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Abstract

Cardamom (*Elettaria cardamomum*) is widely used in folk medicine for the treatment of asthma. This study describes its airways relaxant potential, with elucidation of possible underlying mechanism. Crude extract of cardamom which tested positive for alkaloids, flavonoids, saponins, sterols and tannins, when tested against carbachol-mediated bronchoconstriction in rats under anesthesia, dose-dependently (10-100 mg/kg) suppressed the carbachol (1 μmol/kg)-evoked increase in the inspiratory pressure. In isolated rabbit trachea tissues, crude extract of cardamom caused relaxation of both carbachol (1 μM) and high K⁺ (80 mM)-induced contractions, like that caused by verapamil, suggesting its Ca⁺⁺ channel blockade action. These results indicate that cardamom exhibits bronchodilatory effect, mediated through Ca⁺⁺ antagonist mechanism, which provides sound mechanistic background for its medicinal use in asthma.

Introduction

Elettaria cardamomum Maton (family: Scitamineaceae) commonly known as "cardamom" and locally known as "elaichi" is a perennial herb, indigenous to India, Pakistan, Myanmar and Sri Lanka (Nadkarni, 1976). In addition to its wide use for culinary purpose, cardamom has been used in traditional medicine for asthma, constipation, colic, diarrhea, dyspepsia, hypertension, epilepsy and is considered useful as antibacterial, antifungal, antiviral, carminative, diuretic and stomachic (Kapoor, 1990; Duke et al., 2002). Phytochemical studies revealed that cardamom contains α-terpineol, myrcene, heptane, subinene, limonene, cineol, menthone, α-pinene, β-pinene, linalol, nerolidol, β-sitostenone, phytol, eugenyl acetate, bisabolene, borneol, citronellol, geraniol, geranyl acetate, stigmaterol and terpinene (Gopalakrishnan et al., 1990; Duke, 1992). Despite the fact that cardamom has been used medi-

inally, it has not been widely studied to rationalize its use in hyperactive status of airways, asthma. In this study, we evaluated that the bronchodilatory effect of cardamom is mediated through Ca⁺⁺ channel blockade, which provide pharmacological rational for its effectiveness in the asthma.

Materials and Methods

Plant material and preparation of extract

Dried fruits of cardamom were purchased from a local market in Karachi and the sample voucher (EC-SE-07-04-54) was submitted to the Department of Biological and Biomedical Sciences herbarium, Aga Khan University, Karachi. After cleaning of adulterant material, the fruits were ground with an electric grinder into a coarse powder. Extraction and fractionation was carried out as



described previously. About 986 g of ground material was soaked in 4 liters of the aqueous-methanol (70%) for three days with occasional shaking. It was filtered through a muslin cloth and then through a Whatman qualitative grade 1 filter paper. This procedure was repeated twice and the combined filtrates were evaporated on rotary evaporator under reduced pressure (-760 mmHg) to a thick, semi-solid pasty mass of dark brown color; i.e. the crude extract of cardamom, yielding approximately 10.8%, soluble in saline/distilled water.

Animals

Animals used in this study, such as Sprague-Dawley rats (230-260 g) and rabbits (1.5-2.0 kg) of either sex and local breed were housed at the Animal House of the Aga Khan University, maintained at 23-25°C. Experiments performed complied with the rulings of the Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council (1996) and approved by Ethical Committee of Aga Khan University.

Chemicals

Carbachol, salbutamol and pentothal sodium (thiopental sodium) were respectively obtained from Sigma Chemicals Co., USA, Glaxo Wellcome and Abbot Laboratories, Karachi, Pakistan. Chemicals for Krebs solutions include: Potassium chloride (Sigma Chemical Company), calcium chloride, glucose, magnesium sulfate, potassium dihydrogen phosphate, sodium bicarbonate and sodium chloride (E. Merck, Germany). The chemicals used in phytochemical analysis include: Acetic anhydride, aluminum chloride, ammonium hydroxide, Dragendorff's reagent, ferric chloride (Sigma Chemical Co, USA), benzene, chloroform, hydrochloric acid and petroleum ether (BDH Laboratory supplies, England). All the chemicals used were of analytical grade available.

Phytochemical screening

Preliminary screening of the plant extract for various phytochemical classes was carried out following the reported methods (Gilani et al., 2007). Alkaloids were tested by using Dragendorff's reagent. Appearance of yellow color with $AlCl_3$ reagent and green or black with aqueous $FeCl_3$ detects flavonoids and tannins respectively. Plant material treated with petroleum ether and subsequently extracted with $CHCl_3$ was noted for green to pink or pink to purple color after reaction with acetic anhydride and HCl in succession to detect sterols and terpenes respectively. Saponins were detected on the basis of froth upon vigorous shaking. The observation of yellow fluorescence under UV light on filter paper impregnated with the vapors from boiling extract indicates the presence of coumarins. Benzene extract prepared from acidified plant material was treated with

NH_4OH for anthraquinones based on the appearance of pink, violet or red color.

