

Antiulcer And Antiinflammatory Activity Of Fresh Leave Extracts Of *Polyalthia Longifolia* In Rats

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Abstract

The present study was designed to investigate the antiulcer and anti-inflammatory potential of ethanolic extracts of *Polyalthia longifolia* and aqueous extracts of *Polyalthia longifolia*.

Antiulcer activity was evaluated by pylorus ligation, aspirin induced and ethanolic induced ulcer models. Effect of concurrent administration of ethanolic and aqueous extracts of leaves extract *Polyalthia longifolia* at dose of 200 and 300 mg/kg b.w. respectively was given by oral route. Ethanolic and aqueous extracts of *Polyalthia longifolia* dose dependently decrease gastric content, total acidity, ulcer index, and increase in pH of gastric pylorus ligation ulcer model. Anti-inflammatory activity was performed using Cotton pellet granuloma in rats. Ethanolic and aqueous extracts of higher dose (300 mg/kg) being the most active, exhibited maximum anti-inflammatory activity. Extracts of *Polyalthia longifolia* may be useful as a natural antioxidant in the treatment of ulcer, inflammation and pain.

Key words:

Anti-inflammation, Antiulcer, *Polyalthia longifolia*

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Introduction:

Herbal drugs constitute a major part of therapeutics in all the traditional systems of medicine. Herbal medicine is a triumph of popular therapeutic diversity. There are evidences for the participation of

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reactive oxygen species in the etiology and pathophysiology of human disease, such as neurodegenerative disorders, inflammation, viral infections, autoimmune, gastrointestinal inflammation and gastric ulcer.

“Peptic ulcer disease” refers to breaks in the mucosa at the stomach and small intestine, principally the proximal duodenum, which are produced by the action of gastric secretion. Peptic ulcer is one of the major gastro intestinal disorders, which occurs due to an imbalance between the offensive (gastric acid secretion) and defensive (gastric mucosal integrity) factors. Consequently, reduction of gastric acid production as well as re-improvement of gastric mucosal production has been the major approaches for therapy of peptic ulcer disease. As a result drugs, of both herbal and synthetic origin are coming up offering newer and better options for treatment of peptic ulcer. The type of drugs varies from being proton-pump inhibitors to H₂ antagonist or a cytoprotective agent. At the same time, each of these drugs confers simpler to several side effects like arrhythmias, impotence, gynaecomastia, hyperplasia and haemopoetic changes.

This has been the major stimulus for the development of new antiulcer drugs and anti-inflammatory for novel molecules has been extended to herbal drugs that offer better protection and decreased relapse. Medicinal plants provide an important source of new chemical substances with potential therapeutic effects. These have been used in traditional medicine for the treatment of several diseases [1].

Inflammation is a cardinal last defense response to injury, tissue ischemia, autoimmune responses or infectious agents. Inflammation is a major component of the damage caused by autoimmune diseases and is also a fundamental contributor to diseases such as cancer, diabetes and cardiovascular disease [2]. Chronic inflammation is the reaction arising when the acute responses is insufficient to

eliminate the pro-inflammatory agents. Chronic inflammation includes a proliferation of fibroblast and infiltration of neutrophils with exudation of fluids. It occurs by means of development of proliferation cells which can either spread or form granuloma. Efficacy of anti-inflammatory agents in inflammatory states is indicated by their ability to inhibit the increase in the number of fibroblast during granular tissue formation [3]. Biochemical investigations on the mechanism of action of flavonoids have shown that these compounds can inhibit a wide variety of enzymes.

Polyalthia longifolia (sonn.) Thwaites is a large genus of shrubs and trees distributed in tropics and subtropics. It belongs to the family *Annonaceae*. This plant is used for the treatment of skin diseases, fever, diabetes and hypertension. A number of biologically active compounds have been isolated from this non-volatile fraction of the plant.

