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## Protective effect of *Polyalthia longifolia* var. pendula leaves on ethanol and ethanol/HCl induced ulcer in rats and its antimicrobial potency

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## ABSTRACT

**Objective:** To explore antiulcer and antimicrobial properties of methanolic extract of *Polyalthia longifolia* var. pendula. **Methods:** Gastroprotective potential of *Polyalthia longifolia* was studied on ethanol and ethanol/HCl induced ulcers at 2 different doses (270 and 540 mg/kg/body weight). Antimicrobial efficacy of *Polyalthia longifolia* (25 mg/mL) was also studied against six gram positive, seven gram negative bacteria and five fungi by agar well diffusion method. Minimum inhibitory concentration was determined by agar well diffusion method in two fold serial dilution, in the range of 97–25 000  $\mu$ g/mL. **Results:** The reduction of ulcer index in *Polyalthia longifolia* treated animals was found to be statistically significant with respect to control animals. The *Polyalthia longifolia* exhibited ulcer protection activity in dose dependent manner and was also better than the standard. In antimicrobial activity, gram positive bacteria were more susceptible to *Polyalthia longifolia* than gram negative bacteria and fungal strains. **Conclusions:** Results obtained confirm the antiulcer and antimicrobial potential of the *Polyalthia longifolia*.

### 1. Introduction

Gastric hyperacidity and gastroduodenal ulcer is a very common global problem today<sup>[1]</sup>. The pathophysiology of these disorders has focused on an imbalance between aggressive and protective factors in the stomach, such as acid–pepsin secretion, mucosal barrier, mucus secretion, blood flow, cellular regeneration, prostaglandins and epidermal growth factors<sup>[2]</sup>. The current medicinal treatment of peptic ulcer is generally based on the inhibition of gastric acid secretion by histamine H<sub>2</sub>– antagonists, proton pump inhibitors, and antimuscarinics, as well as on acid–independent therapy provided by sucralfate and bismuth cholinergics<sup>[3]</sup>. However, the majority of these drugs produce adverse reactions, such as hypersensitivity, arrhythmia, impotence, gynecomastia and hematopoietic changes<sup>[4]</sup>.

The rise in gastric acidity and peptic activity are usually a manifestation of physiological disturbance affecting one or more mechanisms which normally regulate gastric secretion. Activity of the gastric secretory cells has been found to be stimulated by alcohol, hydrochloric acid, caffeine, sodium chloride, non–steroidal anti–inflammatory drugs

(NSAIDs) and stress. Even the normal rate of acid secretion may cause ulceration in the breached mucosa when some gastroprotective factors are lost<sup>[5]</sup>. There are many drugs for the treatment of gastric ulcers but most of the drugs produce several adverse reactions. Plant extracts are among the most attractive sources for developing new drugs and have shown promising results in the treatment of gastric ulcers<sup>[6]</sup>.

Infectious diseases remain an important cause of morbidity and mortality in developing and developed nations. They account for approximately one half of all deaths in tropical countries of which bacterial infections are the most prevalent<sup>[7]</sup>. The increase in prevalence of multiple drug resistance has slowed down the development of new synthetic antimicrobial drugs, and has necessitated the search for new antimicrobials from alternative sources. In general, bacteria have the genetic ability to transmit and acquire resistance to drugs used as therapeutic agents. One way to prevent antibiotic resistance is by using new compounds which are not based on the existing synthetic antimicrobial agents<sup>[8]</sup>.

There is growing interest in correlating the phytochemical constituents of a medicinal plant with its pharmacological activity<sup>[9,10]</sup>. Screening active compounds from plants has led to the discovery of new medicinal drugs which have efficient protection and treatment roles against various diseases, including cancer<sup>[11]</sup> and Alzheimer's disease<sup>[12]</sup>. There is therefore a need for continuous search for new, effective and affordable antimicrobial agents<sup>[13]</sup>. Our aim of the present study is to access the possible antiulcer and antimicrobial activities of methanolic extract of *Polyalthia*

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*longifolia*.

