DISCUSSION

As discussed before, studies on the pharmacological effects of the essential oil were planned so as to bring to light the possible usefulness of this oil and also to know the active constituents responsible for the hypnotic and local anaesthetic (Kirtikar and Basu, 1933)\textsuperscript{19(c)} effects of the oil.

It was found that the hypnotic effect of the oil depends on its content of both methyl cinnamate and linalool. When given alone in doses equivalent to those present in the essential oil, they were ineffective, but together they caused hypnotic effects almost identical to that of the oil. Thus it is clear that one of these substances potentiates the effect of the other. From the fact that higher doses of linalool caused hypnoses, but methyl cinnamate did not, it may be said that linalool is the main hypnotic principle and that methyl cinnamate potentiates the effects of a non-hypnotic dose of linalool leading to the sleeplike state. A second more interesting possibility is based upon the suggested ability of certain terpenoids in drug latentiation (Harper, 1959)\textsuperscript{162}.

The ability of methyl cinnamate to cross the blood-brain barrier is not known, but in case this compound is less permeable and if linalool possesses the ability to act as a carrier for methyl cinnamate then this could possibly lead to the concentration of higher amounts of methyl cinnamate into the brain centers leading to central depression. It would be interesting to study the rate of permeability of labelled
methyl cinnamate into the brain and the influence of linalool on this. The author intends to pursue this study and also to extend the study to other therapeutically-useful substances that are known to be relatively impermeable through the blood-brain barrier (e.g., dopamine in the treatment of Parkinsonism) and hence have a limited usefulness.

To the author's knowledge, the general anesthetic effects of linalool has hitherto not been reported. Though the present studies showed that general anesthesia is produced by linalool only in higher doses and that it has a short duration of action, nevertheless structural modification of this compound might lead to more potent therapeutically useful hypnotic agents.

Decrease in the motor activity of animals, potentiation of barbiturate hypnosis and analgesic effect are shown by many central depressant drugs. It is known that a number of tranquillizers, especially those of the phenothiazine group, possess all these properties (Riley and Spinks, 1958)\textsuperscript{180}. The probable influence of linalool in enhancing the permeability of barbiturate may not be a factor in its enhancement of barbiturate hypnosis because it is well-known that pentobarbitone sodium crosses the blood-brain barrier with ease. It is likely that one or more of the constituents of the oil, most probably linalool, might have sensitized the brain areas to the action of the barbiturate. The analgesic effect of the oil could be either due to a morphine-like effect on the brain leading to an elevation of pain threshold of the centers or it might be related to the tranquillizing effect of the drug making aversive stimuli more bearable to the animal. The results obtained on the CAR of trained animals show that this oil
is only a weak tranquillizer, it seems that the analgesic effect may not be due entirely to this effect of the oil. Study of the influence of a drug on body temperature can yield much valuable pieces of information. A decrease in the temperature would indicate that the drug either causes depression of the temperature regulating centers situated in the hypothalamus or causes dilatation of peripheral blood vessels leading to heat loss from the body. An opposite effect is usually produced by central stimulants, especially by those drugs that have a peripheral vasoconstriction effect. In the present study the essential oil caused a moderate decrease in body temperature which indicates that the oil exerts one or more of the above effects.

The local anesthetic effect of the oil was tested especially because of the reported use of the powdered seeds of *X-alatum* in the relief of toothache by natives (Kirtikar and Basu, 1933)\(^{(c)}\). Applications of a drug over the affected tooth implies that the drug was applied directly over an exposed nerve and it was felt that a simulated experimental model should be used to test this effect of the drug. Injection of the oil directly over the tail nerve of mouse provides such a model and in these studies it was found that the oil possesses local anesthetic effects in somewhat high doses.

