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OPEN ACCESS International Journal of Pharmacology

ISSN 1811-7775
DOI: 10.3923/ijp.2019.

Research Article
Possible Mechanism(s) Underlying the Antidiarrheal, Antispasmodic and Bronchodilatory Activities of the Pericarp of *Albizia lebbeck*

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Abstract

Background and Objective: *Albizia lebbeck* is famous plant for its medicinal use in hyperactive gut and airways disorders. The objective of this study was therefore to provide a scientific rationale for the medicinal utility of *Albezia lebbeck* in diarrhea, gut spasm and bronchospasm, with the possible mode of action explored. **Materials and Methods:** The hydro-alcoholic extract of the pericarp of *Albezia lebbeck* (Al.Pericarp) was tested using *in-vivo* and *in-vitro* assays. **Results:** *Albezia* Pericarp, at 100 and 300 mg kg^{-1} showed 40 and 80% protection of castor oil-induced diarrhea in mice, whereas loperamide (10 mg kg^{-1}) showed complete protection. In isolated rabbit jejunum, *Albezia*. Pericarp completely inhibited spontaneous, carbachol (CCh; 1 μM) and low K^+ (25 mM)-induced contractions but had only a weak effect against high K^+ (80 mM). When tested for bronchodilatory activity in anesthetized rats, *Albezia*. Pericarp (3-30 mg kg^{-1}) inhibited the CCh-induced bronchospasm in a dose-dependent manner, similar to aminophylline. In isolated guinea-pig tracheal preparations, Al.Pericarp selectively inhibited contractions induced by CCh and low K^+. The inhibitory effect of Al.Pericarp against low K^+ was reversed in the presence of tetraethylammonium (TEA), a non-specific blocker of K^+-channels, whereas no significant inhibition was observed in the presence of glibenclamide (Gb) or 4-aminopyridine (4-AP), which are ATP-dependent and voltage-dependent K^+ channel blockers, respectively. The plant extract (0.03 and 0.01 mg mL^{-1}) also potentiated isoprenaline-inhibitory concentration-response curves (CRCs) by a shift to the left, in both jejunum and trachea, showing phosphodiesterase inhibition, similar to papaverine. **Conclusion:** These results indicated that the crude extract of *Albizia lebbeck* Pericarp possesses anti diarrheal, antispasmodic and bronchodilatory activities, mediated possibly through dual pathways, namely activation of a non-specific type of K^+-channels and inhibition of phosphodiesterase enzyme. Thus, this study offered a sound basis for *Albizia lebbeck* to be developed for hyperactive gut and airways disorders.

Key words: *Albizia lebbeck*, anti diarrheal, spasmolytic, bronchodilator, K^+-channel opener, phosphodiesterase inhibition

Received: Accepted: Published:

Citation: Aslam Khan, Najeeb-ur-Rehman, Anwarul-Hassan Gilani, Zunirah Ahmed, Shaza Al-Massarani, Ali. El-Gamal and Mohamed Farag, 2019. Possible mechanism(s) underlying the antidiarrheal, antispasmodic and bronchodilatory activities of the pericarp of *Albizia lebbeck*. Int. J. Pharmacol., CC: CC-CC.

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

The genus *Albizia* (Fabaceae) comprises approximately 150 species, mostly trees and shrubs native to tropical and subtropical regions of Asia and Africa[1]. *Albizia lebbeck* Benth. was imported many years ago from South Asia and adapted well to the harsh environmental conditions of the central part of Saudi Arabia. *Albizia lebbeck* is a tree well known in the Indian subcontinent for its wide range of medicinal uses. The tribal people in Himachal Pradesh and Kashmir use the plant to treat inflammation[2-4], while the tribes of Tamil Nadu utilize the plant in the treatment of bone fractures[5]. *Albizia lebbeck* is used in South Asian folk medicine to treat several inflammatory pathologies such as diarrhea[6,7], asthma, bronchosis[8], arthritis and burns[9,10]. In addition, the flowers are being commonly used to treat anxiety, depression and insomnia in traditional Chinese medicine[11].

