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RESEARCH ARTICLE

BENEFICIAL EFFECT OF *Azadirachta indica* LEAF EXTRACT ON THE CARDIOVASCULAR SYSTEM IN DIFFERENT ANIMAL MODELS

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ABSTRACT

Neem (*Azadirachta indica*), an indigenous plant is reported to have antidiabetic, anti-inflammatory, antifungal and several other medicinal properties. More than 135 active principles have been isolated from different parts of Neem tree and several reviews have been published regarding their beneficial effect. In this experiment, anti arrhythmic action was observed within two minutes of NLE administration and this was persistent in nature. Present work demonstrates the various beneficial effects of low dose NLE like lowering of blood pressure and terminating cardiac tachyarrhythmia.Neem seed oil was obtained in pure form from Indian Herbs Research Supply Company Limited, Saharanpur, UP. The Ethical Committee approval was taken from the Institutional Ethics Committee of Veer Surendra Sai Medical College and Hospital, Burla, Odisha.

INTRODUCTION

Neem tree (*Azadirachta indica*) is well known in India and neighboring countries for over 2000 years for its medicinal properties. Neem has been extensively used in Ayurveda, unani and Homeopathy systems of medicine and has become a cynosure of modern medicine. Neem compounds have shown to posses anti inflammatory, anti fungal hypoglycemic and diuretic properties. Chattopadhya R.R[1] has shown that hydro alcoholic leaf extract of *Azadirchta indica* possesses dose dependent hypotensive activities, and few others have speculated the possible beneficial effects in heart diseases. The beneficial effects have been ascribed to its blood pressure lowering, cholesterol lowering, blood clot preventing and anti arrhythmic properties[2, 3, 4]. Present study was under taken to explore the possible beneficial effect of *Azadirachta indica* leaf extract in differ animal models.

MATERIALS AND METHODS

NLE was obtained from Indian Institute of Herbs, Saharanpur (Batch NO.RD-01). As per the written instructions NLE was dissolved in the Luke warm distilled water, filtered and was used for the experiment. Effect of NLE was studied on three different animal models. Effect of NLE on frog's heart was observed in four different parts.

OBSERVATION AND RESULTS

Effect of NLE on perfused toad's heart preparation

Effect was observed by adding graded doses of NLE to Traube's tube through which frog Ringer Fluid was provided as bathing fluid to frog heart. Different cardiac parameters like rate, rhythm, tone and amplitude was noted in observation table. Arrhythmia was induced in the isolated frog's heart by applying current of 100- 200 pulses per second (according to the need of the tissue) directly on the heart surface through a 'Student Stimulator'. Adrenaline (1:1000) was added to Traube's tube to produce arrhythmia.

In the second phase, effect of NLE was observed on ECG changes of Guinea pigs.ECG changes were monitored in guinea pigs by using ECG machine (BPL). Recording leads were replaced by needles and inserted subcutaneously. Guinea pigs were anaesthetized by injecting urethane at the dose of 1.5gram per kg. Intraperitoneally (C.A. Desai *et al*, Department of Pharmacology, Seth G.S. Medical College and K.E.M. Hospital, Parel, Mumbai). ECG was recorded at a speed of 50mm per second and current of 1 amp. Lead II waves were recorded because it is the best lead for experimental studies. ECG was recorded in normal guinea pigs and NLE pretreated groups (graded doses). Pretreatment of NLE was done orally by tube.

Effect of NLE on Blood Pressure of anaesthetized dogs

Graded doses of NLE were administered through an intravenous catheter to femoral vein of anaesthetized dogs. Anesthesia was induced by ether and was maintained by Chloralose.

Effect of NLE on isolated frog's heart

At low doses (0.5mg – 2mg) NLE did not alter any cardiac parameters significantly. At higher doses (2.5 – 10mg) it reduced tone; amplitude, increased heart rate and also facilitated arrhythmia generation. Slight increase in dose did not produce any significant change in cardiac parameters suggesting its high margin of safety. Cardiac depressant action with high doses was persistent even after atropinization suggesting non-cholinergic mechanism involved. The cardiac depression action became more aggravated in presence of atropine (atropine like action).