Bronchodilatory activity

Rats were anaesthetized with sodium thiopental (Pentothal, 80-100 mg/kg, i.p.), then incubated with a tracheal tube and ventilated with a volume ventilator (Miniature ideal pump, Bioscience, UK) adjusted at a rate of 70-80 strokes/min to deliver 7-10 mL/kg of room air. A polyethylene catheter was inserted into the jugular vein for drugs administration. Changes in airways resistance (mmHg) were measured by a pressure transducer (MLT -1199) connected to side arm of tracheal cannula and recorded by PowerLab 4/25 with running chart software via Quad bridge amplifier (ADInstruments, Australia). Bronchoconstriction was induced with carbachol (1 μ mol/kg), which was reversed within 7-10 min. The test drug was given to the animals 5-8 min prior to administration of carbachol. The responses were expressed as the percent reduction of the carbachol-evoked bronchospasm (Khan and Gilani, 2009).

Isolated rabbit trachea

Trachea from rabbit, sacrificed by blow on back of head was dissected out and kept in Krebs's solution. The tracheal tube was cut into rings, 2-3 mm wide, each containing about two cartilages. Each ring was opened by a longitudinal cut on ventral side, forming a tracheal chain with smooth muscle in the center and cartilaginous portions on the edges. Each preparation was then mounted in 20 mL tissue bath containing Krebs's solution, maintained at 37°C and aerated with carbogen (5% CO_2 in 95% O_2). The composition of Krebs's solution was (mM): NaCl 118.2, $NaHCO_3$ 25.0, $CaCl_2$ 2.5, KCl 4.7, KH_2PO_4 1.3, $MgSO_4$ 1.2 and glucose 11.7 (pH 7.4). A tension of 1 g was applied to each of the tracheal strip and was kept constant throughout the experiment. The tissue was equilibrated for 1 hour before the addition of any drug. Then sustained contractions of the agonists, carbachol (1 μ M) and/or K^+ (80 mM) were obtained and tracheo-relaxant effect of the test material was assessed by adding in a cumulative fashion. Carbachol is a cholinergic agonist, known to cause bronchoconstriction via stimulation of muscarinic receptors (Gilani et al., 2010). High K^+ (>30 mM) is known to cause smooth muscle contractions through opening of voltage-dependent L-type Ca^{++} channels, thus allowing influx of extracellular Ca^{++} causing a contractile effect and the substance causing inhibition of high K^+ -induced contraction is considered as inhibitor of Ca^{++} influx (Godfraind et al., 1986). The changes in isometric tensions of the tracheal strips were measured via a force-displacement transducer (FT-03) using a Grass model 7 Polygraph (Grass Instrument Company, Quincy, MA, USA).

Statistical analysis

The data expressed are mean \pm standard error of mean (SEM, n = number of experiment) and the median effective concentrations (EC_{50}) with 95% confidence intervals (CI), analyzed by using GraphPad program (GraphPAD, San Diego, CA, USA).

Results

Crude extract of cardamom was found to contain alkaloids, flavonoids, saponins, sterols and tannins while tested negative for the rest of classes (data not shown).

Crude extract of cardamom at the doses of 10, 30 and 100 mg/kg caused 9.0 ± 2.1 , 37.7 ± 5.4 and $83.4 \pm 4.4\%$ (n = 4) respective inhibition of carbachol ($1 \mu\text{mol/kg}$)-evoked increase in inspiratory pressure of anaesthetized rats. Salbutamol suppressed the carbachol ($1 \mu\text{mol/kg}$)-induced bronchoconstriction at 0.3 mg/kg by $78.7 \pm 3.9\%$ (n = 4; Figure 1).

In tracheal preparations, pre-contracted with carbachol ($1 \mu\text{M}$) and K^+ (80 mM), crude extract of cardamom caused concentration-dependent relaxant effect, being more potent against K^+ , with respective EC_{50} values of 0.85 (0.6-1.3, 95% CI, n = 5) and 0.37 mg/mL (0.3-0.4, n = 4; Figure 2A). Verapamil also caused inhibitory effect, possessing higher potency against K^+ , with EC_{50} values of 0.26 (0.2-0.3, n = 3) and $0.1 \mu\text{M}$ (0.06-0.14, n = 3) respectively (Figure 2B).