Albizia lebbeck has previously been investigated for a number of pharmacological activities using *in vitro* and *in vivo* experiments. In Baruach *et al.*[12] reported that *A. lebbeck* inhibits passive cutaneous anaphylaxis and mast cell degranulation in rats, in addition to its protective effect in sensitized guinea pigs from antigen induced anoxic convulsion. Recently, it was found that the alcoholic extract of *A. lebbeck* has an antihistaminic property, by neutralizing the histamine directly or due to a corticotrophic action, as evidenced by raising cortisol levels in the plasma[13]. Moreover, saponins from *A. lebbeck* have been claimed to be useful in treatment of Alzheimer's and Parkinson's diseases[14]. Leaves have been claimed to have anticonvulsant activity[15] and a nootropic effect[16], which may be due to the presence of certain important compounds like alkaloids and flavonoids. The aqueous extract of *A. lebbeck* leaves has been shown to have antioxidant activity in diabetic rats[17]. The seeds were shown to have anti-fertility effects on male rats[18], while the seeds extract of *A. lebbeck* has been investigated for its antidiarrheal activity, using the conventional rodents models of diarrhea[19]. Some reports also showed beneficial effects of *A. lebbeck* in antigen challenged guinea pigs[20] and in bronchial asthma patients[21], in addition to its anti-inflammatory[22,23] and hypoglycemic[24-26] actions.

Despite the extensive biological evaluation of this plant, where it had been tested for a number of pharmacological activities including antidiarrheal[19] and antiasthmatic[21] properties, there are no detailed studies available that look into the possible mechanism(s), responsible for its antispasmodic, antidiarrheal and bronchodilatory activities; therefore, the aim of this study was to evaluate the hydro-alcoholic crude extract of its pericarp for antidiarrheal, antispasmodic and bronchodilator effects with detailed possible mode of action. Interestingly, the crude extract of *Albizia lebbeck* possesses antispasmodic and bronchodilatory activities mediated through a unique combination of activities, namely activation of K^+-channels and inhibition of phosphodiesterase, which provides sound evidence for the medicinal use of the plant in gut and airways disorders.

MATERIALS AND METHODS

Plant material: The fruits of *A. lebbeck* were obtained from trees grown in the district of Riyadh, Saudi Arabia, during the year 2012. Taxonomical identity was kindly verified by Dr. Mohammed Yousef, Pharmacognosy Department, College of Pharmacy, King Saud University, Saudi Arabia. A voucher specimen number 16182 was deposited at the department.

Extract preparation and chemicals: The seeds were removed manually from fruits, to isolate the pericarp. The air-dried powdered pericarp (200 g) was exhaustively extracted with 70% ethanol in a continuous extraction apparatus for 8 h. The solvent was distilled off under reduced pressure to give 20 g of hydro-alcoholic extract (Al.Pericarp).

The following reference chemicals were obtained from the sources specified: acetylcholine chloride, glibenclamide (Gb), 4-aminopyridine, tetraethylammonium (TEA), loperamide hydrochloride, potassium chloride, aminophylline, carbamylcholine (Sigma Chemical Company, St. Louis, MO, USA) and castor oil (Karachi Chemical Industries, Karachi, Pakistan). Chemicals used for making physiological salt solutions including potassium chloride, calcium chloride, glucose, magnesium chloride, magnesium sulfate, potassium dihydrogen phosphate, sodium bicarbonate, sodium dihydrogen phosphate and sodium chloride were obtained from Merck (Darmstadt, Germany). All chemicals used were of the highest purity grade. Stock solutions of all the chemicals were made in distilled water for *in vitro* experiments and the dilutions were made fresh in normal saline for *in vivo* experiments, on the day of experiment.

Animals: BALB/c mice (weighing 20-25 g), Wistar rats (weighing 200-250 g), locally bred guinea-pigs (weighing 400-600 g) and rabbits (weighing 1-1.5 kg) of either sex were housed at the animal house of the Aga Khan University under a controlled environment of 23-25°C and a 12 h light-dark cycle was maintained in the animal house. The animals were kept in respective cages with sawdust (changed every 48 h) and were fasted for 24 h before starting the experiment. In

routine, they were given tap water *ad libitum* and a standard diet consisting of g kg^{-1}: flour 380, fiber 380, molasses 12, NaCl 5.8, nutrivet L 2.5, potassium metabisulfite 1.2, vegetable oil 38, fish meal 170 and powdered milk 150. The experiments were performed according to the rulings of the Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council[27].

In vivo experiments

Antidiarrheal activity: The antidiarrheal activity was studied using castor oil-induced diarrhea in mice as described previously[28]. Mice (20-25 g) of either sex were fasted for 24 h before the experiment. The animals were housed in individual cages and divided in four equal groups, each containing 5 animals. The first group received saline (10 mL kg^{-1}, p.o.), acting as negative control. The second and third groups received Al.Pericarp, 100 and 300 mg kg^{-1}, respectively. The fourth group received loperamide (10 mg kg^{-1}), as positive control. One hour after the treatment, each animal received castor oil (10 mL kg^{-1}, p.o.) through a feeding needle. After 4 h of the castor oil dosing, the individual mouse cages were inspected for the presence and absence of typical diarrheal droppings; the absence of diarrheal droppings was noted as a positive result, indicating protection from diarrhea.