In view of the reported active constituents present in the various parts of the plant *Polyalthia longifolia* like flavonoids, alkaloids, sesquiterpenes, diterpenes, saponins etc. and its use in folk lore medicine, The plant *Polyalthia longifolia* has been reported to contain alkaloids, clerodane di-terpines^[4], quercetin, bulbocapnin,β-sitosterol, stigmasterol campesterol^[5], enihalimane diterpenes, and sesquiterpenoids^[6]

A phytochemical study on the hexane extract of the stem bark of *Polyalthia longifolia* has led to the characterization of clerodane and enihalimane diterpines (2, 3), two of which have demonstrated significant antibacterial and antifungal activities [6]. *Polyalthia longifolia* is reported to contain quercetin, bulbocapnin, steroids (β- sitosterol, stigmasterol and campesterol), which may contribute to the analgesic activity observed [5]. It is also reported to have antimicrobial⁴, hypoglycemic and antihyperglycemic^[7], and hypotensive actions^[8]. An attempt is made to evaluate anti-inflammatory and antiulcer potential of the ethanolic and aqueous extracts of leaves of *Polyalthia longifolia*.

Material and Method

Plant material:

The leaves of *Polyalthia longifolia* (sonn.) Thwaites was procured and authenticated by Dr. Siddamallaya, survey officer, Regional Research Institute (Ay.), Bangalore, Karnataka. A voucher specimen of same has been deposited (voucher specimen no. RRCBI MCW /8).

Preparation of the leaves extract:

The authenticated leaves were shade dried and powdered coarsely. Extraction was done according to standard procedures using analytical grade solvents. The powdered drug was defatted by extracting with pet-ether (60-80° C). The coarse powder of the leaves was Soxhlet extracted with 90% ethanol. The aqueous extract was prepared by the processes of maceration^[9]. The extracts obtained were concentrated under reduced pressure to yield ethanolic extracts (18.70%) and aqueous extracts (2.51%).

Animals:

The healthy Wistar albino rats of either sex weighing between 150-200 g were taken for the study. They were housed under controlled conditions of temperature (23±2°C), humidity (55±5%) and 12h light and 12h dark cycles. The animals were fed with standard pellet diet and water *ad libitum*. Approval of the Institutional Animals Ethics Committee was taken (ref. no. IAEC/KLECP/ BNG/06/2008).

Acute toxicity study:

Acute toxicity studies for aqueous and ethanolic extracts as *Polyalthia longifolia* were conducted as per OECD guidelines 423 using Albino wistar rats. Each animal was administered aqueous and ethanolic solution of the extract by oral route. The animals were observed for any changes continuously for the first 2 h and upto 24 h for mortality.^[10]

Antiulcer activity

Animals were randomly divided into six groups of six animals each. Group I served as control, Group II to Group VI were the drug treated groups. The Group II to Group VI animals received *Polyalthia longifolia* ethanolic and aqueous extracts 200 and 300 mg/Kg body weight and ranitidine 20 mg/Kg body weight respectively by oral route for a period of 5 days in both aspirin as well as ethanol induced ulcer models.

Ethanol induced ulcers

On day 5, one hour after the administration of extracts / Ranitidine all the animals received absolute ethanol (1ml/rat p.o.). One hour after administration of ethanol, the animals were sacrificed and the stomach was then excised and cut along the greater curvature, washed carefully with 5.0 ml of 0.9% NaCl and ulcers were scored by a person unaware of the experimental protocol in the glandular portion of stomach.^[11]

Pylorus ligation

Ranitidine 20mg/kg was used as standard drug. After keeping the animals on fasting overnight, One hour after the administration of extracts/Ranitidine, pylorus ligation was done under ether anaesthesia. Four hours after pylorus ligation, rats were sacrificed, stomach were isolated and opened along the greater curvature. Gastric fluid was collected for measurement of total gastric volume and estimation of free and total acidity.^[12]