The development of tranquillizers during the last decade necessitated a search for suitable laboratory methods for the evaluation of such drugs. Clinically these drugs cause a reduction in the tension and anxiety of patients and it is clear that behavioral technics with an anxiety component would be most suitable for the evaluation of tranquillizers. A tranquillizer should also not cause clouding of
perception. Thus an ideal method should be able to measure this aspect too. The development of conditioned avoidance response for the evaluation of tranquillizers more or less seems to meet the above requirements. In this technic the electric shock provides the aversive stimuli and the animals are anxious to avoid this. A tranquillizer would decrease anxiety which will be indicated by the decreased response of the animal to the warning signal. If the mind were clear, the animals would escape after receiving the shock.

In the present study the essential oil blocked the CAR of trained rats. This positive test along with the other findings indicate that the essential oil possesses mild tranquillizing effects though results obtained on the amphetamine toxicity in aggregated mice and the neuro-hormonal changes in the brain do not necessarily favour this conclusion.

The report of Chance (1946)\textsuperscript{175} that the toxicity of d-amphetamine is greatly enhanced in grouped mice has led to a great amount of work to understand the mechanism involved in this interesting pharmacological action of d-amphetamine. These studies have led to the following conclusions i) d-amphetamine causes an increase in body temperature which is further enhanced in aggregated mice leading to death of animals (Greenblatt and Osterberg, 1961)\textsuperscript{181}. ii) d-amphetamine causes a release of norepinephrine from storage sites in the brain and aggregations potentiates this effect leading to death (Moore, 1964)\textsuperscript{182} and iii) a combination of i and ii (Menon and Dandiya, 1967)\textsuperscript{183}. Other investigators have shown that a number of tranquillizers protect animals from such toxic effect of d-amphetamine (Lasagna and McCann, 1957; Proctor et al., 1966)\textsuperscript{184,185} and so this experiment has been suggested as a method to evaluate the tranquillizing effect of a drug (Burn and Hobbs, 1958)\textsuperscript{176}. 
Thus, when the essential oil of *X-alatum* was found to produce depressant effects in experimental animals, it was felt that it would also protect animals from the toxic effects of d-amphetamine. On the contrary, pretreatment of mice with the oil enhanced the toxic effects of d-amphetamine in aggregated mice. An explanation for this effect could be obtained from the brain neurohormonal changes produced by the oil. It has already been said that d-amphetamine causes a release of norepinephrine from the brain and any situation enhancing this would also enhance the toxicity of amphetamine. The present study showed that the essential oil caused an increase in the level of norepinephrine in the brain of mice and it is quite likely that this factor has played an important role in enhancing the toxicity of d-amphetamine.

The anticonvulsant effect of the essential oil was tested because its hypnotic effect gave an indication of a possible generalized depression of both motor and sensory areas of the cerebral cortex. In general, drugs useful in the treatment of epilepsy are anticonvulsants. So the anticonvulsant property of the essential oil was tested to see whether it possesses anti epileptic effect. One of the most commonly-used methods for producing experimental convulsions in animals is by the administration of maximal electroshocks and in the present study this method was employed. The results showed that the essential oil possessed marked anticonvulsant effect. The fact that this effect was seen even after the hypnotic phase of drug effect indicated that the hypnotic and anticonvulsant effects could be dissociated. This is especially noteworthy because a central depressant effect leading to sleepiness is considered an undesirable side effect of an antiepileptic drug. These findings
show that detailed investigations of the antiepileptic property of this essential oil and its major constituents are warranted.

Recent concepts regarding the function of the central nervous system and the regulation of behaviour centers around the involvement of certain monoamines acting as modulators or transmitters at central synapses. By its facilitating effect on the passage of nerve impulses from the neural terminals to the effector cells, these amines regulate the flow impulses. Thus the rate of release of these amines regulates the function of brain centers. The three amines that have been designated as neurotransmitters are norepinephrine (NE), dopamine (DA) and serotonin (5-hydroxytryptamine, 5-HT). The presence of higher amounts of NE and 5-HT in the hypothalamus than in other areas of the brain (Robinson and Stacey, 1962)\textsuperscript{186}, together with the presence of greater amounts of enzymes responsible for the synthesis and destruction of these amines in this area indicate that these two amines probably regulate the function of the hypothalamus (an area in which centers regulating autonomic nervous system, hunger, thirst, body temperature, sexual activity, etc.). A number of other experimental evidences also indicate such a possibility. Evidences also indicate that the mechanism of action of a number of centrally-acting drugs also involve these amines either directly or indirectly. This includes reserpine, chlorpromazine LSD-25, etc.