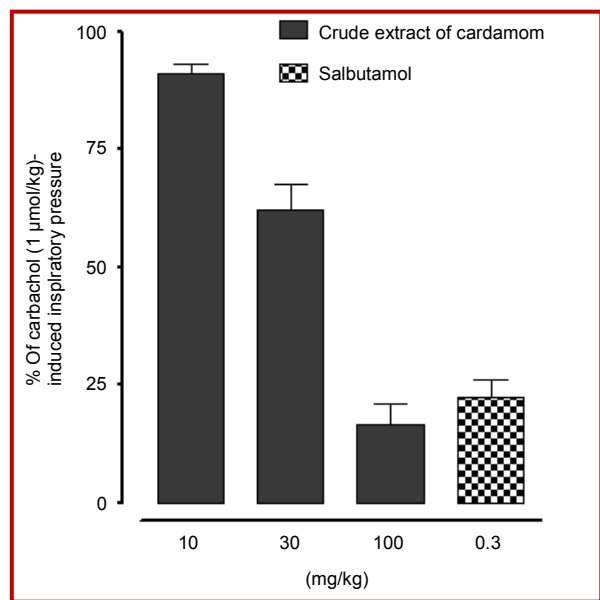


Figure 1: Bar-chart showing inhibitory effect of the crude extract of cardamom and salbutamol on the carbachol-mediated bronchoconstriction in anesthetized rats. Values shown are mean \pm SEM, n = 4

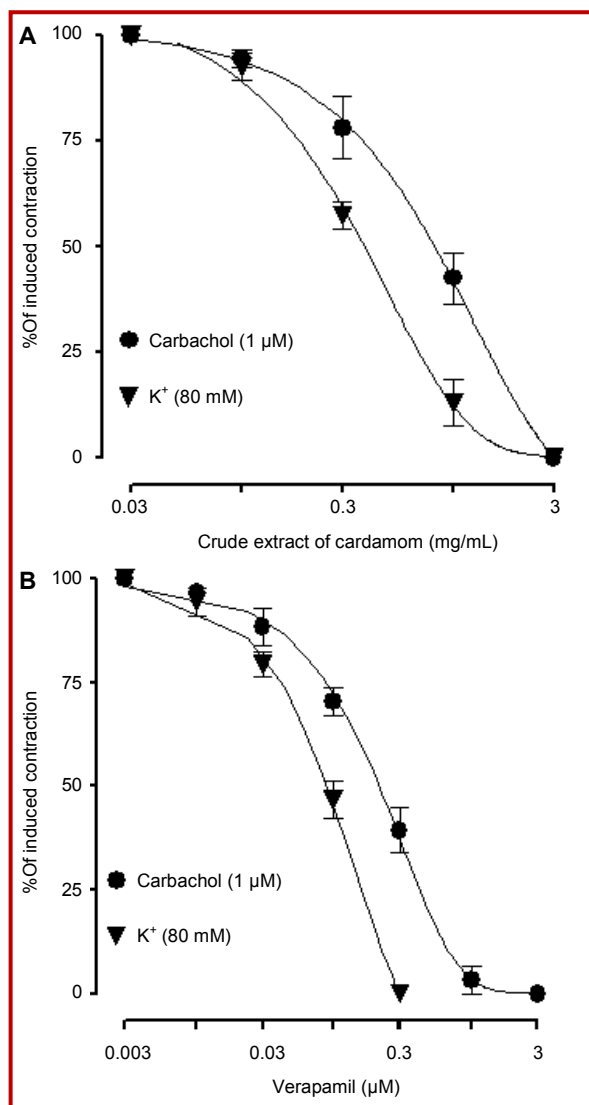


Figure 2: Concentration-dependent inhibitory effect of (A) crude extract of cardamom and (B) verapamil against carbachol and high K^+ -induced contractions in isolated rabbit tracheal preparations. Values shown are mean \pm SEM, n = 3-5

Discussion

In view of the well known medicinal use in asthma, the cardamom was tested for its possible bronchodilatory effect in anaesthetized rats, where it inhibited the carbachol-evoked bronchospasm, like that caused by salbutamol, a standard bronchodilator (Barnes, 2006). The cardamom extract was then studied in isolated tracheal tissues, to elucidate the possible mode of bronchodilator action, where crude extract of cardamom caused relaxation of both carbachol and K^+ -induced contractions, like verapamil, a Ca^{++} antagonist (Fleckenstein, 1977) used as positive control. High K^+ and carbachol are known to cause smooth muscle

contractions through opening of L-type Ca^{++} channel and stimulation of muscarinic receptors respectively, eventually leading to an increase in the intracellular Ca^{++} level, resulting in airways constriction (Gilani et al., 2007). The inhibitory effect of crude extract of cardamom against the two spasmogens, indicates non-specific tracheo-relaxant effect, mediated through Ca^{++} channel blocker-like mechanism (Gilani et al., 2010). Ca^{++} antagonists are known to be effective in asthma (Ann Twiss et al., 2002) and the presence of such activity, as observed in this study may explain the medicinal use of cardamom in such disorder of airways hyperactivity.

The results of phytochemical analysis showed that cardamom contains alkaloids, flavonoids, saponins, sterols and tannins. The flavonoids are well known for their bronchodilatory activity (Ghayur et al., 2007) and the presence of such class of compounds in cardamom is likely to contribute in its airways relaxing action. However, the contribution of other constituents cannot be ignored.

Conclusion

Cardamom exhibits bronchodilatory effect, mediated through Ca^{++} antagonist mechanism, which provides pharmacological basis for its application in the disorder of hyperactive status of respiratory system, known as asthma.

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