drug exerted significant analgesic effect in rats. The effect was observed at 30 min and lasted for less than 2 hr.

VI. *Effect on the CAR of trained rats* : The results given in Table IV show that the essential oil was very effective in blocking the SCR of trained rats but blocked the CAR only in lesser number of animals. On the other hand, chlorpromazine hydrochloride (5 mg/kg) blocked the SCR of all the animals and the CAR of a majority of the animals.

VII. *Interaction with mescaline, iproniazid and d-amphetamine* : Though the oil did not completely antagonize the effect of mescaline, the hallucinogen produced less excitement and hyperactivity in the oil treated animals than in control animals. The antagonism by the oil was more clearly seen for the hyperthermic response induced by mescaline. Whereas in control animals, mescaline increased the rectal temperature by 2.5°C the rise in temperature by mescaline in the oil treated animals was only 1.5°C .

The sedative effect of the oil as seen by SMA and the degree of closure of the eyelids was not modified by pre-treatment with iproniazid but the stimulation and hyperthermia produced by d-amphetamine were markedly increased by pretreatment of the animals with the oil emulsion. The latter group showed an extreme degree of excitement and aggressiveness. Rectal temperature rose by 4°C and all the animals died within 2 hr probably due to excessive hyperthermia. All animals treated with d-amphetamine sulphate (5 mg/kg) alone survived and their rectal temperature did not rise by more than 1°C than those of the untreated animals (37°C).

VIII. *Acute Toxicity*: In the present investigation, a detailed study on the acute toxicity of the oil was not made. An attempt was made to know whether the effective dose of the

TABLE III

Analgesic effect of the essential oil as evaluated by the hot-wire technique

Drug and Dose	No of animals employed	Reaction time in sec (mean \pm S.E.) before drug treatment	Reaction time in sec (Mean \pm S.E.) after drug treatment				No of animals showing* significant analgesia			
			30 min	1 hr	2 hr	3 hr	30 min	1 hr	2 hr	3 hr
Control (D.W.)	15	2.4 \pm 0.01	2.1 \pm 0.05	2.1 \pm 0.03	2.4 \pm 0.2	2.4 \pm 0.02	0	0	0	0
Control (3 per cent Polysorbate-80)	15	2.6 \pm 0.02	2.0 \pm 0.05	2.03 \pm 0.03	2.7 \pm 0.09	2.7 \pm 0.08	0	0	0	0
Oil (150 mg/kg)	10	2.9 \pm 0.11	2.9 \pm 0.4	2.7 \pm 0.08	2.3 \pm 0.5	2.5 \pm 0.08	0	0	0	0
Oil (300 mg/kg)	10	2.5 \pm 0.05	10.5 \pm 1.6 (P < 0.001)	6.2 \pm 0.93 (P < 0.01)	2.9 \pm 0.99	2.6 \pm 0.60	8(8)	6(6)	0	0
Morphine hydrochloride (4.5 mg/kg)	10	2.0 \pm 0.02	11.6 \pm 1.6 (P < 0.001)	10.6 \pm 1.7 (P < 0.001)	5.9 \pm 1.3	4.6 \pm 1.0	8(8)	7(7)	4(4)	2(1)

* Those in which the reaction time exceeded 7 sec. Values in parentheses show the number of animals whose reaction time was more than 12 sec.

TABLE IV

Effect of the essential oil and chlorpromazine hydrochloride on the conditioned avoidance response (CAR) and second conditioned response (SCR) in rats.

Drug and Dose	No of animals	No of animals showing blockade of SCR and CAR after drug treatment							
		15 min		30 min		1 hr		2 hr	
		SCR	CAR	SCR	CAR	SCR	CAR	SCR	CAR
Essential oil (300 mg/kg)	10	10	2	8	4	8	4	10	0
Chlorpromazine HCl (5 mg/kg)	10	10	7	10	7	10	6	10	5

oil was near the toxic dose. In 10 rats, 600 mg/kg of the oil was administered intraperitoneally, and no mortality was observed after 24, 48 and 72 hr.

DISCUSSION

The results clearly show that the essential oil of *Litsea glutinosa* (Lour.) C.B. Robins is a central depressant. From the fact that the sedated animals became alert on slight disturbance, together with the characteristic eye-closure, it seems that the oil exerted a chlorpromazine-type depressant effect.

In its potentiation of barbiturate hypnosis too, the oil was similar to chlorpromazine. In its other actions the effect of the oil differed from that of the major tranquillizer. Chlorpromazine is known to produce marked hypothermia in experimental animals(9), but the oil did not produce any significant reduction in the rectal temperature. The effect of the oil on the CAR was also slightly different from that of chlorpromazine. Chlorpromazine has been shown to cause a blockade of both the CAR(4) and SCR(10), but in the present study the oil was very effective in blocking the SCR whereas the CAR remained unaffected. The analgesic effect was probably caused as a result of its tranquillizing effect.

The present investigation revealed that the oil had a mild 'anti-psychotic' effect and in this respect too it resembled chlorpromazine.

The potentiating effect of the oil on the hyperactivity and hyperthermia of d-amphetamine was not unexpected. Though chlorpromazine is known to antagonize the central stimulant effect of d-amphetamine(2, 8), reserpine is known to potentiate the stimulant effect of d-amphetamine(13, 14, 15). Many investigators believe that d-amphetamine exerts its central stimulant effect in an indirect manner by the liberation of noradrenaline in the hypothalamus(11). It is possible that the oil facilitates catecholamine release by d-amphetamine, thereby enhancing its effect. Pretreatment of animals with iproniazid did not modify the response to the oil, suggesting that the oil itself does not cause the release of noradrenaline from central

sites, otherwise it would have caused a stimulation as in the case of the reserpine—iproniazid-treated animals(12).

The oil exerted interesting central actions, and though in many of its actions the oil resembled chlorpromazine, its mechanism of central depression may not be similar to that of the latter drug. The tranquilizing effect of chlorpromazine has been explained on the basis of its central adrenergic blocking effect(14). Chlorpromazine is also a peripheral adrenergic blocking drug(5, 6). Though the oil also caused a hypotensive response of long duration in anaesthetized dogs like chlorpromazine, unlike the latter drug no adrenergic blocking effect was produced as seen by the absence of any reversal of adrenaline effect in these animals(7). The absence of any peripheral adrenergic blockade by the oil perhaps suggests that it does not exert such an action at the central sites.

SUMMARY

The essential oil of *Litsea glutinosa* (Lour.) C.B. Robins. (family : Lauraceae) was investigated for its central nervous system effects in rats. A marked reduction in the spontaneous motor activity with no concomitant muscle weakness was produced. Though the oil was ineffective in altering the rectal temperature of rats, it prolonged the pentobarbitone-induced hypnosis in these animals. The oil produced analgesia in rats. In animals trained for conditioned avoidance response, the secondary conditioned response was blocked without influencing the conditioned avoidance response. The oil partially antagonized the mescaline-induced hyperactivity and hyperthermia. Pretreatment of the animals with iproniazid did not modify the sedative effect of the oil, but the oil potentiated the central stimulant and hyperthermic effects of d-amphetamine.

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