In traditional medicine, various herbal preparations are used for the treatment of ulcers<sup>[14]</sup>. *Polyalthia longifolia* belongs to family Annonaceae is a tall evergreen tree and cultivated all over India. The plant has been used in traditional system of medicine for the treatment of fever, skin diseases, diabetes, hypertension and helminthiasis<sup>[15]</sup>. The plant extracts and various isolated compounds were studied for biological activities like antibacterial activity, cytotoxicity, antifungal activity, acute toxicity, anti-inflammatory and hepatoprotective potency<sup>[16–23]</sup>. In the present study, effort has been made to establish the scientific validity of antimicrobial and antiulcer properties of methanolic extract of *Polyalthia longifolia* leaves.

## 2. Materials and methods

### 2.1. Plant material

The leaves of *Polyalthia longifolia* var. *pendula* were collected locally at Rajkot, Gujarat, India in the month of August, 2009. The plant was compared with voucher specimen (voucher specimen No. PSN4) deposited by Dr. Nagar PS, at Department of Biosciences, Saurashtra University, Rajkot, Gujarat, India.

### 2.2. Preparation of extract

The leaves were thoroughly washed under running tap water and shade dried. The dried leaves were homogenized to fine powder and stored in air tight bottles. The dried powder was first defatted by hexane and then extracted in methanol by cold percolation method<sup>[24]</sup>. The solvent was evaporated to dryness and the dried crude extract was stored in air tight bottle at 4 °C.

### 2.3. Antiulcer activity

#### 2.3.1. Experimental animals

Wistar albino rats of both sexes were obtained from the animal house of Sun Pharmaceutical Industries Ltd, Vadodara. Animal colonies were maintained at Department of Biosciences, Saurashtra University, Rajkot. Animals were fed with commercial rat and mice food supplied by Pranav Agro Industries Ltd., Amrut Brand, Vadodara and water *ad libitum*. They were maintained in a 12 h light/dark cycle at (25±2) °C. The study was approved by CPCSEA approved local ethical committee.

#### 2.3.2. Experimental design

Wistar albino rats weighing between 200 and 250 g of either sex were used for anti ulcer study. All animals were divided into 4 groups of 6 animals (3 males and 3 females). Fresh drug solutions were prepared in sterile distilled water at the time of administration. Before the experiments, animals were deprived of food but allowed free access to water.

#### 2.3.3. Group designing for ethanol and ethanol/HCl induced ulcer models

Group I (Control): Animals received only distilled water before the ulcerogenic procedure; Group II (PAM 270): Animals received *Polyalthia longifolia* (270 mg/kg, *p. o.*) 1 h before the ulcerogenic procedure; Group III (PAM 540):

Animals received *Polyalthia longifolia* (540 mg/kg, *p. o.*) 1 h before the ulcerogenic procedure; Group IV (Standard): Animals received omeprazole (30 mg/kg, *p. o.*)/ranitidine (100 mg/kg, *p. o.*) 1 h before the ulcerogenic procedure.

### 2.3.4. Ethanol-induced gastric ulcer and ethanol/HCl-induced gastric ulcer

The experiment was performed according to the method of Brzozowski *et al*<sup>[25]</sup> and the method of Mizui and Dotuchi<sup>[26]</sup> with slight modifications. Albino rats were divided into four groups of six (3 males and 3 females) animals each. Rats were fasted for 36 h before administration of absolute ethanol (1.0 mL) or a mixture of 70% alcohol + 5% HCl (1 : 1) (1.5 mL) as ulcerogenic agent. The leaf extract (270 mg/kg, 540 mg/kg, *p. o.*) and omeprazole (30 mg/kg, *p. o.*) or ranitidine (100 mg/kg, *p. o.*), as standard drug, was administered 1h before ethanol administration and 4 h after ethanol/HCl administration. One hour after ethanol administration, animals were sacrificed. The stomach was removed, cut opened along the greater curvature, washed with normal saline and observed for the severity of the ulcers. The pH and volume of gastric juice was measured after centrifugation at 2 000 rpm for 10 min. From the supernatant, aliquots were taken for the determination of total and free acidity. The percentage inhibition of reduction/protection was calculated using the following formula:

$$\% I = (UI \text{ of control} - UI \text{ of test}) \times 100 / UI \text{ of the control}$$

Where, I = Inhibition, UI = Ulcer index.

