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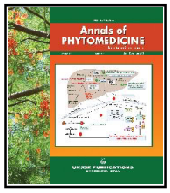

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Anti-inflammatory potential of *Pajanelia longifolia* (Willd.) K. Schum. ethanolic leaf extract

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Abstract

Pajanelia longifolia (Willd.) K. Schum. (*P. longifolia*) commonly known as Pajanelia or tender wild jack has been used as traditional herbal medicine in India for the treatment of a variety of ailments such as arthritis, stomach disorders, wound healing, skin diseases and obesity. Inflammation is a part of the vascular tissue's complicated biological reaction to adverse stimuli like pathogens, damaged cells, or irritants. Inflammation is a common physiological response to various stimuli to limit damage and facilitate tissue healing. The present investigation aimed to determine the effectiveness of *P. longifolia* in inflammation in rats by the carrageenan-induced rat paw oedema method, and to assess the protection of mast cell degranulation by the *in vitro* method. In the carrageenan-induced rat paw oedema model, 2% carrageenan was used for inducing the disease and diclofenac sodium (20 mg/kg) was used as the standard. In the mast cell degranulation method, propranolol was used as the degranulating substance and results were compared for each treatment group. The anti-inflammatory activities were studied by using a digital plethysmometer for measuring paw oedema. Dose-dependent inhibition of propranolol-induced degranulation of mast cells was observed. The finding of the study reveals that *P. longifolia* exhibits dose-dependent anti-inflammatory activity. Molecular docking analysis confirmed its effect on preventing inflammation.

1. Introduction

Inflammation is a part of the vascular tissue's complicated biological reaction to various adverse stimuli like pathogens, damaged cells, or irritants to limit damage and facilitate tissue healing (Ferrer-Miliani *et al*., 2007; Lehra *et al*., 2014). It is also a major component of the damage produced by autoimmune disorders, as well as a substantial contributor to a variety of infectious and non-infectious diseases like cancer, diabetes, cardiovascular disease, and others like arteriosclerosis, rheumatoid arthritis, and Alzheimer's disease (McGeer *et al*., 2002; Howes *et al*., 2003). The five cardinal indicators are swelling, redness, heat, discomfort, and altered function (Murugan *et al*., 2012). Inflammatory cells produce a wide range of reactive oxygen species (ROS), including superoxide (O_2), hydrogen peroxide (H_2O_2), and hydroxyl (OH) radicals, which increase cell membrane permeability through lipid oxidation. This causes capillary dilatation, which causes redness and pain, as well as increased vascular permeability, which allows plasma to escape into the surrounding tissue, creating oedema (Halliwel, 1995).

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Cardiovascular disease, diabetes, inflammation, degenerative diseases, cancer, anaemia, and ischemia are all caused by oxidative stress (Cai *et al.,* 2004). The term "reactive oxygen species" refers to oxygen-centered radicals like the hydroxyl radical and superoxide anion, as well as nonradical derivatives such as hydrogen peroxide and singlet oxygen. ROS is a reactive oxygen species that gets polyunsaturated fatty acids, precursors of lipid peroxide production, and oxidative stress (Gutteridge, 1994). Overproduction of reactive oxygen species (ROS) in humans can result in tissue damage. Cancer, Alzheimer's disease, inflammation, diabetes, atherosclerosis, rheumatoid arthritis, ageing, and other disorders have all been linked to it (Velavan *et al.,* 2020). Antioxidants have been shown to lessen the likelihood of pro-inflammatory reactions and cancer in both *in vitro* and *in vivo* studies.

Corticosteroids, disease modifying anti-rheumatoid drugs and non-steroidal anti-inflammatory drugs (NSAIDs) are used to treat inflammatory disorders. The toxicity of currently available potent anti-inflammatory synthetic medications, as well as the recurrence of symptoms after withdrawal, is a significant disadvantage (Chandran *et al.,* 2012). However NSAIDs induce gastrointestinal ulcers, bleeding and platelet dysfunction, kidney and cardiovascular damage in long term users (Kalgutkar *et al.,* 2003; Essex *et al.,* 2013). Long term usage of corticosteroids can cause hyperglycaemia, insulin resistance, diabetes mellitus, osteoporosis, anxiety and other serious adverse effects (Singh *et al.,* 2006). NSAIDs can also damage the immune

system, which can have catastrophic effects on children, the elderly and especially immune-compromised individuals (Bancos *et al.,* 2009).

