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Possible mechanisms of hypotension produced 70% alcoholic extract of *Terminalia arjuna* (L.) in anaesthetized dogs

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Abstract

Background: The bark of Terminalia arjuna L. (Combretaceae) is used in Ayurveda since ancient times for the treatment of cardiac disorders. Previous laboratory investigations have demonstrated the use of the bark in cardiovascular complications. The present study was aimed to find the effect of 70% alcoholic extract of Terminalia arjuna on anaesthetized dog blood pressure and probable site of action.

Methods: Six dogs were anaesthetized with intraperitoneal injection of thiopental sodium and the blood pressure of each dog (n = 6) was measured from the left common carotid artery connected to a mercury manometer on kymograph. The femoral vein was cannulated for administration of drug solutions. The extract of *T. arjuna* (dissolved in propylene glycol) in the dose range of 5 to 15 mg/kg were administered intravenously in a pilot study and the dose (6 mg/kg) which produced appreciable hypotension was selected for further studies.

Results: Intravenous administration of *T. arjuna* produced dose-dependent hypotension in anaesthetized dogs. The hypotension produced by 6 mg/kg dose of the extract was blocked by propranolol but not by atropine or mepyramine maleate. This indicates that muscarinic or histaminergic mechanisms are not likely to be involved in the hypotension produced by the extract. The blockade by propranolol of the hypotension produced by *T. arjuna* indicates that the extract might contain active compound(s) possessing adrenergic β_2-receptor agonist action and/or that act directly on the heart muscle.

Conclusion: The results indicated the likely involvement of peripheral mechanism for hypotension produced by the 70% alcoholic extract of *Terminalia arjuna* and lends support for the claims of its traditional usage in cardiovascular disorders.

Background

The bark of *Terminalia arjuna* L. (Combretaceae) has been widely used in Ayurvedic system of medicine for cardiac disorders since ancient times [1–3]. Extensive reviews on various aspects of *T. arjuna* have been published [4,5]. Both experimental and clinical studies showed the beneficial effects of the bark in congestive heart failure [6–8] and in ischemic heart disease [9–14] and other cardiovascular

complications [15–19]. The aqueous extract of *T. arjuna* showed contraction followed by relaxation on isolated rat thoracic aorta [15,20]. Results from our laboratory demonstrated that 70% alcoholic extract of *T. arjuna* reduced the platelet count on chronic treatment to dogs [21]. Singh et al. reported that aqueous solution of 70% alcoholic bark extract of *T. arjuna* produced dose-dependent decrease in heart rate and blood pressure in dogs, though the mechanism was not determined [22]. In the present investigation, a systematic study was performed to find the probable mechanism of hypotension produced by 70% alcoholic extract of *T. arjuna* in thiopental anaesthetized dogs.

Methods

Plant material and extraction

The authenticated dried bark of *Terminalia arjuna* was purchased from the local herbal traders and was crushed to coarse powder 20–40 mesh size and then refluxed with 70% v/v alcohol for two hours using Soxhlett's apparatus. The extract was filtered and the filtrate was evaporated to dryness by rotary film evaporator. 1 g of bark extract represents 9.6 g of dried bark

Chemicals used

Acetylcholine, histamine, isoprenaline and adrenaline were purchased from Sigma-Aldrich, St. Louis, USA. Other drugs used were mepyramine maleate (H. Jules & Co., Nagpur, India), propranolol (Imperial Chemical Industries, India), heparin sodium (Biological Evans Ltd., Hyderabad, India), trisodium citrate (SD Fine Chemicals, Boisar, India), thiopental and atropine sulphate (The Central Drug House, Mumbai, India).

Animal experiments

Eight dogs of either sex weighing between 10 – 15 kg supplied by Visakhapatnam Municipal Corporation were used in the study. The animal experiments conducted in the research work were approved by the Institutional Animal Ethics Committee and by the government regulatory body for animal research (Regd. No. 516/01/A/CPCSEA). Thiopental sodium was administered intraperitoneally at a dose of 40 mg/kg body weight to anaesthetize the dogs. The femoral vein was cannulated for administration of subsequent doses of anaesthetic (if required) and drug solutions.