Aspirin induced ulcer

On day 5, Aspirin at dose of 200 mg/Kg was administered to the animals of all the groups (I to VI) one hour after the administration of last dose of the extract/ Ranitidin. Four hours after the administration of Aspirin, the animals were sacrificed and the stomach was then excised and cut along the greater curvature, washed carefully with 5.0 ml of 0.9% NaCl and ulcers were scored by a person unaware of the experimental protocol in the glandular portion of stomach. Ulcer index has been calculated by adding the total number of ulcers per

stomach and the total severity of ulcers per stomach. The total severity of the ulcers was determined by recording the severity of each ulcer.^[13]

The number of ulcers is noted and the severity recorded with the following scores:

Normal coloration: 0, Red coloration: 0.5, Spot ulcer: 1.0, Hemorrhagic stress: 1.5

Ulcer ≥ 3 but ≤ 5 : 2

Ulcer > 5 : 3

Ulcer index (UI) was calculated using the formula^[14]

$$UI = U_S + U_N + U_P \times 10^{-1},$$

Where, U_S = Mean severity of ulcer score.

U_N = Average number of ulcers per animal

U_P = Percentage of animals with ulcer incidence

Percentage protection from ulcers = $C_{UI} - T_{UI} / C_{UI}$

Where, C_{UI} = Ulcer index of control groups

T_{UI} = Ulcer index of treated groups

Cotton pellet granuloma test in rats:

Albino Wister rats weighing between 150-200gm were divided into six groups of six animals each. Group I served as control, Group II to VI received Aqueous extracts and ethanolic extracts (200mg/Kg and 300mg/Kg body weight) of *Polyalthia longifolia* and Indomethacin 10 mg/Kg body weight respectively, 30 min later, two autoclaved cotton pellets 30 ± 1.0 mg were aseptically implanted sub cutaneously in the region of axillae in rats anesthetized with diethyl ether. Extracts was administered once daily for the next 7 days.^[15]

On the day 8, animals were anesthetized again and cotton pellets were removed surgically, freed from extraneous tissue and dried in the oven overnight at 60°C. The dried pellets were weighted and the mean weight of granuloma tissue formed around each pellet was

determined. % inhibition of granuloma tissue development was calculated using the formula:

$(T_c - T_t) / T_c \times 100$, where T_c = weight of granuloma tissue of control groups

T_t = weight of granuloma tissue of treated groups

Statistical analysis:

The interpretation of the results was done after subjecting the data obtained from various studies to statistical analysis which included one way ANOVA followed by test like Dunnett and Tukey. $P < 0.05$ is considered as statistically significant.

RESULT

Acute toxicity test:

Acute toxicity studies for aqueous and ethanolic extracts of *Polyalthia longifolia* were conducted as per OECD guidelines 423 using albino wistar rats. The animals were observed for any changes continuously for the first 2 h and upto 24 h for mortality. There was no mortality and noticeable behavioral changes in all the groups tested. The extracts were found to be safe upto 2000 mg/kg body weight.

Antiulcer activity

At the end of the study, the stomach was isolated and washed with saline, it was than observed for ulceration and ulcers were scored, Ulcer index and percentage protection against ulcers was calculated.

Ethanol induced ulcer model:

PALE and PALA at both the doses produced significant ($P < 0.01$) reduction in ulcer score when compared to the control. The percentage protection against ulcers by ranitidine, PALE 200, 300 and PALA 200, 300 was found to be 95.32, 66.96, 92.10, 66.87, and 66.26. (Table 1).

Pylorus ligation induced ulcer model:

The control animals showed ulceration, redness, and hemorrhagic streaks, after pylorus ligation. There was also an increase in gastric volume, free acidity, total acidity and pH. PALE and PALA at the both the doses and ranitidine produced significant ($P < 0.05$ and $P < 0.01$) reduction in ulcer score when compared to the control. The percentage protection against ulcers by ranitidine, PALE 200, 300 and PALA 200, 300 was found to be 99.54, 33.52, 49.22, 82.15 and 32.72 respectively. *Polyalthia*

