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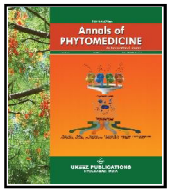

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Evaluation of a fruit peel ethanolic extract of *Ananas comosus* (L.) Merrill (pineapple) as an anti-inflammatory agent in an experimental animal model

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Abstract

The Bromeliaceae family includes *Ananas comosus* (L.) Merrill (Pineapple), which is well recognised for having a wide range of pharmacological effects. The pineapple contains the enzyme bromelain, which has a variety of uses, such as morphogenesis, regeneration, angiogenesis, cell regulation, and decreasing injury swelling, discomfort, and recovery time. The current research aims to open up new pathways for the therapeutic benefits of pineapple peel for their anti-inflammatory action, along with the screening of phytochemicals present in the ethanolic extract of *A. comosus* (EPAC). The acute and chronic anti-inflammatory activities were performed on carrageenan-induced paw edema and the cotton pellet method, respectively, at different doses of 200 and 400 mg/kg. The phytochemical analysis of EPAC results in the presence of flavonoids, sterols, terpenes, saponins, and carbohydrates. The acute anti-inflammatory activity showed noteworthy inhibition of 28.77% and 51.69% compared with standard indomethacin (10 mg/kg), which showed 82.98% of inhibition. The chronic model, on the other hand, showed inhibitions of 12.16% and 23.58%, respectively. From this study, we conclude that the EPAC, which is rich in bromelain enzyme along with other phytoconstituents like terpenoids and phenolic acids that possess anti-inflammatory activity and could be considered a promising phytochemical in inflammation-associated disorders.

1. Introduction

Several types of illnesses are now found in and around the world as a result of a lack of nutrition and diet. Many natural primary health care remedies were widely used to combat this. Because modern drugs are not widely available, 80% of people in our world rely on herbal medicine. Environmentally friendly processes have produced a plethora of medicines to treat the illness. Herbal drugs play an essential role in the development of potent therapeutic agents (Latha *et al*., 2021). India is acknowledged as a land of herbal plants, and those plants are clinically used. India has a vast collection of herbal plants that have been used extensively since the dawn of human civilization. There are many hazardous disorders that may be treated using medicinal herbs. Specific medical conditions have been treated using the various components of healing plants. For decades, people have utilised herbs as sources of nutrition and medicine (Sri Bhuvaneswari *et al*., 2021; Vijayalakshmi *et al*., 2021). Additionally, they are effective antioxidants without any negative side effects (Aiyegoro *et al*., 2010). Conventional medicine makes extensive use of plants, and it is generally known that they have therapeutic potential. They serve as a source of several potent and strong medications that are utilised medicinally in multiple countries. People in a region use the abundance of plants for food, medicine, and a variety of other uses. A wide range of phytochemicals, including alkaloids, tannins, flavonoids, steroids, glycosides, saponins, and oxalates, are present in many therapeutic plants (Alagesaboopathi *et al.*, 2011).

Inflammation is a condition characterised by localised increases in a range of leukocytes and complex mediator molecules such as prostaglandins, as well as different pathological alterations linked with localised vascular and cellular responses (Mantri and Witiak, 1994). Modern medications, on the other hand, are useful in the treatment of inflammation and related disorders, but their usage is frequently restricted due to adverse effects (Lipsky *et al.*, 1999). Ethnomedicinal plants are increasingly being used as a substitute for contemporary pharmaceuticals (Gupta *et al*., 1994). Furthermore, the practise of employing phytotherapy as a treatment option has gained attention in recent years, necessitating the development of novel anti-inflammatory medicines with minimal detrimental reactions (Prabha *et al.*, 2019). Biochemical targets that interact with peroxidation include proteins, amines, and DNA. A recent study linked the antioxidant properties of several plants to cellular oxidative prevention and a variety of human illnesses,

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including cancer, atherosclerosis, ageing, inflammation, and some nervous system problems (Dhalwal *et al.*, 2005).

In numerous indigenous cultures, the *A. comosus* (Pineapple) from the family Bromeliaceae has been used as a medicine (Mondal *et al.*, 2011) due to the presence of the enzyme bromelain, a protein digestive enzyme. The crude extract from pineapple contains closely related thiol proteases and exhibits fibrinolytic, anti-edematous, antithrombotic, and anti-inflammatory activities both *in vitro* and *in vivo*. Chemically speaking, bromelain has been used as a phytotherapeutic agent since 1875 (Pavan *et al.*, 2012). In the human gut, bromelain may be absorbed without decreasing its biological action. It is readily accessible to the general public in pharmacies and health food shops in the USA and Europe and is also regarded as a dietary supplement (Ley *et al.*, 2011).