Bronchodilatory activity: Rats were anaesthetized with sodium thiopental (Pentothal, 80-100 mg kg^{-1}, i.p.), then intubated 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^{-1} of room air as described previously[29]. A polyethylene catheter was inserted into the jugular vein for drug administration. Changes in airway resistance (mmHg) were measured by a pressure transducer (MLT-1199) connected to a side arm of the tracheal cannula and recorded by Power Lab 4/25 with running chart software via a Quad bridge amplifier (AD Instruments, Bella Vista, NSW, Australia). Broncho constriction was induced with CCh (100 µg kg^{-1}), which was reversed within 7-10 min. The test drug was given to the animals 5-8 min prior to administration of CCh. The responses were expressed as reduction (%) of the CCh-induced bronchospasm.

In vitro experiments

Effect on rabbit jejunum: Rabbits were sacrificed by cervical dislocation and the abdomen was cut open and the jejunum was dissected out as described previously[30]. Jejunal preparations of 2-3 cm in length were mounted in 10 mL tissue baths containing Tyrode's solution maintained at 37°C and aerated with a mixture of 5% carbon dioxide and 95% oxygen (carbogen). The composition of Tyrode's solution (mM) was: KCl 2.68, NaCl 136.9, $MgCl_2$ 1.05, $NaHCO_3$ 11.90, NaH_2PO_4 0.42, $CaCl_2$ 1.8 and glucose 5.55 (pH 7.4). A pre load of 1 g was applied to each tissue and the contractile responses were recorded using an isotonic transducer (50-6360, Harvard Apparatus, Holliston, MA, USA) coupled with a Power Lab (ML-845) data acquisition system (AD Instruments; Sydney, Australia) and a computer using chart software (version 5.3). The tissues were allowed to equilibrate for a period of 30 min and then stabilized with a sub-maximal concentration of acetylcholine (ACh, 0.3 µM). The tissues were presumed stable only after the reproducibility of the said responses. The test material was examined later for any gut relaxant effect on spontaneous contractions of jejunal preparations. To assess the involvement of a K^+-channel opening (KCO) effect[31], phosphodiesterase (PDE)-inhibitory[32] and Ca^{++} antagonist-like mechanisms[33], the antispasmodic effect of the plant extract was tested on low K^+ (25 mM), CCh (1 µM) and high K^+ (80 mM)-induced contractions, respectively, in isolated jejunal preparations. Following a sustained contraction in response to K^+ and CCh, the test material was added in a cumulative fashion, to obtain concentration-dependent inhibitory responses. The relaxation of the tissue preparation was expressed as percentage of the control contraction as mediated by the added spasmogen.

To further characterize the type of K^+-channels involved in the antispasmodic effect, the inhibitory effect of the plant extract was reproduced in preparations pretreated with selective antagonists of the K^+-channels, such as glibenclamide (an ATP-dependent K^+-channel antagonist[34]), 4-aminopyridine (a voltage-dependent blocker of K^+-channels)[35] and TEA (a non-specific K^+-channel blocker)[36]. The PDE-inhibitory effect was studied indirectly through constructing isoprenaline-induced inhibitory CRCs against CCh-induced contractions in the absence and presence of the test substance, as PDE-inhibitors are known to potentiate the effect of isoprenaline[37, 38].

Effect on guinea-pig tracheal preparations: Tracheas were dissected out of guinea-pigs after cervical dislocation of the animals and kept in Kreb's solution. The tracheal tube was cut into rings, 2-3 mm wide, each containing about two cartilages[39]. Each ring was opened by a longitudinal cut on the ventral side opposite to the smooth muscle layer, forming a tracheal strip with a central part of smooth muscle in between the cartilaginous portions on the edges. The preparation was then mounted in a 20 mL tissue bath containing Kreb's solution, maintained at 37°C and aerated with carbogen. The

composition of Kreb'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 strips and was kept constant throughout the experiment. The tissue was equilibrated for 1 h before the addition of any drug. CCh (1µM), low K^+ (25 mM) and high K^+ (80 mM) were used to stabilize the respective preparations until constant responses of each agonist were achieved (usually after 3-4 concentrations). Then sustained contractions were obtained and the relaxant effect of the test substance was assessed by adding it in a cumulative fashion. Isometric responses were recorded using an isometric transducer (50-7996, Harvard Apparatus, Holliston, MA, USA), attached to the setup as described for the intestinal preparations.

To study the bronchodilatory effect of the test material and its further mechanism(s), the method detailed in the section on the isolated jejunum was followed.