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Effect of NLE on electrical and Adrenaline Induced arrhythmia

At low dose NLE (0.5 – 2mg) was quite effective in preventing cardiac abnormality. Here again NLE at high dose (5 – 10mg) rather aggravated arrhythmia suggesting pro-arrhythmic potential.

Effect of NLE on ECG of Guinea Pigs

Pretreatment with 2mg NLE 1 hour before ECG recording showed no significant change where as at the dose of 5mg of NLE, there was a disappearance of P wave. But both at 8mg and 10mg of NLE, there was appearance of Q wave which was quite significant. At higher doses there was also increase in heart rate (180/ min.). This property of NLE shows features of myocardial ischemia and damage by NLE at high dose.

Effect of NLE on dog blood pressure

NLE at different doses, starting from 2mg i.v. produced significant dose dependant hypotensive action. This action was not blocked by atropine rather potentiated by it. At the dose of 10mg the marked fall of BP, led to death of one dog. Hypotensive action was persistent in nature, as base line was not coming to normal during the experiment both the dogs urinated twice suggesting the diuretic property of NLE.

Table 1. Effect of NLE on perfused toad's heart

Dose of NLE	Rate	Rhythm	Tone	Amplitude
0.5mg	-	-	-	-
1mg	-	-	-	-
1.5mg	-	-	-	↓
2mg	↑	-	-	↓
2.5mg	↓	-	↓	↓
5mg	↓	-	↓	↓
10mg	↓	Altered	↓	↓

DISCUSSION

NLE at low dose (0.5 – 2mg) had no significant effect on different cardiac parameters of frog's heart. But at higher doses (>2.5mg) possess cardiac depressant properties. This findings is consistent with the finding of R.R. Chattopadhyay, who had shown that low dose of NLE dose not alter rate and force of contraction of perused toad's heart but at higher dose produces temporary cardiac arrest in diastole[2] suggesting the cardiac depressant property. At the dose between 2.0 – 2.5mg NLE was quite effective in preventing both electrical and adrenaline induced arrhythmia. The higher dose of, NLE (5.0 – 10mg) possess severe cardiac depressant potential in amphibian heart.

This feature of NLE was observed in all the three animal models like depression of frog's heart, ECG abnormality in guinea pigs and severe hypotensive action in anesthetized dog. Thompson and Anderson have proved that NLE returns heart rate to normal within 8 minutes of administration of NLE in artificially induced arrhythmia[3]. In this experiment, anti arrhythmic action was observed within two minutes of NLE administration and this was persistent in nature. Few workers have shown that NLE produces significant and immediate decrease in blood pressure Thompson and Anderson, 1978; Pillai Santhakumari, 1984; Koley and Lal 1994. Thompson and Anderson have ascribed this effect of NLE to Nimbidin in leaf extracts, which causes vasodilatation because of its anti-histaminic properties. Hypotensive action of NLE may be due to its diuretic action, which was suggested by Mitra *et al* by demonstrating diuretic property of NLE in people with congestive cardiac failure. Present work demonstrates the various beneficial effects of low dose NLE like lowering of blood pressure and terminating cardiac tachyarrhythmia. However at higher doses (5mg and above) these beneficial effects are converted into detrimental consequences like sharp fall of blood pressure in dog and cardiac arrest in isolated frogs heart. This toxic potential of NLE was further confirmed by demonstrating various abnormalities of guinea pig ECG.

Conclusion

Thus Neem leaf extract at optimal doses possesses beneficial effect on cardiovascular system of cardiovascular system of different animal models used in the present study. A further study regarding its cardiovascular effects is very much essential for its possible therapeutic and prophylactic application in various cardiovascular diseases.

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