The fruit juice of the pineapple is used by the Garo tribal population in Bangladesh's Netrakona area to treat fever, while pineapple leaf juice is used to treat helminthiasis and jaundice. Phytochemical constituents of pineapple include 2, 5-dimethyl-4-hydroxy-3(2H)-furanone, 5-hydroxytryptamine, acrylic acid, ananasic acid, beta-methyl-thiopropionicacid methyl ester, beta-methyl-thiopropionic acid ethyl ester, ergosterol peroxide, and stigmast-5-ene-3-beta-7-alpha-diol. The plant's leaves have been used to make chemicals including, ananasate, 1-O-caffeoylglycerol, 1-O-p-coumaroyl-glycerol, caffeic acid, p-coumaric acid, beta-sitosterol, and daucosterol (Borokini *et al.*, 2013). *A. comosus*, which is rich in bromelain (Huang *et al.*, 2015) along with other phytoconstituents like terpenoids and phenolic acids, *viz.*, limonene, butyric acid, isoamyl acetate, gallic acid, ethyl hexanoate, ethyl heptanoate, and water. Bromelain is a glycoprotein that contains an oligosaccharide in its molecular structure consisting of xylose, fructose, mannose, and N-acetylglucosamine.

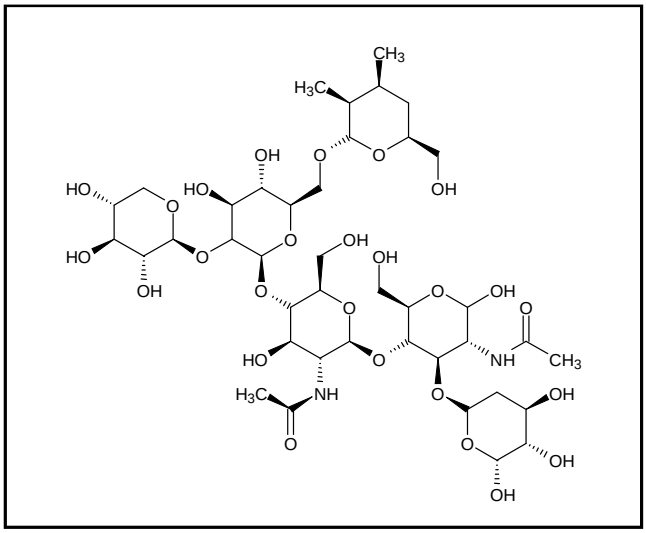

Figure 1: Structure of bromelain.

In this present study, aimed to extract the ethanolic extract of *A. comosus* (EPAC) *peel* along with screening of phytochemicals present in EPAC. The acute and chronic anti-inflammatory activity was performed on carrageenan-induced paw edema and cotton pellet method in rat models.

2. Materials and Methods

2.1 Chemicals

Ascorbic acid, 1 mM ferric chloride, 5 mM potassium ferric cyanide, and organic reagents such as methanol, ethanol, carrageenan, indomethacin, and others were purchased from Sigma Aldrich and SD Fine Chemical in Mumbai and were of analytical grade.

2.2 Preparation of *A. comosus* peel extract

The peel of *A. comosus* (Family-Bromeliaceae) was collected from Tamil Nadu, India, and identified by the Agriculture University, Coimbatore, Tamil Nadu, India. The whole plant was washed thoroughly with distilled water, and then the peels were dried at room temperature for 4-5 weeks and powdered by using a blender, which was subsequently sieved for powder, and the soaked powder was filtered. The coarse particles collected were used for further studies. 100 g of powdered. *A. comosus* was mixed with 500 ml of ethanol and extracted for 72 h in a Soxhlet apparatus. The crude extract obtained was further concentrated under vacuum, and this was used for further phytochemical analysis and anti-inflammatory activity.

2.3 Phytochemical analysis

To identify the phytoconstituents, the peel extract of EPAC was subjected to preliminary phytochemical screening for the presence of various secondary metabolites by using a standard procedure (Harborne *et al.*, 2005).

2.4 Determination of amount of ascorbic acid in EPAC

2.4.1 Preparation of standard ascorbic acid solution

A standard solution of ascorbic acid is prepared by dissolving 100 mg in 100 ml of distilled water. A working standard solution of 100 µg/ml was prepared by further dilution of the above standard stock solution with distilled water (Terpos *et al.*, 2012).