Statistical analysis: The data expressed are Mean±Standard error of mean (SEM, n = number of experiments) and the median effective concentrations (EC_{50} values) with 95% confidence intervals (CI). The concentration-response curves (CRCs) were analyzed by non-linear regression. The Chi-square-test was applied to assess the antidiarrheal effect, while one-way analysis of variance (ANOVA) followed by Dunnett's test was used to assess the bronchodilator activity. All the graphs, calculations and statistical analysis were performed using GraphPad Prism 4 for Windows (GraphPad Software, San Diego, California, USA).

RESULTS

In vivo findings

Effect on castor oil-induced diarrhea in mice: In our experimental settings, Al.Pericarp showed a dose-dependent antidiarrheal effect in terms of protection (%) against castor oil-induced diarrhea. All animals in the castor oil-treated group showed diarrhea. Animal groups pretreated with Al.Pericarp showed 40 and 80% protection from diarrhea at respective doses of 100 and 300 mg kg^{-1}, while the group pretreated with loperamide (10 mg kg^{-1}) exhibited 100% protection. Further details are presented in Table 1.

Effect on carbachol-induced bronchospasm: Al.Pericarp (3-30 mg kg^{-1}) caused a dose-dependent protection against the CCh (100 µg kg^{-1})-induced increase in respiratory pressure of anaesthetized rats, similar to aminophylline (Fig. 1).

Table 1: Antidiarrheal effect of the hydro-alcoholic extract of the pericarp of *A. lebbeck* (Al.Pericarp) in mice with castor oil (10 mL kg^{-1})-induced diarrhea

Treatment (p.o.), dose (mg kg^{-1})	No. of mice out of five with diarrhea	Protection (%)
Saline (10 mL kg^{-1})+castor oil	5/5	0
Al.Pericarp+castor oil		
100+10	3[a]/5	40
300+10	1[a]/5	80
Loperamide+castor oil	0[b]/5	100

[a]p<0.05 and [b]p<0.01vs. Saline+castor oil treated group (c^2-test)

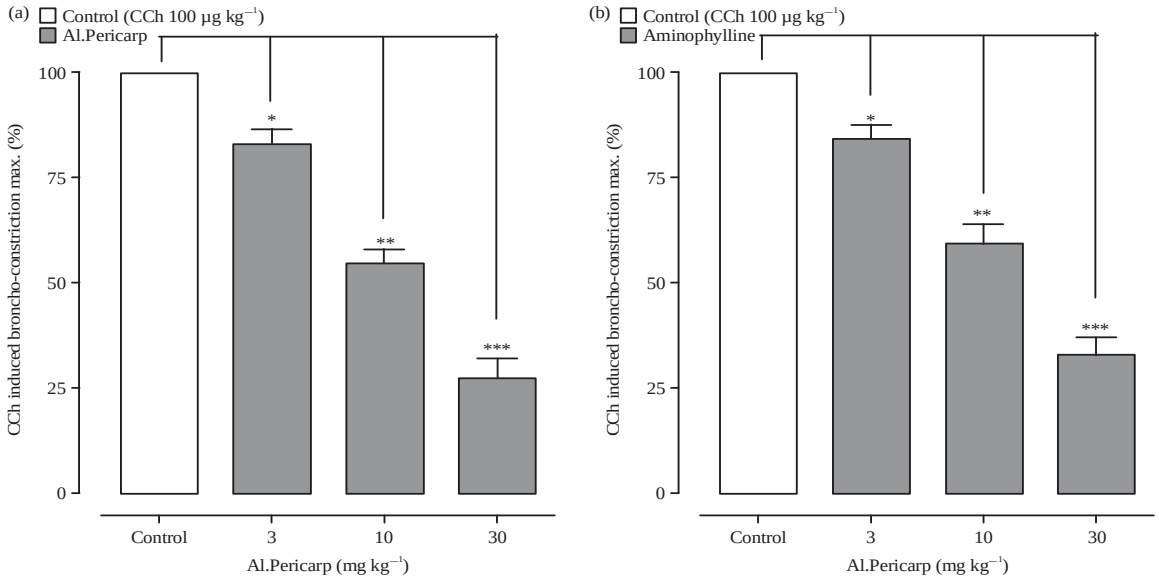

Fig. 1(a-b): Dose-dependent suppressant effect of the (a) Crude extract of pericarp of *A. lebbeck* (Al.Pericarp) and (b) Aminophylline on carbachol (CCh, 100 µg kg^{-1})-induced broncho-constriction in anaesthetized rats. Values shown are Mean±SEM from 4-5 determinations