#### 2.3.5. Ulcer indexing

The mucosal layer of the stomach was observed under a magnifying lens and was checked for ulcers. The area (mm<sup>2</sup>) of all lesions was measured using digital calipers to derive a gastric damage score consisting of the total area of ulceration. The ulcer index<sup>[27]</sup> was calculated using the following formula:

$$UI = 10/X$$

Where, UI = Ulcer index, X = total area of stomach mucosa / total ulcerated area.

#### 2.3.6. Determination of total acidity and free acidity<sup>[28]</sup>

1.0 mL of gastric juice was taken in a 50 mL conical flask. Two drops of phenolphthalein indicator for total acidity determination and Topfer's reagent for free acidity determination was added to it. It was titrated with 0.01 N NaOH until a permanent pink color (total acidity determination) or canary yellow color (free acidity determination) was observed. The volume of 0.01 N NaOH consumed was noted. The total/free acidity is expressed as meq./L by the following formula:

$$\text{Total/free acidity} = n \times 0.01 \times 36.45 \times 1\ 000$$

Where, n is volume of NaOH consumed, 0.01 is normality of NaOH, 36.45 is molecular weight of NaOH, 1 000 is the factor (to be represented in litre).

## 2.4. Antimicrobial activity

### 2.4.1. Microbial strains

Tested microbial strains are listed in Table 2. All bacterial

strains were obtained from National Chemical Laboratory (NCL), Pune, India. The bacteria were grown in the nutrient broth and maintained on nutrient agar slants at 4 °C while fungal strains were grown in Sabouraud dextrose broth and maintained on MGYP slants also at 4 °C. The microorganisms studied are clinically important ones causing several infections, food born diseases, spoilages, skin infection and it is essential to overcome them through some active therapeutic agents.

#### 2.4.2. Antimicrobial assay

A loop full of strain was inoculated in 25 mL of nutrient broth/Sabouraud dextrose broth in a conical flask and incubated at room temperature on a rotary shaker over

