ABSTRACT

A Study of the Pharmacological Actions of Compounds from Cleome viscosa L., with Special Reference to Effects on the Cardiovascular and Neuromuscular Systems.

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In this thesis, investigations were undertaken to determine the pharmacological properties of some chemical compounds extracted from Cleome viscosa L., a herb used in folklore medicine for the treatment of earache and hypertension.

Initial screening of an ethanol extract of the whole plant ("CV"), which contained glycosides and alkaloids, revealed that CV was of low toxicity to mice and rats. It reduced the blood pressure of the rat and inhibited the contractions of the rat hemidiaphragm elicited by phrenic nerve stimulation. There was also evidence that CV had local anaesthetic activity in guinea pigs, analgesic activity in mice, laxative effect in rats and potentiated the barbiturate sleeping time in rats. CV also antagonised the contractions of the rat uterus to oxytocin and of the guinea pig ileum to acetylcholine and histamine.

Further investigations identified the hypotensive principle in CV as the polar alkaloid stachydrine present mainly in the seeds. The results obtained with

this alkaloid (ALK) suggest that its hypotensive effect was mainly due to a direct action on the peripheral blood vessels. Evidence to support this suggestion include the following results. ALK lowered the blood pressure of both normal and pithed rats. However, ALK did not significantly alter the rate and force of contraction of the heart in vivo and in vitro at the hypotensive doses. In contrast, ALK increased the flow rate in the perfused artery of the rabbit ear preparation. These results suggest that the hypotensive effect of ALK was mediated peripherally, perhaps at the level of the blood vessel, but ALK did not show any selective action in vivo on receptors commonly involved in the control of blood pressure.

At the level of the blood vessel, the alkaloid antagonised the phenylephrine-induced contractions of isolated strips (spirally cut) of the rat aortic artery. Additional studies revealed that this antagonism was not observed in the presence of haemoglobin, a nitric oxide scavenger. The alkaloid also inhibited the phenylephrine-induced contractions of rat aortic strips denuded of endothelium. But this inhibition was prevented by pre-treatment with methylene blue, which is an inhibitor of guanylate cyclase and it was potentiated by 3-isobutyl-1-methylxanthine, an inhibitor of phosphodiesterase, which prevents the metabolism of cyclic GMP. These results suggest that the hypotensive effect of ALK was due to a direct action of ALK on the blood vessel walls: this action seemed to have involved the activation of a guanylate cyclase pathway with the production of cyclic GMP leading to relaxation of the vascular smooth muscles.

Another extract (in 5% dimethyl sulphoxide) prepared from the sticky material on the surface of the leaves of Cleome viscosa L. showed neuromuscular blocking action. A pure compound (CP) isolated from this extract inhibited the contractions of the rat hemidiaphragm to phrenic nerve stimulation. This CP-induced inhibition of the contraction was not reversed by physostigmine, an anticholinesterase. However, contractions produced by direct electrical stimulation of the muscle were not inhibited by CP. Also, CP did not antagonise the acetylcholine-induced contractures of the frog rectus abdominis muscle. These results suggest that CP was acting mainly on nerve conduction to inhibit the neurally-induced contractions of the hemidiaphragm.

Further evidence of this neural action of CP was obtained from studies on the toad sciatic nerve preparation. In these studies, CP reduced the slope of the rising phase and the amplitude of the electrically-induced compound action potential, but both of these components of the action potential depend on the influx of Na^+ ions into the nerve. Therefore when the nerve bath concentration of Na^+ was gradually reduced, CP was more effective in inhibiting the slope of the rising phase and the amplitude of the action potential. However, when the nerve bath concentration of Na^+ was gradually increased from 40% to 100%, CP showed a progressive loss in effectiveness to inhibit the components of the action potential. Similar results were also obtained with lignocaine, which is known to block voltage-gated Na^+ channels in nerves. From these results, the CP-induced

inhibition of the neurally-induced muscle contraction may be attributed to interference with Na^+ influx into the nerve.

In general, the evidence presented in this study indicate that Cleome viscosa L. has chemical components with a wide range of pharmacological properties, two of which were prominent on the cardiovascular and the neuromuscular systems. On the cardiovascular system, a hypotensive effect was attributed to the activation of vascular guanylate cyclase by stachydrine leading to cyclic GMP production and vasodilation. On the neuromuscular system, contractions were inhibited by a lipid compound which appeared to have produced this effect by interference with Na^+ influx into the nerve.