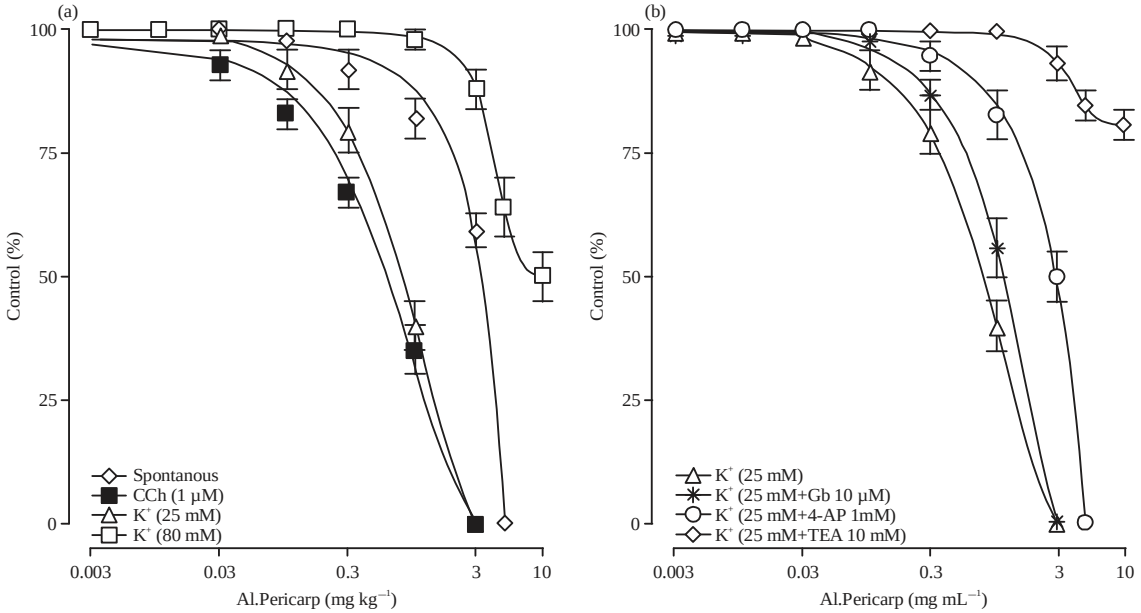

Fig. 2(a-b): Dose-dependent inhibitory effect of the crude extract of pericarp of *A. lebbeck* (Al.Pericarp) on (a) Spontaneous, CCh (1 µM), low K^+ (25 mM) and high K^+ (80 mM)-induced contractions and (b) Against low K^+-induced contractions in the absence and presence of glibenclamide (Gb 10 µM), 4-aminopyridine (4-AP 1 mM) and tetraethyl ammonium (TEA 10 mM), in isolated rabbit jejunum preparations. Symbols represent Mean±SEM, n = 4-5

In vitro findings

Effect on rabbit jejunum: Al.Pericarp caused a dose-dependent inhibition of spontaneous, CCh (1 µM) and low K^+ (25 mM)-induced contractions of isolated rabbit jejunum preparations, with respective EC_{50} values of 3.12 (2.98-3.27, n = 5), 0.54 (0.48-0.59, n = 5) and 0.74 mg mL^{-1} (0.68-0.78, n = 5), whereas a partial inhibitory effect was observed against high K^+ (80 mM) at rather larger doses as shown in Fig. 2. When tested in tissues pre-treated with Gb (10 µM), 4-AP (1 mM) or TEA (10 mM), the inhibitory effect of Al.Pericarp against low K^+ was significantly reduced ($p>0.05$) in the presence of TEA, whereas glibenclamide and 4-AP did not show any significant ($p>0.05$) effect. Pre-treatment of jejunal preparations with Al.Pericarp shifted the isoprenaline-induced inhibitory CRCs to the left in a concentration-dependent manner (0.03 and 0.1 mg mL^{-1}), similar to that caused by papaverine (1 and 3 µM) as shown in Fig. 3, thus exhibiting a potentiating effect.

Effect on guinea-pig trachea: When tested on guinea-pig tracheal strips, Al.Pericarp caused complete relaxation of CCh and low K^+ (25 mM)-induced contractions by showing comparable potencies, with respective EC_{50} values of 0.40 (0.33-0.46, n = 4) and 0.64 mg mL^{-1} (0.54-0.68, n = 4), whereas it was less potent against high K^+ showing only a partial effect (Fig. 4). The tracheal strips were pretreated with Gb (10 µM), 4-AP (1 mM) or TEA (10 mM) to assess the type of K^+ channels involved. The inhibitory effect of Al.Pericarp against low K^+ was significantly reduced ($p<0.05$) in the presence of TEA, whereas Gb and 4-AP did not show any ($p>0.05$) effect on the action of Al.Pericarp. Pretreatment of tracheal preparations with Al.Pericarp shifted the isoprenaline-induced inhibitory CRCs to the left in a concentration-dependent manner (0.03 and 0.1 mg mL^{-1}), similar to that caused by papaverine (1.0 and 3.0 µM) as shown in Fig. 5, thus exhibiting a potentiating effect.