longifolia ethanolic and aqueous extracts at both the doses and ranitidine significantly ($P<0.01$) reduced the gastric volume when compared to control. PALE 200 produced decrease in gastric volume comparable ($P<0.05$) to that of ranitidine, whereas PALE 300, PALE 200 and 300 produced decrease in gastric volume better ($P<0.01$ and $P<0.001$ respectively) than ranitidine. Aqueous extracts produced better ($P<0.001$) reduction in gastric volume, when compared to ethanolic extracts and ranitidine. Ethanolic and aqueous extracts of *polyalthia longifolia* at both the doses significantly ($P<0.01$) reduced free acidity when compared to control. PALE 200 produced reduction in free acidity comparable ($P<0.05$) to that of ranitidine whereas PALA 200 and 300 produced reduction in free acidity better than ranitidine and also ethanolic extracts ($P<0.001$). Significant ($P<0.01$) reduction in total acidity was produced by ethanolic and aqueous extracts at both the doses and ranitidine when compared to control. PALE and PALA at both the doses produced reduction in total acidity better ($P<0.001$) than that of ranitidine. Ranitidine produced significant ($P<0.01$) decrease in pH when compared to that of control. There was an increase in pH by ethanolic and aqueous extracts at both doses (Table2).

Aspirin induced ulcer model

Significant ($P<0.01$) reduction in ulcer score was produced by ranitidine, aqueous, ethanolic extracts at the both the doses 200, and 300mg/Kg body weight, when compared to the control. PALE 200 and PALE 300 produced reduction in ulcer score comparable ($P<0.05$) when compared to ranitidine. PALE 200, 300 and PALA 200, 300 was found to be 99.24, 83.13, 90.95, 34.53, and 17.63. (Table 3).

Cotton wool granuloma

In the cotton pellet granuloma study which is a sub-acute anti-inflammatory model, the weight of cotton pellet was determined at the end of the study and the percentage decrease in granuloma tissue was also found out. Investigation of the effect of ethanolic

and aqueous extracts of *Polyalthia longifolia* on the proliferative phase of inflammation has revealed the following results (Table 4). All the extracts were found to produce significant ($P<0.001$) decrease in the granuloma tissue as evident by the decrease in the weight of cotton pellet when compared to the control. PALA 200 and 300 produced anti-inflammatory activity comparable ($P<0.05$) to that of indomethacin extracts. The aqueous extracts produced better ($P<0.05$) anti-inflammatory activity when compared to the ethanolic extracts at dose of 200mg/kg body weight.

Discussion

It is generally accepted that gastric ulcers results from an imbalance between aggressive factors and the maintenance of the mucosal integrity through the endogenous defense mechanism [16]. The role of free radicals is also reported in the indication of ulcers. Prostaglandins (PG) offer protection to duodenum through both increases in mucosal resistance as well as decrease in aggressive factors, mainly acid and Pepsin [17]. Ethanol induced gastric ulcers have been widely used for the evaluation of gastro protective activity. Ethanol is metabolized in the body and releases superoxide anion and hydroperoxy free radicals. The incidence of ethanol induced ulcers is predominant in the glandular part of stomach. It was reported to stimulate the formation of leukotriene C₄ (LTC₄), mast cell secretory products and reactive oxygen species resulting in the damage of rat gastric mucosa [18]. It has been found that oxygen derived free radicals are implicated in the mechanism of acute and chronic ulceration in the gastric mucosa and scavenging these free radicals can play an appreciable role in healing these ulcer [19]. When aspirin is in the lipid soluble undissociated form it can damage the gastric mucosa. Aspirin causes a dose dependent reduction in mucosal prostaglandins - PGE₂ and PGI₂ bio-synthesis accompanied by an increase in the mean area of gastric ulcerations.

Aspirin is known to inactivate irreversibly the PG synthetase system, which mediates synthesis of prostaglandin in the mucosa [20, 21]. An increase in acid secretion and back diffusion at H⁺ ions is also noticed. It is reasonable to assume that the observed gastric mucosal lesions induced by aspirin are due to a deficiency of mucosal prostaglandin [22]. Aspirin induced ulcer is mediated through tissue damaging free radicals, which are produced from the conversion of hydroperoxyl to hydroxyl fatty acids, which leads to cell destruction. The hydroperoxyl fatty acids are generated from the degeneration of mast cells and generalized lipid per oxidation accompanying cell damage [19].