P. longifolia a deciduous tree mainly distributed in the Western Ghats of India, has been proven to possess various therapeutic properties such as antioxidant, antiviral, antiplasmodial, antidiarrhoeal and antimicrobial activity (Steffy *et al.,* 2017). *P. longifolia* is recorded as one of the oldest medicines in India, described in Charaka Samhita (1000 BC) which has been mainly used for the treatment of stomach disorders, arthritis, urinary disorders, liver ailments, skin infections, *etc*. Various hepatoprotective, wound healing, antimicrobial, and antioxidant activities have been recorded (Saha *et al.,* 2017; Padyana *et al.,* 2011). Mast cell degranulation *in vitro* method and carrageenan-induced paw oedema an *in vivo* method are commonly used to assess anti-inflammatory activity in animal models. The present study was undertaken to investigate the anti-inflammatory potential of *P. longifolia* ethanolic leaf extract.

2. Materials and Methods

2.1 Animal selection

Male or female albino 4-7 weeks old Wistar rats weighing about 180-200 g were procured from the animal house of NGSM Institute of Pharmaceutical Sciences, Deralakatte, Mangaluru. The animals were divided into accurate groups and kept separately. The cages were kept under standard lab conditions of temperature 25 ± 2°C with an appropriate light and dark cycle of 12 h. Animals were given standard food and water *ad libitum*. Animals were divided into 5 groups of 6 animals each. The experimental procedures were conducted as per CCSEA (Committee for the Control and Supervision of Experiments on Animals), New Delhi, India, and the research work was permitted and approved by the Institutional Animal Ethics Committee (NGSMIPS/IAEC/AUG-2022/319).

2.2 Selection of doses

To investigate the anti-inflammatory activity of *P. longifolia*, 2 dose levels were selected. Based on the acute oral toxicity study (OECD guidelines, Test No. 425), 1/10th of the maximal dose was considered as X, 50% of X as the minimum dose (100 mg/kg), and two times the dose of X as the maximum dose (400 mg/kg).

2.3 Experimental design for the anti-inflammatory activity

The evaluation of the anti-inflammatory activity of *P. longifolia* was carried out using a digital plethysmograph apparatus and *in vitro* technique.

2.4 Anti-inflammatory activity assessment using the *in vitro* method

2.4.1 Mast cell degranulation

The modified Keley and Weiner approach was used to conduct an *in vitro* test for mast cell degranulation. Albino rats were sacrificed, and the mesentery was extracted carefully and divided into 1 cm long pieces. These bits were incubated for 5 min in a tyrode solution containing varying quantities of *P. longifolia*. A mast cell degranulating substance like propranolol (50 µg/ml) was added to the incubation and the bits were removed after 10 min. They were spread out carefully on glass slides and dyed with 1% toluidine blue. Under a high-power objective field, mast cells were counted in separate fields at random. Each treatment group's percentage of degranulated mast cells was calculated. For comparison, sodium cromoglycate (10 µg/ml), a well-known mast cell stabilizer which is used as standard, was included in the study (Keley and Weiner, 1971; Reddy *et al.,* 1986; Vasigar and Batmanabane, 2013).

% of degranulation = (1"T/C) × 100

where,

T = mast cell count in the experimental tissues

C = mast cell count in the control

2.5 Anti-inflammatory activity assessment using *in vivo* method

2.5.1 Carrageenan-induced paw oedema model

The animals were starved overnight and the tails of rats were marked for identification. The rats were allowed to consume water for adequate hydration. The rats were categorized into 6 animals in 5 categories (Table 1).

Table 1: Experimental design of carrageenan-induced rat paw oedema method

Group	Treatment
1	Vehicle (Normal control) (2 ml/kg)
2	Carrageenan solution (Disease) (0.1 ml)
3	Standard drug (10 mg/kg) + Carrageenan solution (0.1 ml)
4	Carrageenan solution (0.1 ml) + *P. longifolia* (100 mg/kg) - Low dose
5	Carrageenan solution + *P. longifolia* (400 mg/kg) - High dose

The lateral malleolus of the paw was marked. In subsequent reading, the paw was dipped up to this mark and using digital plethysmograph paw volume was measured. Normal saline with 1% carrageenan was injected into the sub-plantar region of the left hind paw 30 min after administration of *P. longifolia*. The paw volume was measured at 0 h, 3 h and 5 h.