In contrast to NE and 5-HT, DA is concentrated in the caudate nucleus (Carlsson, 1959)\textsuperscript{187} which regulates extrapyramidal functions. A deficiency of this amine leads to extrapyramidal disorders manifested as tremors and difficulty in movements seen in patients suffering from Parkinsonism. In experimental animals, blockade of the synthesis of
DA by the tyrosine hydroxylase inhibitor α-methyl-p-tyrosine has been found to produce symptoms reminiscent of Parkinsonism (Bedard et al., 1970)\textsuperscript{188}. Recent introduction of L-dopa in the treatment of Parkinsonism (Cotzias, et al., 1971)\textsuperscript{189} has also given ample evidence to its proposed role of dopamine in bovine function.

From the foregoing discussion it is clear that one mechanism by which centrally-acting drugs would exert their action would be changing the levels of these amines in the brain. Moreover, a number of studies have implicated 5-HT to regulate sleep-wakefulness cycle. This is borne out from studies which showed that blockade of the synthesis of 5-HT would lead to decrease of sleep (Jouvet, 1969)\textsuperscript{191} and the later depletion of this amine would antagonize the above effect (Delorme et al., 1966; Jouvet, 1969)\textsuperscript{190,191}. Thus when it was found that the essential oil of X-alatum causes hypnosis, it was thought worthwhile to investigate the changes produced by this drug on the monoamine levels of the brain.

The results showed that certain brain amine changes are in fact produced by this oil, but, since the maximum changes are seen at 60 min and not at 5 min, (at which time the drug exerted maximum hypnotic effect) it is clear that there is no correlation between the sleep induced by the essential oil and the amine changes.
SUMMARY

1. Pharmacological studies were made to evaluate the actions of the essential oil of X-alatum on intact animals and also to know the active constituents responsible for its major actions.

2. The essential oil in doses of 140 and 210 mg/kg caused marked reduction in the spontaneous motor activity of mice.

3. In doses above 350 mg/kg, the oil caused hypnotic effect in rats and mice, the mean sleeping time being 13.4 ±1.2 min and 14.2±2.4 min respectively, for mice and rats.

4. The major constituents of the oil, namely methyl cinnamate and linalool were administered to mice in order to know which of these is the hypnotic principle. It was found that, when administered in doses equivalent to that present in the hypnotic dose of the oil, they do not cause any hypnotic effect when given alone, but a combination of these causes sleep in mice. It was concluded that both linalool and methyl cinnamate are essential for the hypnotic effect. On increasing the dose, linalool alone was capable of producing the anaesthetic effect.

5. The essential oil in subhynpnotic doses potentiated the hypnotic effect of pentobarbitone sodium.

6. Doses of 210 mg/kg and 400 mg/kg of the oil caused maximal fall of 1.1°C and 1.4°C in the rectal temperature of mice.

7. When administered in doses of 140 and 210 mg/kg, the essential oil caused analgesic effect in rats.
8. Administration of the oil at the base of the tail of the mice so as to be in contact with the nerve caused an elevation in the pain threshold indicating that the oil possesses local anaesthetic properties.

9. The essential oil blocked the conditioned avoidance response of trained rats, but was much weaker than chlorpromazine in this regard.

10. The essential oil caused enhancement of amphetamine toxicity in aggregated mice.

11. In a dose of 400 mg/kg, the essential oil acted as an anticonvulsant to rats.