Recording of blood pressure

Haemodynamic setup was used to record the blood pressure of anaesthetized dog. The blood pressure of each animal was recorded from left common carotid artery connected to a mercury manometer on kymograph paper.

The normal blood pressure of dogs was recorded after stabilization for 30 minutes. The different doses 5, 6, 8, 10 and 15 mg/kg body weight of 70% alcoholic extract of *T. arjuna* were administered to all the animals (n = 6) while the dose 20 mg/kg body weight was studied in only 2 animals. The 6 mg/kg body weight dose of the extract which produced appreciable blood pressure lowering activity was used further to determine the change in its blood pressure response before and after administration of atropine (1 mg), mepyramine maleate (20 μg) and propranolol (30 μg).

Results

The extract produced dose-dependent hypotension in the dose range of 5 to 15 mg/kg body weight while 20 mg/kg body weight doses was found to be fatal (Table 1). The hypotension produced by 6 mg/kg body weight was not blocked by prior administration of atropine (1 mg) or mepyramine maleate (20 μg) which blocked acetylchloine (8 μg) and histamine (8 μg) responses respectively. The hypotension of *T. arjuna* was blocked by propranolol (30 μg) which blocked the isoprenaline (10 μg) response. The responses observed with 6 mg/kg dose

Table 1: Influence of atropine, mepyramine and propranolol on the hypotensive response of *T. arjuna* in dogs.

Drug	Dose (n = 6)	Response			
			After Antagonist		
		Before Antagonist	Atropine (1 mg)	Mepyramine (20 μg)	Propranolol (30 μg)
T. arjuna	5 mg/kg	Hypotension	NS	NS	NS
T. arjuna	6 mg/kg	Hypotension	No Blockade	No Blockade	Blockade
T. arjuna	8 mg/kg	Hypotension	NS	NS	NS
T. arjuna	10 mg/kg	Hypotension	NS	NS	NS
T. arjuna	15 mg/kg	Hypotension	NS	NS	NS
T. arjuna	20 mg/kg(n = 2)	Severe Hypotension	NS	NS	NS

NS – not studied; n – number of animals.