2.4.2 Preparation of working standard

Aliquots of the working standard solution of ascorbic acid (1.0-6.0 ml) were accurately measured and transferred into a series of 10 ml volumetric flasks. For each of the above aliquots, 1 ml of 1 mM ferric chloride and 1 ml of 5 mM potassium ferric cyanide were mixed together by vigorous shaking for 10 min (Terpos *et al.*, 2012). When the Prussian blue colour complex is formed, the absorbance is measured at 709 nm by using UV-V is spectroscopy (Shimadzu UV-V is double beam spectrophotometer, Model LTV 1800). The calibration graph is constructed by plotting the absorbance against the concentration of the drug.

2.5 Evaluation of anti-inflammatory activity

2.5.1 Animals

The albino wistar rats (weighing 150-200 g) were obtained from our institutional animal house, Nandha College of Pharmacy, Erode, Tamil Nadu, India, and maintained under a constant 12 h light and dark cycle at 21-23°C. The animals were maintained under the guidelines of the National Institute of Nutrition, Hyderabad, India. The study was approved by the Institutional Ethics Committee, Reg. No. 688/PO/Re/S/02/CPCSEA. Throughout, the experimental

period, all rats were fed normal laboratory chow, a standard pellet diet, and water.

2.5.2 Carrageenan-induced paw edema in rats (acute model)

The rats were split into four groups of six each. Group I received 0.5% CMC and served as the normal control; Group II received Indomethacin (10 mg/kg) and served as the standard; and Groups III and IV received the EPAC at doses of 200 and 400 mg/kg, respectively. Acute inflammation was produced by the administration of 0.1 ml of 1% w/v carrageenan in normal saline to the subplantar aponeurosis of the right hind paw of rats. Drugs were administered 1 h before the injection of carrageenan, and the paw thickness was measured by using vernier calliper at 0 min, 30 min, 1 h, 2 h, and 4 h, respectively, after the carrageenan injection (Prabha *et al*., 2019). The percentage inhibition of that paw edema was calculated by using the formula:

% inhibition=Tc × Tt /Tc ×100

where,

Tt-thickness of paw perimeter in test;

Tc-thickness of paw perimeter in control.

2.5.3 Cotton pellets induced granuloma in rats (chronic model)

The granuloma in rats was induced by implanting 50 mg of cotton pellets (Prabha *et al*., 2019; Punit *et al*., 2019). The cotton pellet granuloma model investigates the proliferation phase of inflammation. The rats were divided into four groups of six each and given the EPAC at different doses, *viz*., 200 mg/kg and 400 mg/kg. Standard indomethacin at 10 mg/kg was administered orally for seven consecutive days. On the eighth day, all the rats were sacrificed, and the cotton pellets covered by the granulomatous tissue were excised and dried in a hot air oven at 60°C till a constant weight was achieved. Granuloma weight was obtained by subtracting the weight of the cotton pellet on day 0 (before the start of the experiment) from the weight of the cotton pellet on the eighth day. Granuloma formation was measured by the increase in the pellets, dry weight using the following formula:

% inhibition = C × T/C × 100

where,

T = test and C = control.

3. Results

The ethanolic peel extract of *A. comosus* was subjected to phytochemical analysis, and the presence of flavonoids, tannins, saponins, sterols, carbohydrate, and glycosides were found in this extract as secondary metabolites.The presence of ascorbic acid in the ethanolic peel extract of *A. comosus* was confirmed by UV-Vis spectroscopy, which showed a linearity graph that had been plotted using the standard ascorbic acid concentration of 100 µg/ml. From the result, the concentration of ascorbic acid present in the ethanolic peel extract of *A. comosus* was found to be 0.42 µg/ml.

The EPAC showed significant anti-inflammatory activity in a dose-dependent manner, *viz*., 200 and 400 mg/kg on the carrageenin-induced model, and the percentage of inhibition at 4th h ($p \leq 0.01$) were found as 28.77 % and 51.69 %, respectively, when compared to standard drug as 82.98 % (Table 1).

The cotton pellet-induced granuloma formation is studied to understand its potential in the sub-acute inflammatory phase. Administration of indomethacin at 10 mg/kg resulted in a 42.25 % wet weight reduction, whereas, the ethanolic peel extract of *A. comosus* at 200 and 400 mg/kg reduced by 12.16 %, 23.58 % and 32.52 % of wet weight, respectively. The EPAC at different doses (200 and 400 mg/kg) showed a suggestive reduction in dry weight as well as 18.62%, 27.83%, and 38.72%, respectively. Thus, the standard drugs indomethacin and EPAC produced significant anti-inflammatory activity by inhibiting the wet and dry weight of cotton pellets (Table 2).

