PHARMACOLOGY SECTION

PHARMACOLOGY AND CHEMISTRY OF NARDOSTACHYS JATAMANSI DC

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Nardostachys jatamansi (Valerianaceae) is a perennial herb found commonly in the Alpine Himalayas at altitudes of above 6000 ft. Its sable-tail, brown, hairy and highly aromatic rhizomes are reported to be useful in the treatment of a variety of disorders such as spasmodic hysteric fits, intestinal colic, epilepsy and other nervous disorders (Chopra 1933). The rhizomes are long, stout and woody and are covered with fibres from the petioles of withered leaves, matted into a reddish brown complex network (Dutta and Mukerji 1950).

The greenish yellow aromatic essential oil, which resinifies rather readily on exposure to air, is the main constituent of the rhizomes which has been investigated in some detail. It has been observed that the composition of the essential oil varies in the different samples of the rhizomes, depending on their age, time of collection and storage conditions. Such an observation is not surprising because a majority of terpenes are known to be liable to undergo rather readily transformations due to polymerisation, oxidation and hydrolysis.

Saponification of the essential oil furnishes isovaleric acid and an alcohol $C_{15}H_{24}O$, which may also be obtained from the fraction of the oil distilling over at 116-125°C. Heating of the essential oil with selenium under reflux at 300° leads to the formation of a blue azulene (Chaudhry, Sharma and Kaul 1958).

A crystalline water-insoluble acid, named Jatamanshic acid (Chaudry, Sharma and Siddiqui 1951) was isolated in a yield of 3 percent from the air dried rhizomes. Jatamanshic acid m.p. 123°C. conforms to the molecular formula $C_{15}H_{22}O_2$ and on the basis of its physical data and chemical behaviour structure I has been assigned to the acid (Chaudry, Dhar, Anand and Dhar 1958).

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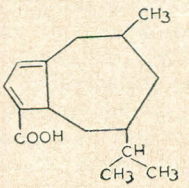

Recently, a sample of *N. jatamansi* has been reported to furnish a new bicyclic sesquiterpene ketone named Jatamansone $C_{15}H_{26}O$, which is reduced by lithium aluminium hydride to an alcohol $C_{15}H_{26}O$. This alcohol furnishes on dehydrogenation, a blue violet azulene $C_{15}H_{18}$ which may be 4,5-dimethyl-2-isopropyl or 2,7-dimethyl-4-isopropyl azulene (Govindachari, Rajadurai and Pai 1958).

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The essential oil does not possess marked antiprotozoal or antibacterial properties, dilutions of 1 in 1000 are ineffective against *S. aureus*, *E. coli*, *S. typhosum*, *V. cholerae* and *Sh. flexner* (Chopra, Jaiswal and Khjuria 1954). 0.5 cc. to 1 c.c./kg. lowers the blood pressure of dogs anaesthetized with phenobarbitone. The fall is temporary but it does not return to the original level. The heart rate is slowed with increase in amplitude. The fall of blood pressure is followed by a decrease in the intestinal volume. Myocardiographic experiments in anaesthetized dogs reveal a diminution in the amplitude of contractions of both auricles and ventricles with doses of 0.05-0.1 c.c./kg. The frequency of the auricular and the ventricular contractions is also lowered. Isolated rabbit heart perfused with the essential oil, 1 in 10,000

to 1 in 20,000 shows depression with the lowering of the amplitude and retardation of the beats. The heart recovers gradually after perfusion with the essential oil is stopped.

In phenobarbitone anaesthetized. dogs intravenous administration of the oil (0.05-0.1 c.c. /kg.) produces an immediate respiratory depression with subsequent stimulation accompanied by fall in blood pressure. These effects are, however, transitory. Larger doses of the oil lead to the complete arrest of respiration. The intestinal movement is relaxed at 0.05 to 0.1 c.c./kg. level and in concentrations of 1:1000 to 1:10000, the oil causes appreciable relaxation of strips of rabbit intestine, previously induced to contract by treatment with acetyl choline and barium chloride.

Moderate doses of the oil lead to a distinct depression of CNS of the guinea pigs and albino rats. When administered intraperitoneally in sublethal doses, the oil induces marked depression. The animals are apathetic and tend to lie on the side. Motor functions are slowed but perception to touch is not lost. In about one hour, the animals become deeply unconscious, with eye reflexes sluggish, pain sensation is lost and respiration is slow and difficult. Lethal doses lead to deep narcosis followed by death in a few hours. M.L.D. for guinea pigs and rats is 0.2 c.c./100g. and 0.15 c.c./100g. body weight respectively.

The drug has been tried in some cardiovascular disturbances (Vakil and Dalal 1955) and is reported to be efficacious in experimental auricular fibrillation (Arora and Madan 1955).

The essential oils lengthens the refractory period of isolated rabbit auricles but in this action it is inferior to quinidine (Arora and Madan 1956).

Likewise, Jatamanshic essential oil is less active than quinidine in its effect in the experimental auricular flutter, produced by injury-stimulation procedure in innervated and decentralised hearts of anaesthetized dogs, and in aconite or acetylcholine induced auricular fibrillation of the same animal. It did not prove effective in digitalis induced ventricular arrhythmias.

The essential oil was found, on comparison with quinidine, on the electrocardiogram of the cat, to cause a lesser prolongation of the refractory period and a lesser slowing of conduction, which is an obvious advantage. Besides, the acute intravenous toxicity of the essential oil in mice is distinctly lower than that of quinidine; LD^{s}_{0} of the essential oil has been found to be 80.3 mg./kg. while that of quinidine it is 55 mg./kg.

An alkaloidal fraction isolated from the rhizomes (Bose et al. 1957), has been found to be hypotensive and muscle relaxant and has a marked depressant effect on tissue respiration in brain, liver and heart of rats as studied by Warburg's techniques.

It has been shown recently (Arora, Sharma and Kapila 1958) that Jatamansone is more effective than the Jatamansi essential oil or quinidine in suppressing ectopic ventricular tachycardia, produced by the two-stage technique of cornory ligation, without producing any undesirable side effects in the unanaesthetized coronary dogs. It may be recalled that the experimental ectopic ventricular tachycardia produced in this manner resembles aetiologically the ventricular arrhythmia, exhibited by patients with myocardial infarction. Jatamansone and quinidine reduce the intensity of ectopic excitatory activity in the boundary of the infarct and this diminishes effectively the chances for the initiation of ventricular fibrillation. Jatamansone has been shown to be more effective than quinidine in this respect. Jatamansone has also been shown to be nearly as effective as quinidine in abolishing aconite—induced auricular fibrillation and auricular flutter produced by injury stimulation procedure. It is, however, much less active than quinidine in combating acetylcholine-induced auricular fibrillation in anaesthetized dogs. The antiarrhythmic action of Jatamansone appears to be due to a direct depressant action on muscles because the action persists even in the denervated hearts.

Jatamansone and the Jatamansi essential oil have anticonvulsant properties and the former is more effective than diphenylhydantoin sodium in the maximal electric shock seizure. However, both the ketone and the essential oil are, like diphenylhydantoin sodium, ineffective in metrazol seizures.

It is clear, therefore, that *Nardostachys jatamansi* does possess to an appreciable extent antiepileptic action ascribed to it in the Ayurvedic and the Unani systems of medicine. The ketone and the essential oil are much less toxic than quinidine or diphenylhydantoin and as such extended clinical trials with *N. jatamansi* in ventricular arrhythmias resulting from acute myocardial infarction and epilepsy are indicated.

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