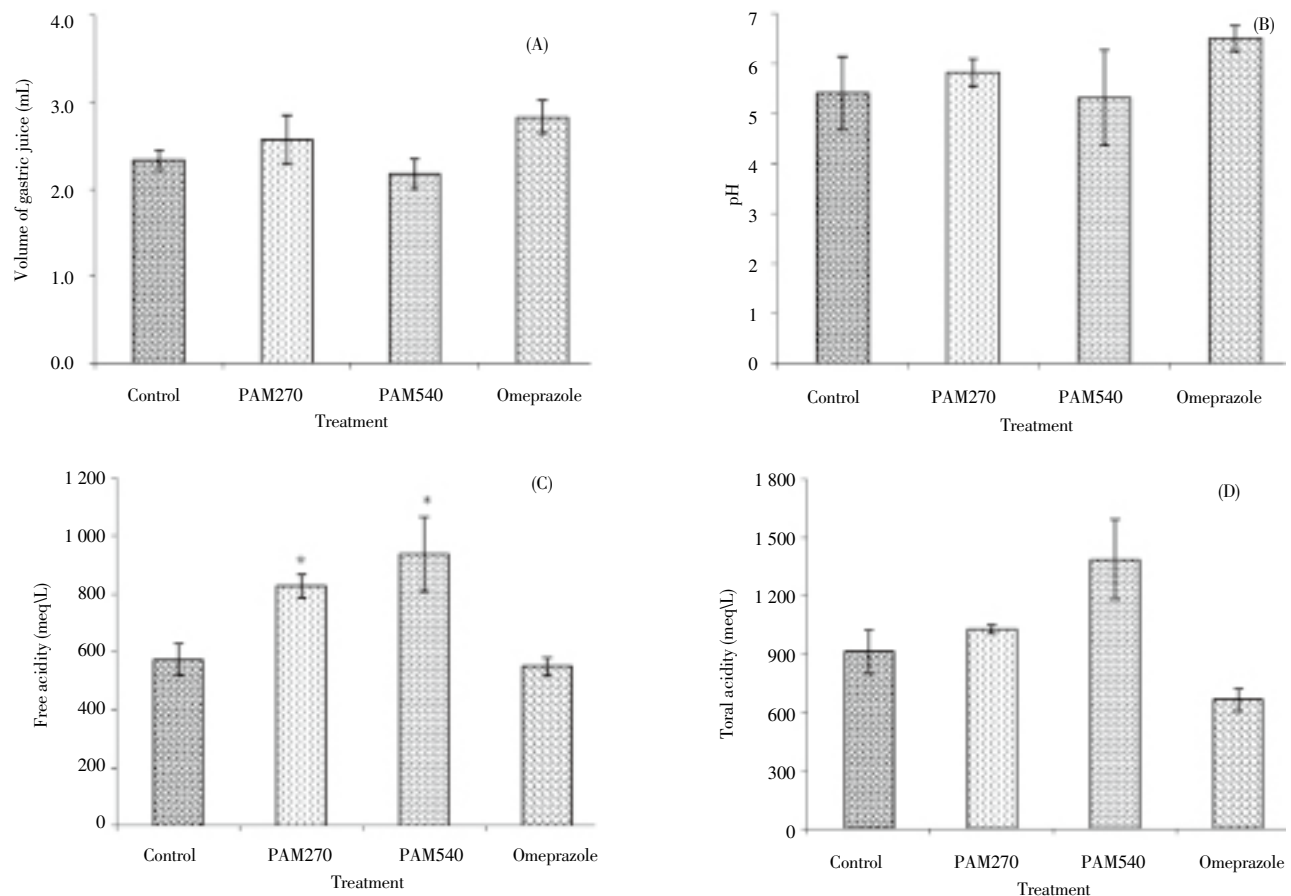
night to activate the test microbial strains. The inoculum's size was  $1 \times 10^8$  cells/mL. Muller Hinton No. 2/ Sabouraud dextrose agar (Hi-media) was used for the antibacterial and antifungal susceptibility test, respectively. The antimicrobial activity was tested against all the microorganisms by agar well diffusion method<sup>[29,30]</sup>. The methanolic extract was dissolved in dimethyl sulfoxide (DMSO) at a concentration of 25 mg/mL and 0.1 mL was used for the study. DMSO was used as the negative control. The plates were incubated at 37/28 °C for 24/48 h for bacteria and fungi, respectively. After incubation period the antimicrobial activity was evaluated by measuring the inhibition zones. The experiment was performed three times to minimize the error and the mean values  $\pm$  SEM are presented.

**Table 1**

Effect of *Polyalthia longifolia* and omeprazole/ranitidine on gastric lesions induced by ethanol and ethanol/HCl.

Model	Group	Treatment	Dose (mg/kg body weight)	Ulcer index	% Inhibition
Ethanol	I	Ethanol	–	1.11 $\pm$ 0.15	–
	II	<i>Polyalthia longifolia</i>	270	0.36 $\pm$ 0.05*	67.56
	III	<i>Polyalthia longifolia</i>	540	0.16 $\pm$ 0.04*	85.58
	IV	Omeprazole	30	0.31 $\pm$ 0.07*	72.07
Ethanol/HCl	I	Ethanol/HCl	–	4.08 $\pm$ 1.27	–
	II	<i>Polyalthia longifolia</i>	270	1.59 $\pm$ 0.25	61.02
	III	<i>Polyalthia longifolia</i>	540	0.31 $\pm$ 0.09*	92.40
	IV	Ranitidine	100	2.03 $\pm$ 0.57	50.24

Values are mean  $\pm$  SEM from six rats in each group; \*As compared with control,  $P < 0.05$  (Student's  $t$ -test).