Pylorus ligation induced ulcers are due to auto digestion at the gastric mucosa and breakdown of the gastric mucosal barrier. In case of pyloric ligation, ulcer formation is mainly due to the stasis at the gastric juice and stress [11, 23].

Polyalthia longifolia produced antiulcer activity in all the three models taken up for the study. Ethanolic and aqueous extracts at both the doses, reduced ulcer incidence significantly ($P < 0.01$) when compared to the control as evident by decrease in ulcer score in all the three models. Protection against ulcerations in aspirin and ethanol induced ulcer models indicate cytoprotective action by extracts of *Polyalthia longifolia*. Anti-secretory activity of the extracts was noticed in pylorus ligation induced ulcer model. There was decrease in gastric volume and reduction in free and total acidity in the animals treated with ethanolic and aqueous extracts. *Polyalthia longifolia* is reported to contain quercetin [24] apart from other flavonoids, tannins, alkaloids and terpenoids. From the phytochemical tests done on the extracts of *Polyalthia longifolia*, it was confirmed that the same classes of active constituents were present. Quercetin is reported to prevent gastric mucosal lesions induced by various models (pylorus ligation, ethanol induced, cold restraint stress). Quercetin may increase the amount of natural glycoproteins, the

most important proteins in the gastric mucosa, which may in turn facilitate the defense against an aggressive action. Quercetin also stimulates the synthesis of cyclooxygenase and of local prostaglandins. Other mechanism proposed includes inhibition of the gastric proton pump, lipoxygenase pathway, or inhibition of lipid peroxidation [25]. *Polyalthia longifolia* may owe its antiulcer activity to its active constituents like flavonoids and especially quercetin. From the phytochemical tests done on the extracts of *Polyalthia longifolia*, it was confirmed that the same classes of active constituents were present.

Cotton pellet granuloma studies are a sub-acute inflammation model. The repair phase of the inflammatory process begins with the proliferation of fibroblasts as well as multiplication of small blood vessels. Such proliferating cells penetrate and the exudates production of a highly vascularized and reddened mass known as granulation tissue [15]. Kinin is said to be the main mediator of granuloma, as it both causes vasodilatation and increase vascular permeability in the early stages of inflammation.

Many investigations have proven that varieties of flavonoid molecules possess anti-inflammatory activity in various animal models of inflammation. Especially, some flavonoids were found to inhibit chronic inflammation of several experimental animals models. Quercetin results in decreased oxidative injury. Quercetin in particular is known for its iron-chelating and iron-stabilizing properties. Direct inhibition of lipid peroxidation is another protective measure [26, 27].

The aqueous extracts of *Polyalthia longifolia* at both the doses were found to show significant anti-inflammatory activity as evident by decrease in the weight of granuloma tissue when compared to the standard drug Indomethacin.

B-ring substituted flavones are found to be capable of inhibiting cotton pellet induced granuloma in rats [26]. The results from subacute model (cotton

pellet granuloma studies) suggest that the anti-inflammatory activity may be by the virtue of the plants active constituents mainly the flavonoids.

Conclusion

Both extracts of *Polyalthia longifolia* reduced ulcer incidence, when compared to the control as evident by decrease in ulcer score in all the three models. Anti-secretory activity of the extracts was noticed in pylorus ligation induced ulcer model. There was decrease in gastric volume and reduction in free and

total acidity in the animals treated with ethanolic and aqueous extracts. *Polyalthia longifolia* were found to produce decrease in the granuloma tissue as evident by the decrease in the weight of cotton pellet when compared to the control. This indicates that the leaf extracts of *Polyalthia longifolia* has anti-inflammatory activity. The leaf extracts of PAL was found to possess anti-inflammatory and antiulcer activities.