DISCUSSION

In castor oil-induced diarrhea in mice, Al.Pericarp caused protection, similar to loperamide, a known antidiarrheal agent[40]. When studied for its bronchodilator activity, the plant extract caused a dose-dependent protection against CCh-induced broncho constriction in anesthetized rats, similar to the aminophylline[41]. In isolated rabbit jejunal preparations, Al.Pericarp used a dose-dependent inhibition of spontaneous contractions thus showing antispasmodic effect. Castor oil is known to increase intestinal fluids and causes diarrhea indirectly through the formation of ricinoleic acid, which ultimately alters the electrolyte and water transport and

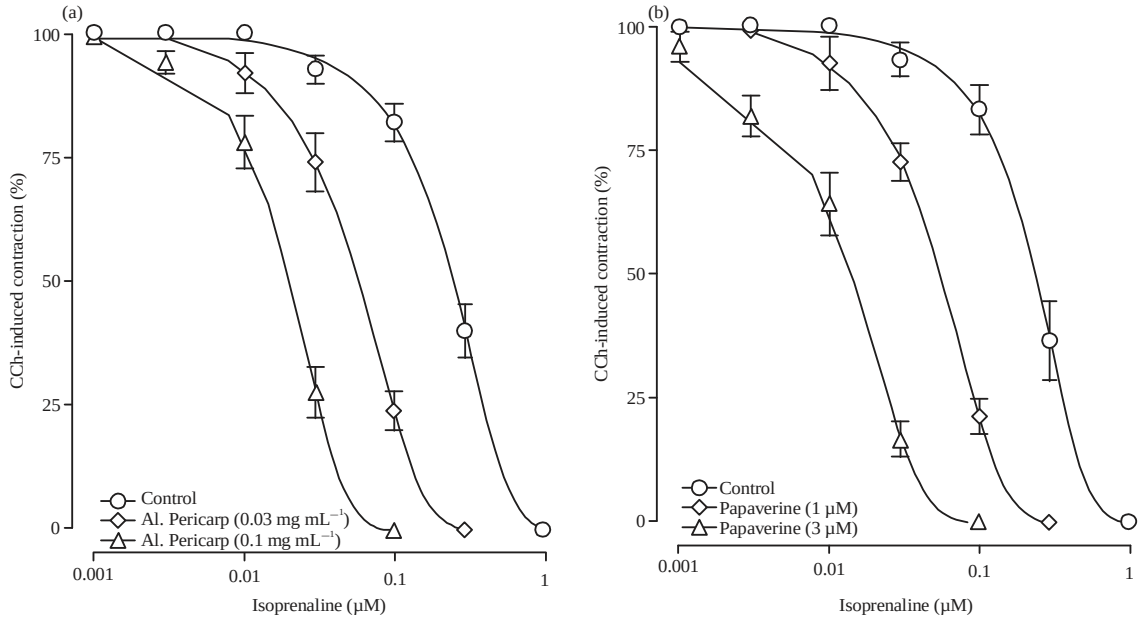

Fig. 3(a-b): Inhibitory concentration response curves (CRCs) of isoprenaline against carbachol (CCh)-induced contractions in the absence and presence of different concentrations of (a) crude extract of pericarp of *A. lebbeck* (Al.Pericarp) and (b) papaverine, in isolated rabbit jejunum preparations. Values shown are Mean±SEM from 4-5 determinations