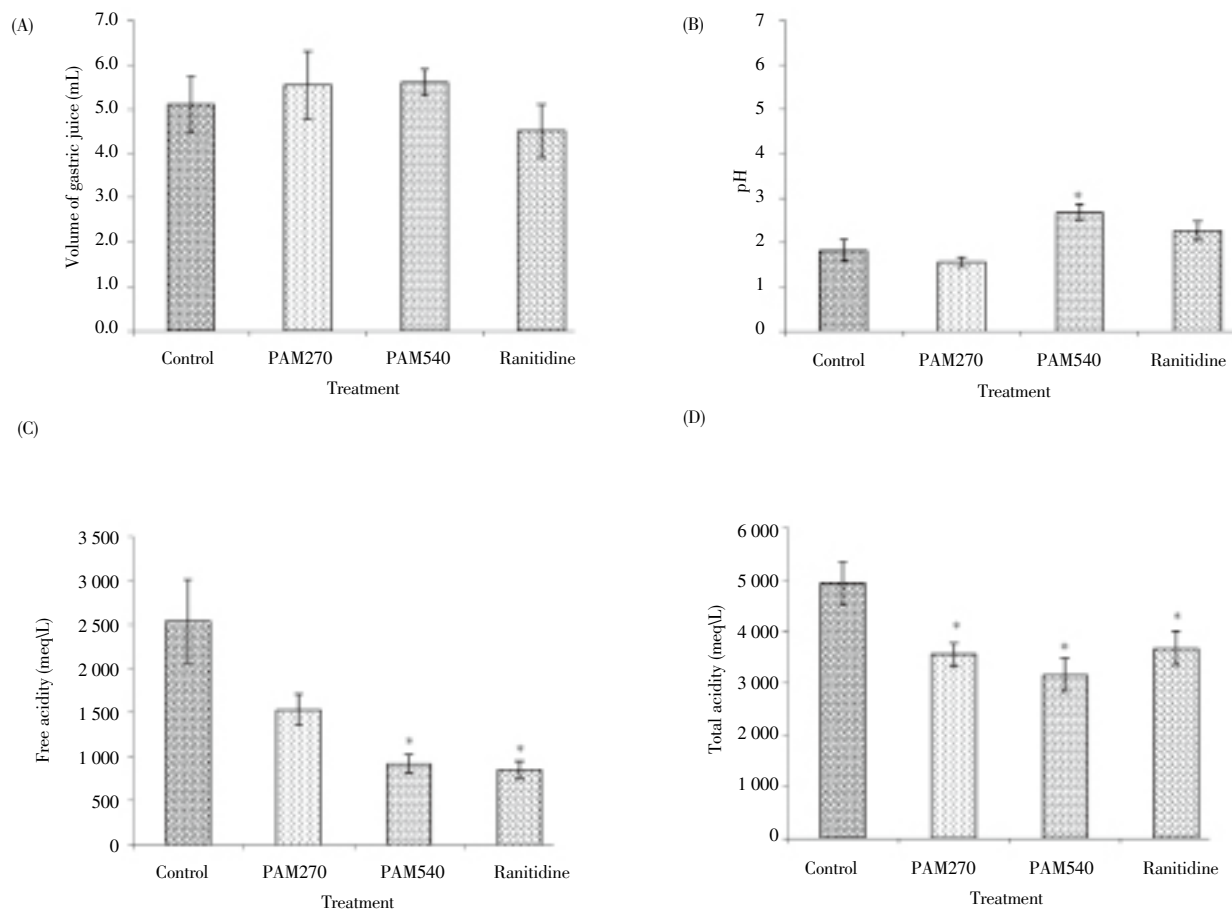


**Figure 1.** Effect of *Polyalthia longifolia* and omeprazole on gastric secretion collected from rats induced by ethanol.

(A) volume of gastric juice; (B) pH; (C) free acidity and (D) total acidity. Values are mean  $\pm$  SEM ( $n=6$ ); \*As compared with control,  $P < 0.05$  (Student's  $t$ -test).