% inhibition of oedema = (1 – D/C) × 100

where,

D = paw volume in drug-treated animals

C = paw volume of the control group

The increase in paw volume after 0 h, 3 h and 5 h was calculated as percentage inhibition and compared to the volume measured immediately after receiving carrageenan. Animals that were treated

effectively exhibited less amount of oedema. For each treated and control group the difference of average values was calculated for each time interval and statistical calculation was carried out (Hajhashemi *et al.,* 2003).

2.6 Statistical analysis

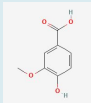
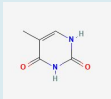
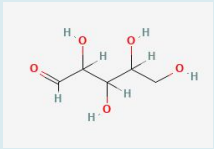
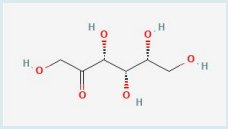
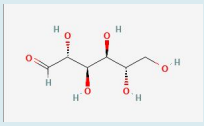
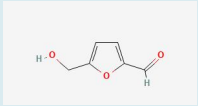
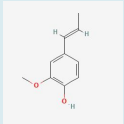
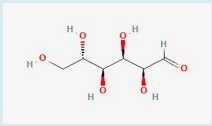
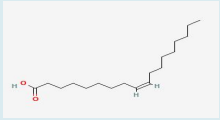
Data obtained were analyzed by one-way analysis of variance (ANOVA) and Dunnett's test using version 9 of the Graph Pad prism program. A statistically significant value of p less than 0.05 was set.

2.7 Anti-inflammatory activity assessment using *in silico* method

2.7.1 Selection of compounds of *P. longifolia* for molecular docking study

In this study, the chemical components which are responsible for anti-inflammatory activity in garlic were selected. The compounds were docked for the target protein. The structures of the chemical compounds were obtained from the PubChem compound repository (https://pubchem.ncbi.nlm.nih.gov/) (Table 2).

Table 2: Chemical components of *P. longifolia*

S.No.	Component	PubChem ID	Chemical structure 2D	Molecular formula and molecular weight
1	Vanillic acid	8468		MF: $C_8H_8O_4$ MW: 168.15 g/mol
2	Thymine	1135		MF: $C_5H_6N_2O_2$ MW: 126.11 g/mol
3	Cyclopentane	9253		MF: C_5H_{10} MW: 70.13 g/mol
4	DL-Arabinose	854		MF: $C_5H_{10}O_5$ MW: 150.13 g/mol
5	L-(-)-Sorbose	6904		MF: $C_6H_{12}O_6$ MW: 180.16 g/mol
6	L-Mannose	82308		MF: $C_6H_{12}O_6$ MW: 180.16 g/mol
7	5-Hydroxymethylfurfural	237332		MF: $C_6H_6O_3$ MW: 126.11 g/mol
8	Trans-isoeugenol	853433		MF: $C_{10}H_{12}O_2$ MW: 164.2 g/mol
9	L-Glucose	10954115		MF: $C_6H_{12}O_6$ MW: 180.16 g/mol
10	Oleic acid	445639		MF: $C_{18}H_{34}O_2$ MW: 282.5 g/mol

2.7.2 *In silico* platform

All computational analysis was carried out on the Maestro 12.3 version (LigPrep, Glide XP docking, QikProp-ADMET properties) (Schrödinger 2020-4, LLC, New York). This software package was programmed on a DELL Inc.27" workstation machine running with Linux-x86_64 as the operating system.

2.7.3 Ligand and enzyme preparation

The Schrödinger 2020-4:LigPrep tool (included in Schrödinger suite-Maestro version 12.3) was used to prepare the Ligand, and the following settings were used: Using Epik 2.2 to neutralise at pH 7.0 and the OPLS 2005 force field to minimise. The 3D crystallographic structures of the target receptor of anti-inflammatory activity with internal complex diclofenac were obtained from the protein data bank (PDB: 2B17) (Specific binding of non-steroidal anti-inflammatory drugs NSAIDs to phospholipase A2), processed and prepared by Protein Preparation Wizard.

2.7.4 Glide docking

A molecular docking experiment was conducted to determine the potential mode of action of the chosen chemicals responsible for *P. longifolia's* anti-inflammatory effects on the target. Glide standard precision docking, which was integrated into the Schrodinger suite-Maestro version 12.3 was used for docking experiments.