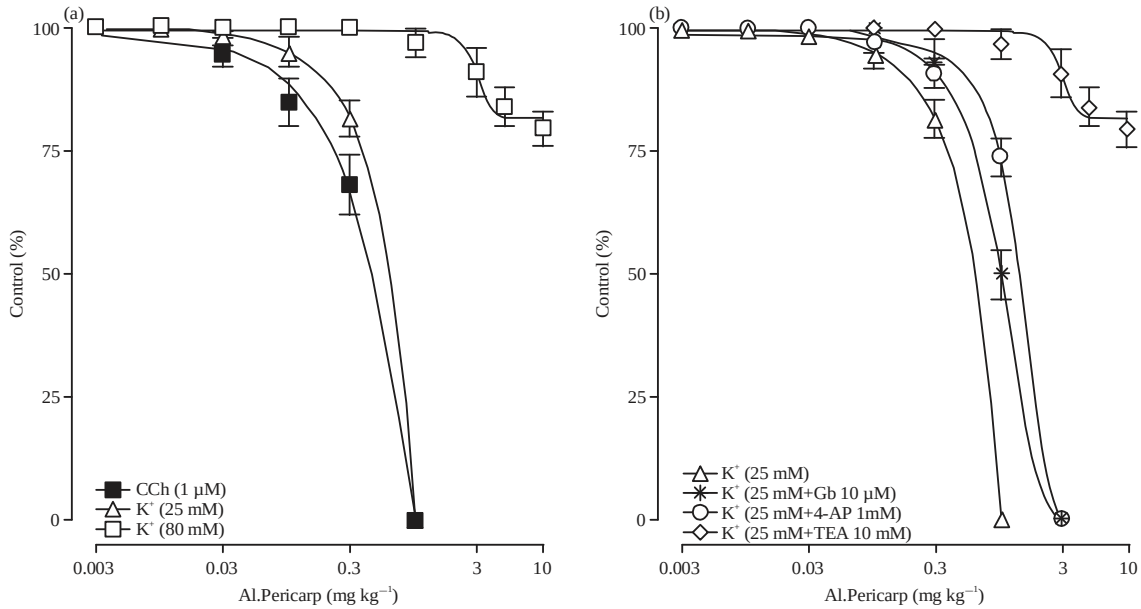

Fig. 4(a-b): Dose-dependent inhibitory effects of the crude extract of pericarp of *A. lebbeck* (Al.Pericarp) on (a) CCh (1 µM), low K^+ (25 mM) and high K^+ (80 mM)-induced contractions and (b) Against low K^+-induced contractions in the absence and presence of glibenclamide (Gb 10 µM), 4-aminopyridine (4-AP 1 mM) and tetraethylammonium (TEA 10 mM), in isolated guinea-pig tracheal preparations. Values shown are Mean±SEM from 4-5 determinations

elicits excitations in the transverse and distal segments of the colon[42,43]. The observed antidiarrheal and bronchodilator effects of the Al.Pericarp appear to be mediated through the presence of antispasmodic components in *Albizia lebbeck*.

To explore the possible underlying mechanism(s) of its antidiarrheal effect, the plant extract was studied on isolated jejunal preparations from rabbits, while isolated guinea-pig tracheal preparations were used to explore possible

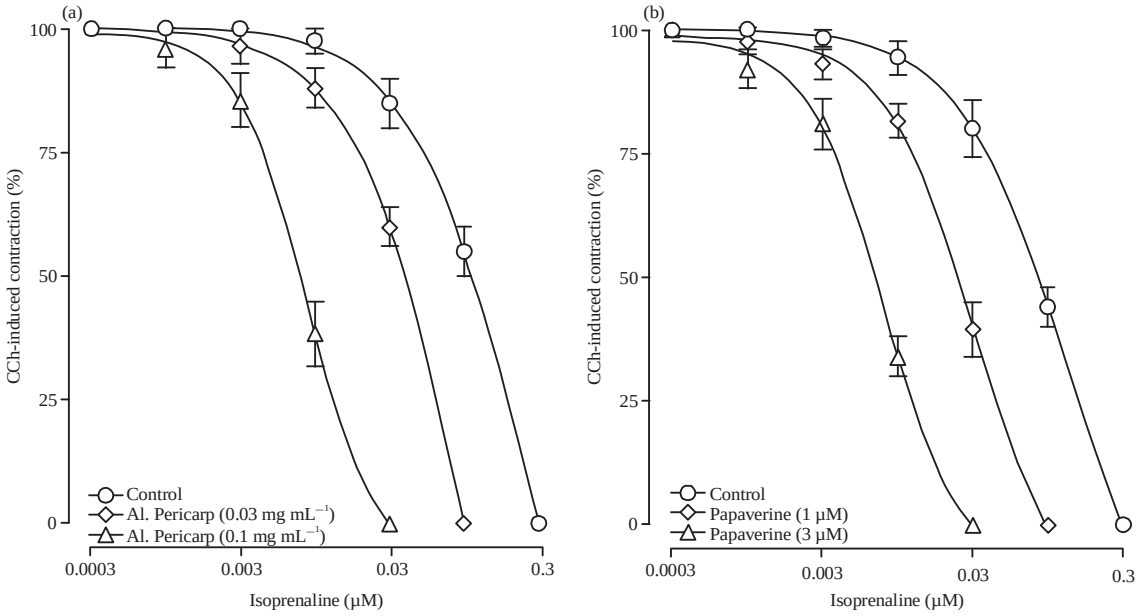

Fig. 5(a-b): Inhibitory CRCs of isoprenaline against carbachol (CCh)-induced contractions in the absence and presence of different concentrations of (a) Crude extract of pericarp of *A. lebbeck* (Al.Pericarp) and (b) Papaverine, in isolated guinea-pig tracheal preparations. Values shown are Mean±SEM from 4-5 determinations