**Table 2**Inhibition zone and MIC value of *Polyalthia longifolia*.

	Microorganisms	Zone of inhibition (mm)*	MIC value ( $\mu$ g/mL)
Gram positive	<i>Staphylococcus aureus</i> ATCC25923	10.50 $\pm$ 0.29	3,125
	<i>Staphylococcus epidermidis</i> ATCC12228	–	NA
	<i>Staphylococcus subflava</i> NCIM2178	13.00 $\pm$ 0.00	390
	<i>Bacillus megaterium</i> ATCC9885	20.00 $\pm$ 0.58	1 562
	<i>Bacillus subtilis</i> ATCC6633	18.50 $\pm$ 0.29	390
	<i>Corynebacterium rubrum</i> ATCC14898	17.00 $\pm$ 0.00	3 125
Gram negative	<i>Proteus morgani</i> NCIM2040	10.50 $\pm$ 0.29	6 250
	<i>Proteus mirabilis</i> NCIM2241	14.00 $\pm$ 0.00	781
	<i>Klebsiella pneumoniae</i> NCIM2719	9.50 $\pm$ 0.00	390
	<i>Pseudomonas testosterone</i> NCIM5098	–	NA
	<i>Citrobacter freundii</i> ATCC10787	9.00 $\pm$ 0.00	25 000
	<i>Enterobacter aerogenes</i> ATCC13048	–	NA
	<i>Salmonella typhimurium</i> ATCC23564	–	NA
Fungi	<i>Candida albicans</i> ATCC2091	12.00 $\pm$ 0.00	3 125
	<i>Candida tropicalis</i> ATCC4563	12.50 $\pm$ 0.29	3 125
	<i>Candida glabrata</i> NCIM3448	–	NA
	<i>Candida neoformans</i> NCIM3542	–	NA
	<i>Cryptococcus luteolus</i> ATCC32044	–	NA

\* Values are expressed as mean  $\pm$  SEM; –: No inhibition; NA: Not applicable.**Figure 2.** Effect of *Polyalthia longifolia* and ranitidine on gastric secretion collected from rats induced by ethanol/HCl.(A) volume of gastric juice; (B) pH; (C) free acidity and (D) total acidity. Values are mean  $\pm$  SEM ( $n=6$ ); \*As compared with control,  $P < 0.05$  (Student's  $t$ -test).

### 2.4.3. Determination of minimum inhibitory concentration (MIC)

The end point MIC is the lowest concentration of compound at which the microorganisms tested does not demonstrate visible growth. The broth tube dilution method utilizes relatively large amounts of test agent and is not suitable for high throughput screening. Therefore, agar well diffusion method was used in the present study<sup>[31]</sup> to determine MIC of methanol extract of *Polyalthia longifolia* in which two– fold serial dilution was prepared in the range of 97–25 000  $\mu$ g/mL.

## 3. Results

### 3.1. Antiulcer activity

#### 3.1.1. Ethanol induced gastric ulcer

In the present study, *Polyalthia longifolia* was evaluated for its anti–ulcer activity against ethanol induced gastric ulcer in rats. The results were shown in Table 1. Oral administration of ethanol produced severe ulceration. *Polyalthia longifolia* as well as standard drug Omeprazole significantly reduced the incidence and severity of ulceration in ethanol induced ulcer model (Table 1). *Polyalthia longifolia* and standard drug Omeprazole showed a significant change in ulcer index and total acidity as compared to the control group, while pH, total acidity and volume of gastric juice showed slight change but not to a significant level as compared to the control group (Table 1, Figure 1).

#### 3.1.2. Ethanol/HCl induced gastric ulcer

PAM 540 showed a significant reduction in the ulcer index, free acidity, total acidity and pH when compared with the control group, and results were better than that of standard ranitidine treated rats (Table 1, Figure 2). It is interesting to note that the results of effect of *Polyalthia longifolia* treatment on various parameters are comparable with that of Ranitidine.