2.7.5 ADMET studies

All the phytochemical components were predicted for their ADMET (absorption, distribution, metabolism, excretion and toxicity) properties by using the QikProp program (Schrodinger 2019c). The standard range of ADMET properties was given in the Qikprop manual. According to the manual, the standard range ADMET are; (a)QPPCaco - Â25 considered as poor and Ã500 is considered as great, (b)% human oral absorption- Ã80 is high and Â25% is poor, (c)QPlogKhsa should be in between -1.5 to 1.5, (d) SASA (Total solvent accessible surface area) lies between 300-1000, (e) Rule of 5-maximum up to 5, (f) Rule of 3 maximum up to 3.

3. Results

3.1 Evaluation of *in vitro* anti-inflammatory activity by mast cell degranulation method

Propranolol (50 µg/ml) produced 43.40 ± 0.67% degranulation of rat mesenteric mast cells. Treatment with *P. longifolia* significantly reduced the percentage of degranulation by about 18.2 ± 0.58% induced by propranolol at *P. longifolia* dose 20 mg/ml (Table 3).

Table 3: Effect of *P. longifolia* in mast cell degranulation

S.No.	Treatment	% Degranulation
1	Saline	11.80 ± 0.5831[b]
2	Sodium cromoglycate (10 µl/ml) + Propranolol (50 µg/ml)	15.60 ± 0.50[a]
3	Propranolol (50 µg/ml)	43.40 ± 0.67[a,b]
4	*P. longifolia* (5 mg/ml) + Propranolol (50 µg/ml)	33.60 ± 0.92[a,b]
5	*P. longifolia* (20 mg/ml) + Propranolol (50 µg/ml)	18.2 ± 0.5831[a,b]

Data obtained was analysed by one-way ANOVA, followed by Dunnett's test using Graph Pad computer software version 9. Values were expressed as Mean ± SEM, (n=5). a = $p<0.05$ is statistically significant when compared to control, b = $p<0.05$ is statistically significant when compared to the standard.

3.2 Evaluation of *in vivo* anti-inflammatory activity

3.2.1 Carrageenan-induced rat paw oedema method

In a dose-dependent manner, orally administered *P. longifolia* at doses of 100 mg/kg and 400 mg/kg was found to significantly ($p<0.05$), inhibit the oedema formed. After the injection of carrageenan at 0 h, there was only slight oedema observed but at 3 h, the oedema was more in the disease group compared to standard and test *P. longifolia*. At 3 h, paw oedema decreased in standard and test *P. longifolia* (400 mg/kg) was better compared to rest (Table 4).

Table 4: Effect of *P. longifolia* on carrageenan-induced rat paw oedema method in rats

S.No.	Treatment	0 h	3 h	5 h
1	Saline (2 ml/kg)	0.46 ± 0.01095[b]	0.46 ± 0.019[b]	0.46 ± 0.0195[b]
2	Diclofenac sodium (10 mg/kg) i.p. + Carrageenan (0.1 ml)	0.620 ± 0.128[a]	0.61 ± 0.007[a]	0.516 ± 0.00812[a]
3	Carrageenan (0.1 ml) s.c.	0.648 ± 0.007[a]	1.662 ± 0.06[a,b]	1.418 ± 0.0816[a,b]
4	*P. longifolia* (100 mg/kg) p.o. + Carrageenan (0.1 ml)	0.624 ± 0.0258[a]	1.080 ± 0.021[a,b]	0.882 ± 0.0151[a,b]
5	*P. longifolia* (400 mg/kg) p.o. + Carrageenan (0.1 ml)	0.62 ± 0.016[a]	0.746 ± 0.012[a,b]	0.652 ± 0.0086[a]

Data obtained was analysed by one-way ANOVA, followed by Dunnett's test using GraphPad computer software version 9. Values were expressed as Mean ± SEM, (n = 5). a = $p<0.05$ is statistically significant when compared to control, b = $p<0.05$ is statistically significant when compared to the standard.

3.3 Exploring the anti-inflammatory activity of *P. longifolia* using the *in silico* molecular docking method

In this study, the anti-inflammatory activity of *P. longifolia* was determined using a computational model. Here, the computational study was carried out to identify the potential lead compounds for anti-inflammatory activities. *P. longifolia* was docked for affinity towards the target receptor of anti-inflammatory activity with internal complex diclofenac which belongs to hydrolase class (PBD: 2B17)

and the result of the docking study is shown in Table 5, demonstrating the highest binding affinity for anti-inflammatory activity. Diclofenac was used as the standard and the affinity binding score was 6.892 kcal/mol. The results also reveal that components of *P. longifolia* and diclofenac had better human oral absorption scores, SASA and human serum binding within the recommended range. Lipinski's rule of five and rule of three was followed. As a result, compounds will have no difficulty with oral bioavailability. The hydrogen bond was triggered by their interaction. However, some parameters were not in the standard range for properties like the QPPCaco-2 permeability score.