mechanism for its bronchodilator effect. In our earlier studies, it observed that the spasmolytic effect of medicinal plants is usually mediated through K^+-channel opening[31,44], phosphodiesterase-inhibitory[45,46] or Ca^{++} channel blocking[39,46] effects. To assess whether the spasmolytic effects of Al.Pericarp was also mediated via similar mechanism(s), it was tested on CCh (1 μM), low K^+ (25 mM) and high K^+ (80 mM)-induced contractions. Interestingly, the plant extract showed higher potency with complete inhibition of the contractions induced by CCh and low K^+, in contrast to high K^+-induced contractions, where only weak effects were observed, even at very high doses. The selective inhibitory response of the test material against low K^+ indicates the presence of K^+ channel opener (KCO)-like spasmolytic activity. To confirm the KCO activity and the nature of K^+ channels involved as one of the antispasmodic mechanisms in Al.Pericarp, the inhibitory CRCs of the plant against low K^+ were reconstructed in the presence of specific blockers of K^+ channels, namely Gb (a blocker of ATP-dependent K^+-channels, K_{ATP})[34], 4-AP (a blocker of voltage-dependent K^+-channels, K_v)[35] and TEA (a non-specific K^+-channel blocker[36]). Interestingly, the inhibitory effects of the plant extract on low K^+ induced contractions was inhibited in the presence of TEA, while Gb and 4-AP had no effect, which indicates that the antispasmodic effects of the plant was solely mediated through the activation of non-specific K^+ channels. The plant extract also inhibited CCh-induced contractions in isolated jejunal preparations, which indicates the involvement of the additional antispasmodic mechanism of PDE-inhibition, as PDE-inhibitors are also known to inhibit CCh-induced contractions in smooth muscles[47]. Application of CCh to smooth muscles of gut preparation was known to cause contraction by stimulating phosphatidylinositol 4,5-bisphosphate (PIP_2) hydrolysis, inositol 1,4,5-trisphosphate (IP_3) production and phosphatidic acid (PA) formation, while addition of isoprenaline produces an increase in cyclic adenosine monophosphate (cAMP) levels in smooth muscles of tissues pre-contracted with CCh, thus causing a sequential attenuation of PIP_2-hydrolysis, IP_3-production and PA formation, which consequently leads to relaxation[48]. Hence, a substance that causes potentiation of the inhibitory effect of isoprenaline, possibly by augmenting the increase in cAMP initially achieved by isoprenaline, could be speculated to possess PDE-inhibitory activity, as PDE-inhibitors are known to enhance tissue cAMP levels, though through a different mechanism[49]. To see, whether the inhibitory effect of the plant extract against CCh-induced contractions in rabbit jejunum involves a PDE-inhibitory-like effect, the inhibitory CRCs of isoprenaline were constructed in the absence and presence of low doses of the extract (0.03 and 0.1 mg mL^{-1}), which shifted the inhibitory curves of isoprenaline to the left, thus showing potentiation, similar to papaverine, indicating a papaverine-like PDE-inhibitory activity[50].

The bronchodilatory effect of the plant extract seen in anesthetized rats was further tested for its mechanism(s) in

isolated tracheal preparations of guinea-pig. The mechanism(s) observed in the bronchodilatory effects were similar to that observed earlier in jejunum, thus showing the involvement of non-specific K^+-channels, in addition to PDE-inhibition.

CONCLUSION

In the *in vivo* antidiarrheal and bronchodilator animal models, the aqueous-alcoholic crude extract of *A. lebbeck* pericarp showed dose-dependent antidiarrheal and bronchodilator actions. The *in vitro* experiments on isolated gut and tracheal preparations showed that the antispasmodic and bronchodilator actions of the plants extract were mediated through a combination of K^+ channel opening and phosphodiesterase inhibition, which may explain the possible underlying mechanisms for its antidiarrheal and anti-asthmatic use.

This study provides a sound pharmacological basis for the medicinal use of *A. lebbeck* in hyperactive gut and airways disorders, due to its multi-targeted actions. Furthermore, this study recommends Al.Pericarp as a strong candidate for further clinical studies.

SIGNIFICANCE STATEMENT

This study discovers underlying mechanisms for the therapeutic potential of a famous medicinal plant, *Albizia lebbeck* for its antidiarrheal, antispasmodic and bronchodilator activities, acting through multiple target sites thus making it effective and safe remedy for diarrhea and asthma. Currently available drugs are not only costly but also exhibit multiple side-effects and this study will help the researchers to design clinical studies for development of plant extracts usable for such diseases.

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