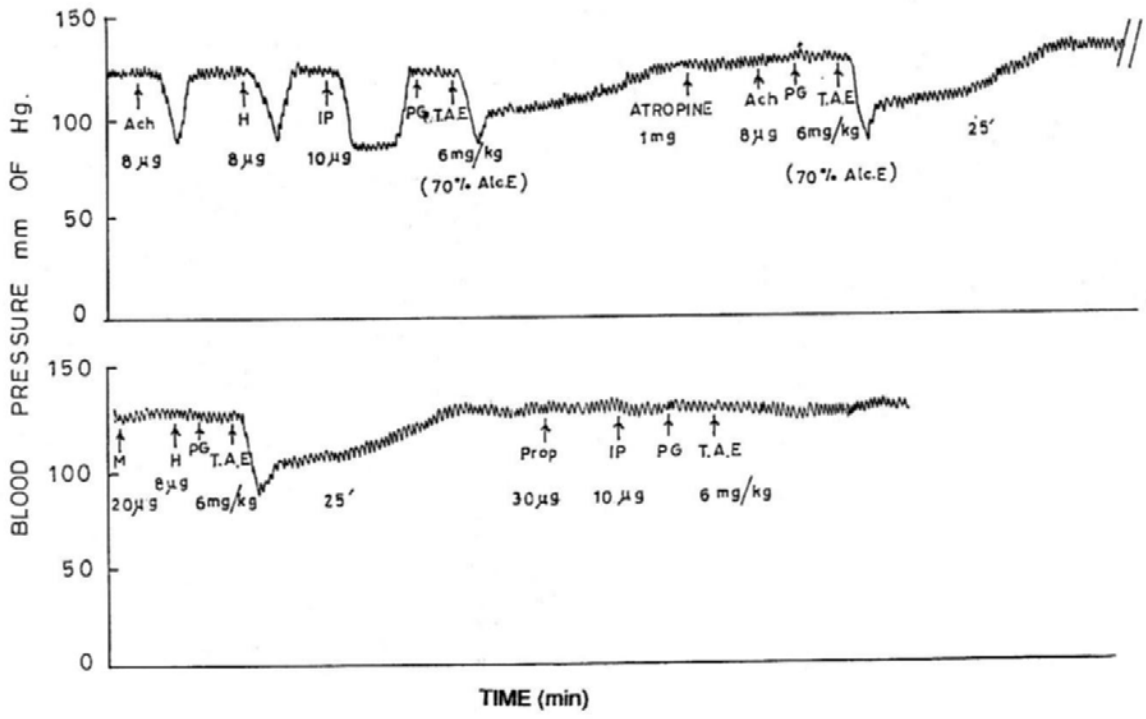

Figure 1
Effect of 70% alcoholic extract of *Terminalia arjuna* on anaesthetized dog blood pressure. TAE – 70% alcoholic extract of *Terminalia arjuna*, Ach – Acetylcholine, H – Histamine, IP – Isoprenaline, M – Mepyramine, PG – Propylene glycol, Prop – Propranolol.

of the extract before and after administration of the antagonists are shown in Fig 1. The vehicle propylene glycol alone did not alter the blood pressure in the doses studied.

Discussion

The hypotension produced by 6 mg/kg body weight dose of the extract was not blocked by atropine which could block the response of selected dose of acetylcholine indicating that the muscarinic mechanism was not involved. Studies with mepyramine maleate indicate that histaminergic mechanism was also not involved in the hypotension produced by the extract. Studies with propranolol which blocked the hypotensive response of the extract indicated that it may contain compounds having adrenergic β-receptor agonist action. Even though propranolol is a non-specific β-blocker, it is clear that the compounds present in the extract might be adrenergic β_2-agonists, since adrenergic β_2-receptor stimulation produces hypotension. Moreover, with the limitations of our study, one cannot completely ruled out the possibility that the observed hypotensive responsive could also be due to the effect of *T. arjuna* directly on the heart there by reducing the cardiac load. Earlier, it was reported that aqueous soluble fraction of 70% alcoholic extract (dried) of *T. arjuna* produced dose-dependent hypotension and decrease in heart rate [22] and were attributed to principles of the extract acting centrally. Our studies with 70% alcoholic extract dissolved in propylene glycol indicate the likely presence of compounds acting peripherally through adrenergic β_2-receptor mechanism and/or by direct action on the cardiac muscle. Mallikarjuna and coworkers [20] studied the influence of aqueous extract of *T. arjuna* on isolated rat thoracic aorta and found contraction followed by relaxant effect. It was felt that the vasorelaxant effect of *T. arjuna* extract could contribute to the

reported decrease in blood pressure in anaesthetized dogs as observed by Singh et al [22]. The same experiment on isolated vascular smooth muscle lends support for our observation that the hypotension could be of peripheral origin. However, Mallikarjuna and co-workers indicated that the vasorelaxant effect of the extract was not blocked by propranolol. The possible reason for this variable effect could be due to the difference in the active principles present in different types of extracts used. This indicates that the 70% alcoholic extract might contain compounds to a higher degree whose activity was blocked by propranolol while the activity produced by the constituents of aqueous extract were not blocked by propranolol. Further investigations are needed on the isolates of *Terminalia arjuna* to study their cardiovascular effects in order to explain more in detail of the observed results.

Conclusions

The present results indicate that the 70% alcoholic extract of *Terminalia arjuna* produced hypotension of peripheral origin and support the claims of its traditional usage as cardiovascular medicine. The observed effect could be due to adrenergic β_2-receptor agonistic and/or direct action on the heart. Detailed studies on the active constituents are needed which might provide new insights in cardiovascular drugs.

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