Table 5: Molecular docking

S.No.	Component	Docking score (kcal/mol)	H bonding	Amino acid
1	Diclofenac	– 6.892	2	GLY30 2B17
2	Vanillic Acid	– 6.09	3	GLY30 2B17
3	L-Mannose	– 6.2	1	GLY30 2B17

4. Discussion

The pathology of many diseases, such as atherosclerosis, rheumatoid arthritis and bronchial asthma involves inflammation and increased capillary permeability. This research was undertaken to investigate the anti-inflammatory activity of *P. longifolia* in experimental animals. Anti-inflammatory activity was evaluated using *in vivo* methods like the carrageenan-induced rat paw oedema method, and *in vitro* method involved mast cell degranulation. It was identified that *P. longifolia* exhibits a significant anti-inflammatory activity. carrageenan-induced rat paw oedema is the most appropriate and frequently employed method to explore a drug's capability to reduce inflammation, as measured by its ability to reduce oedema. Estimation of differences in the paw volume was measured for 5 h after Carrageenan injection into the sub-plantar region of albino Wistar rats was employed (Vasigar and Batmanabane, 2013). The release of histamine and serotonin during the first hour after the injection is said to cause the first phase of carrageenan-induced oedema, which is followed by the release of cyclooxygenase product during the second phase, with kinins acting as a bridge between the two phases. This results in the production of free radicals and inflammatory mediators. The cyclooxygenase inhibitors, as well as lipoxygenase inhibitors, are sensitive carrageenan-induced rat paw oedema methods.

To study the anti-inflammatory activity, protection of mast cell degranulation was used as an *in vitro* method. There is compelling evidence that the primary initiators of allergic inflammation are basophils, mast cells, and the mediators that are released upon degranulation. Many of the negative effects that mast cells mediate are believed to be caused by several proinflammatory substances that are exocytosis after exposure to antigen (Hajhashemi *et al.,* 2003; Reddy *et al.,* 1986; Vasigar and Batmanabane, 2013). The drugs which are capable of preventing mast cell degranulation are chosen in the drug development process for inflammation. In this study, *P. longifolia* offered protection against propranolol-induced degranulation of mast cells.

In our *in silico* studies, the major components of *P. longifolia* were docked for affinity towards the target receptor of inflammation which is the internal complex of diclofenac that belongs to the hydrolase class (PBD: 2B17). To determine the binding affinity of the drug, the result of the docking study is given in Table 5. In the present study, we also focused on the *in silico* ADMET properties of these components. It demonstrated the highest binding affinity of components with the scoring of – 6.2 kcal/mol and – 6.09 kcal/mol, respectively, for anti-inflammatory activity. Diclofenac was standard, and the affinity binding score was – 6.892 kcal/mol. The results also revealed that *P. longifolia* and diclofenac had better human oral absorption scores, SASA and human serum binding within the recommended range. Lipinski's rule of five and rule of three was followed. As a result, it was clear that compounds would have no difficulty with oral bioavailability. The hydrogen bond was triggered by their interaction. However, some parameters were not in the standard range for properties like the QPPCaco-2 permeability score.

These findings suggest that *P. longifolia* can play a key role in anti-inflammatory activity by interacting with target enzymes. The experimental animal-like rats treated with *P. longifolia* produced a significant anti-inflammatory potential in all the animal models as well as in the *in silico* study.

Further, detailed studies are being undertaken to isolate the active constituents responsible for anti-inflammatory activity and the possible mechanism for the said properties.

5. Conclusion

The animal studies were carried out using *in vivo* and *in vitro* models for anti-inflammatory screening as well as *in silico* studies which included docking and ADMET studies. All serve to reveal the potential anti-inflammatory effect of *P. longifolia*. A high dose of *P. longifolia* inhibits inflammation to a greater extent compared to a lower dose. In mast cell degranulation, *P. longifolia* reduces the extent of degranulation of the cells produced by various degranulating agents such as propranolol. Also, the components of *P. longifolia* such as vanillic acid, and L-mannose show a nearly similar docking score compared to the control drug diclofenac sodium which shows an anti-inflammatory effect. Hence, all the methods confirm the anti-inflammatory effect of *P. longifolia*.

Conflict of interest

The authors declare no conflict of interest

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