### 3.2. Antimicrobial activity

The antimicrobial activity of *Polyalthia longifolia* against 18 microorganisms was shown in Table 2. All gram positive bacteria tested were susceptible to methanolic extract except *Staphylococcus epidermidis*. The highest zone of inhibition was shown by *Bacillus megaterium*. Among seven gram negative bacteria tested, the most susceptible bacterium was *Proteus mirabilis* and also showed highest zone of inhibition while *Pseudomonas testosteroni*, *Enterobacter aerogenes* and *Salmonella typhimurium* were resistant bacteria, they did not show any zone of inhibition. Among five fungi tested, the more sensitive fungi were *Candida tropicalis* and *Candida albicans* while the most resistant fungi were *Candida glabrata*, *Candida neoformans* and *Cryptococcus luteolus*.

The MIC of *Polyalthia longifolia* against bacteria and fungi ranged from 97–25 000  $\mu$ g/mL (Table 2). Among six gram positive bacteria, *Staphylococcus subflava* and *Bacillus subtilis* showed similar and the lowest MIC value (390  $\mu$ g/mL); while among seven gram negative bacteria, *Klebsiella pneumoniae* showed the lowest MIC value (390  $\mu$ g/mL). Amongst five fungal strains, *Candida tropicalis* and *Candida albicans* showed similar MIC value (3 125  $\mu$ g/mL).

## 4. Discussion

### 4.1. Antiulcer activity

The gastric mucosa is constantly exposed to potentially noxious stimuli of endogenous (acid, pepsin, bile) and exogenous (alcohol, drugs) origin. It is commonly believed that the tolerance of the gastric mucosa to damage, originates from continuously operating defensive mechanisms, which include mucosal blood flow, mucus and bicarbonate secretion, and gastric mucosal potential difference. It is generally accepted that it results from an imbalance between aggressive factors (such as acid, pepsin) and the maintenance of the mucosal integrity through the endogenous defense mechanism<sup>[32]</sup>. To regain the balance, different therapeutic agents including plant extracts are used to inhibit the gastric acid secretion or to encourage the mucosal defense mechanisms by increasing mucus production, stabilizing the surface epithelial cells, or interfering with the prostaglandin synthesis.

Even though many products are available in the market for the treatment of gastric ulcers, including antacids, proton pump inhibitors, anticholinergics and histamine H<sub>2</sub>– antagonists, most of these drugs produce several adverse reactions such as gynecomastia, hematopoietic changes, acute interstitial nephritis<sup>[33]</sup>, thrombocytopenia<sup>[34]</sup>, anaphylaxis reactions<sup>[35]</sup>, nephrotoxicity and hepatotoxicity<sup>[36]</sup>. Therefore there is need for newer, natural drugs free of side effects and adverse reactions. Medicinal plants are one of the most attractive sources of new drugs, and have been shown to give promising results in treatment of gastric ulcer.

#### 4.1.1. Ethanol induced gastric ulcer

Ethanol–induced damage to gastric mucosa is multi factorial. One of the major factors is its rapid penetration into the gastric mucosa, which leads to an increased mucosal permeability and the release of vasoactive factors, which cause vascular damage and gastric injury<sup>[37,38]</sup>. The high production of free radicals is another factor associated with gastric injury and is due to increased lipid peroxidation and damage to gastric surface. Accumulation of activated neutrophils in the gastric mucosa may be a source of this free radical generation<sup>[39]</sup>. The high degree of protection offered by the test drug in treated group animals may be due to the strong antioxidant property of *Polyalthia longifolia*.

#### 4.1.2. Ethanol/HCl induced gastric ulcer

The HCl/ethanol method of inducing gastric lesions is a rapid and convenient way of screening plant extracts for antiulcer potency, which is assessed in terms of the absence or reduction in macroscopically visible lesions<sup>[40,41]</sup>. A number of mechanisms that include enhanced gastric mucosal defense through increased mucus and/or bicarbonate production, reducing the volume of gastric acid secretion or by simply neutralizing the gastric acidity<sup>[42]</sup>, can mediate the gastric mucosal protection against HCl/ethanol.