Table 1: Acute anti-inflammatory activity by carrageenan induced paw edema method of ethanolic peel extract of *A. comosus*

Groups	Dose (mg/kg)/PO	Paw thickness (mm) ± SD (% inhibition)			
		1 h	2 h	3 h	4 h
Carrageenan (group I)	0.1 ml of 1%	1.79 ± 0.12	1.88 ± 0.15	1.94 ± 0.16	1.97 ± 0.17
Carrageenan + Indomethacin (group II)	10	1.17 ± 0.21 (68.37 %)	1.10 ± 0.54** (76.36 %)	1.06 ± 0.14** (77.35 %)	0.98 ± 0.086** (82.98 %)
Carrageenan + EPAC (group III)	200	1.60 ± 0.154 (23.12 %)	1.55 ± 0.124 (25.16 %)	1.47 ± 0.275 (27.89 %)	1.39 ± 0.006* (28.77 %)
Carrageenan + EPAC (group IV)	400	1.45 ± 0.08 (35.86 %)	1.36 ± 0.143 (42.64 %)	1.29 ± 0.104* (45.73 %)	1.18 ± 0.114** (51.69 %)

All values are presented as mean ± SEM, n=6. One way ANOVA, followed by Dunnett's test was performed as the test of significance *p<0.05 and **p<0.01 Vs control.

Table 2: Chronic anti-inflammatory activity of ethanolic peel extract of *A. comosus*

Groups	Dose (mg/kg)/PO	Weight of cotton pellet granuloma (mg)	Percentage inhibition
Control group (group I)	Distilled water	59.44 ± 1.28	-
Indomethacin (group II)	10	34.12 ± 0.32	42.25 %
EPAC (group III)	200	52.21 ±0.45	12.16 %
EPAC (group IV)	400	45.42 ± 0.31**	23.58 %

All values are presented as mean ± SEM, n=6. One way ANOVA, followed by Dunnett's test was performed as the test of significance **$p<0.01$.

4. Discussion

Inflammation is a reaction to potentially harmful stimuli such as cellular injury and infection (Lumeng and Saltiel, 2011). It is activated to restore tissue or the system to its previous state. Basic concepts of inflammation include increased blood flow, erythema of the affected region due to erythrocyte accumulation, and edema (Punchard *et al.*, 2004). The production of cytokines and early-stage proteins and the movement of leukocytes to the wounded region are all caused by inflammation (Lumeng and Saltiel, 2011). Inflammation is already linked to the advancement of a wide range of human illnesses, including cardiovascular, digestive, dental, and urinary issues. Melanoma is also associated with inflammation and the ageing process, metabolic syndrome, adiposity, neuro degenerative disorders, gastritis (Saltiel and Lumeng 2011; Lalrinzuali *et al.*, 2016).

Carrageenan-induced rat-paw edema is a suitable experimental animal model for investigating the acute anti-inflammatory effect of natural products and is believed to be biphasic. The first phase (1 h) involves the release of serotonin and histamine, and the second phase (over 1 h) is mediated by prostaglandin and the cyclooxygenase products, and the continuity between the two phases is provided by kinins (Duraisami *et al.*, 2021; Zhou *et al.,* 2008). Our findings suggested that the ethanolic peel extract of *A. comosus* could inhibit both phases of carrageenan-induced edema.

Cotton pellet-induced granuloma formation is used as a preclinical model to study how different diseases affect macrophage function, granuloma formation, survival, and growth. Inflammation is induced in three stages when a cotton pellet is implanted transdermally. The pellet's wet weight increased during the transductive phase; Evans blue was released from the circulation around the granulation during the oxidative stage; and finally, the pellet's bulk density increased during the proliferating stage (Olajide *et al.*, 2000). When the ethanolic extract was given at 400 mg/kg, it dramatically decreased the production of granulomatous cells when compared to the control group.

5. Conclusion

This study concluded that the ethanolic peel extract of *A. comosus* was subjected to evaluation for anti-inflammatory activity by carrageenan-induced paw edema (acute model) and cotton pellet granuloma (chronic model) methods. The anti-inflammatory activity of the EPAC may be due to the presence of the enzyme bromelain, a protein digestive enzyme, which is closely related thiol proteases and exhibits fibrinolytic, anti-edematous, antithrombotic, and anti-inflammatory activities both *in vitro* and *in vivo*. However, further studies are required to understand their possible molecular mechanisms of action against inflammation and associated diseases.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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