Table 1: Effects of ethanolic and aqueous extracts of *Polyalthia longifolia* on ethanol induced ulcer model

Treatment	Ulcer score	Ulcer Index	Percentage protection
Control	5.66±0.51	11.03	-----
Ranitidine	0.16±0 ^{**a}	0.01	95.32
PALE 200	1.66±0.98 ^{**a}	3.64	66.96
PALE 300	0.91±0.80 ^{**a}	1.82	92.10
PALA 200	1.91±1.11 ^{**a}	3.65	66.87
PALA 300	2.25±2.40 ^{**a}	3.72	66.26

n=6, mean±SD,

PALE and PALA– *Polyalthia longifolia* ethanolic and aqueous extracts,

*P<0.05, **P<0.01, a- indicates comparison with control groups

Table 2: Effects of ethanolic and aqueous extracts of *Polyalthia longifolia* on pylorus ligation model:

Treatment	Volume of gastric juice	Free acidity	Total acidity	pH
Control	8.36±0.36	36.13±1.27	51.81±0.60	2.59±0.33
Ranitidine	5.12±0.22 ^{**a}	9.5±0.20 ^{**a}	20.49±0.51 ^{**a}	5.64±0.13 ^{**a}
PALE 200	5.92±0.51 ^{**a, *b}	9.68±1.66 ^{**a, *b}	3.98±2.53 ^{**a, ***b}	3±0.68
PALE 300	4.54±1.46 ^{**a, **b}	12.26±3.79 ^{**a}	4.32±1.14 ^{**a, ***b}	3.06±0.94
PALA 200	1.66±0.44 ^{**a, **b}	3.44±0.18 ^{**a, ***b}	3.44±1.55 ^{**a, ***b}	2.3±0.18
PALA 300	2.42±0.57 ^{**a, **b}	3.82±0.43 ^{**a***b}	3.9±0.52 ^{**a, ***b}	2.48±0.28

n=6, mean ± SD,

PALE and PALA– *Polyalthia longifolia* ethanolic and aqueous extracts,

*P<0.05, **P<0.01, ***P<0.001,

a- comparison of both PALE and PALA extracts with control and ranitidine groups,

b- comparison of both PALE and PALA extracts with ranitidine groups.

Table 3: Effects of ethanolic and aqueous extracts of *Polyalthia longifolia* on aspirin induced ulcer model

Treatment	Ulcer score	Ulcer Index	Percentage protection
Control	5.83±0.40	11.06	-----
Ranitidine	0.83±0.57 ^{**a}	0.083	99.24
PALE 200	1.33±1.16 ^{**a, *b}	1.865	83.13
PALE 300	1±0.54 ^{**a, *b}	1.00	90.95
PALA 200	3±1.22 ^{**a}	7.24	34.53
PALA 300	3.83±1.21 ^{**a}	9.11	17.63

n=6, mean±SD,

PALE and PALA– *Polyalthia longifolia* ethanolic and aqueous extracts,

*P<0.05, **P<0.01,

a- indicates comparison with control groups,

b- indicates comparison with standard ranitidine groups

Table 4: Effects of ethanolic and aqueous extracts of *Polyalthia longifolia* leaves on granuloma tissue formation in rats

Treatment	Weight of cotton pellet in mg	% inhibition of granuloma tissue
Control	101.25±011.25	-
Indomethacin	53.75±10.6***a	48.16±10.47
PALE 200	73.75±8.17***a,*b	28.41±8.07
PALE 300	64.5±9.51***a	37.54±9.39
PALA 200	61.37±5.34***a	40.63±5.27
PALA 300	63±3.89***a	39.02±3.84

n=6, mean ± SD,

PALE and PALA– *Polyalthia longifolia* ethanolic and aqueous extracts,

*P<0.05, **P<0.01, ***P<0.001,

a indicates comparison extracts and standard with control

b- indicates comparison of the extracts with standard indomethacin

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