*Polyalthia longifolia* reduced free acidity, total acidity, pH and hence ulcer index showing anti–secretory mechanism<sup>[43]</sup>. HCl–Ethanol induced gastric damage ranging from endothelial microvascular damage to development of macroscopic gastric mucosal lesions, is attributed mainly to the inhibition of biosynthesis of cytoprotective prostaglandins (PG) resulting in

overproduction of leukotrienes and other products of the 5-lipoxygenase pathway<sup>[44]</sup>. These agents break the mucosal barrier, provoke an increase in gastric mucosal permeability to H<sup>+</sup> and Na<sup>+</sup> ions reducing the transmucosal potential difference and induce formation of erosions and ulcers. In this model, *Polyalthia longifolia* was able to produce a significant reduction of the gastric mucosal damage, indicating a probable local increase in PG synthesis<sup>[45]</sup>.

HCl-ethanol induced gastric damage in rat possibly through leukotrienes production and also involvement of 5-lipoxygenase in the formation of ulcer lesion. Prostaglandins also play a role in ethanol-induced ulcer. Thus the protective effect of *Polyalthia longifolia* against the gastric damage might be due to protection against 5-lipoxygenase or leukotriene pathway. The cytoprotective action possibly stimulates the prostaglandin synthesis, which in turn is involved in cytoprotection of the gastric mucosa<sup>[46]</sup>. On the other hand, some triterpenes are known as antiulcer drugs and their action has been suggested to be due to: activation of cellular protection<sup>[40,47]</sup>, reduction of mucosal prostaglandins metabolism-cytoprotective action<sup>[48]</sup>, and reduction of gastric vascular permeability<sup>[49–54]</sup>. At the doses used the animals had no depressive, excitatory or sleepiness symptoms, suggesting that probably centrally acting components involved in antiulcer action are present in extract. The present pre-clinical studies demonstrated that PAM protects the mucosa of the stomach of the rats.

The present study thus confirms antiulcer effect of *Polyalthia longifolia* in ethanol and ethanol/HCl induced gastric lesions. *Polyalthia longifolia* may inhibit the release of gastric hydrochloric acid and afford protection against gastric mucosal damage. Further studies are going on for its exact mechanism of action.

#### 4.2. Antimicrobial activity

The gram positive bacteria were more sensitive than gram negative bacteria and fungi towards *Polyalthia longifolia*, which is similar to previous reports<sup>[24,30,55]</sup>. This difference may be due to structural differences in cell wall of these bacteria. The gram negative cell wall is complex and multilayered structure; it has an outer phospholipid membrane carrying the structural lipopolysaccharide components, which makes a barrier to many environmental substances including synthetic and natural antibiotics. The gram positive bacteria contain a single outer peptide glycan layer, which is not an effective permeability barrier<sup>[9,56]</sup>.

*Polyalthia longifolia* demonstrated significant antimicrobial activity against pathogenic microorganisms, which cause diarrhoea, respiratory infections associated with coughing, urogenital infections including sexually transmitted diseases, skin infections, wounds and ulcers; and bacterial fevers such as typhoid. This promissory extract opens the possibility of finding new clinically effective antimicrobial compounds against many diseases.

In conclusion, it appears that leaves of *Polyalthia longifolia* var. *pendula* possess antiulcerogenic principles, which protect against gastric mucosal damage induced by ethanol and ethanol/HCl. These findings could justify, at least partially, the inclusion of this plant in the management of gastric disorders in ethnomedicine. Remarkable antimicrobial activity of *Polyalthia longifolia* suggests its possible use in prevention of diseases caused by pathogenic microbes. The data so far obtained do not indicate, however,

which specific mechanism(s) is (are) responsible for the antimicrobial and antiulcer activities. Further studies are required to isolate the bioactive compounds and to elucidate their mechanisms of action.

#### Conflict of interest statement

We declare that we have no conflict of interest.

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