International Journal of Phytopharmacy **Research Article**
ISSN: 2277-2928 (Online)
Journal DOI:https://doi.org/10.7439/ijpp

Phytochemical and pharmacological evaluation of *Artocarpus altilis* (Breadfruit) for Anthelmintic Activity

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Abstract

In the current in vitro study, 10 mg/ml concentration of ethanolic extract of Artocarpus altilis (*A. altilis*) produced a statistically significant anthelmintic activity that is comparable with the conventional anthelmintic agent, Albendazole. This finding is additionally in line with the clinical study that confirmed the efficacy of the plant against nematodes in calves and superior to an in vitro study that reported a moderate level of anthelmintic activity from the rind of *A. altilis*. *A. altilis*, is mainly used as an anthelmintic agent in traditional practice. Concordant with this, in EHIA of the present study, ethanolic extract of *A. altilis* fruit induced a significant egg hatching inhibition of 98.67%, at 1 mg/ml concentration. In which fruit extracts are used as an anthelmintic in Pheretimaposthuma infestation of sheep. Furthermore, the genus is a rich source of sesquiterpene lactones and flavonoids that might have anthelmintic activity with low risk of mammalian toxicity.

Keywords: *Artocarpus altilis*, Breadfruit, Anthelmintic

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***Article History:**
Received: 06/7/2025
Revised: 05/08/2025
Accepted: 09/08/2025
DOI: https://doi.org/10.7439/ijpp.v15i1.5857

QR Code

How to cite: Kavita Srivastava, Prashant Soni and Amrita Bhaiji. Phytochemical and Pharmacological Evaluation of *Artocarpus altilis* (Breadfruit) for Anthelmintic Activity. *International Journal of Phytopharmacy* 2025; 15(1): e5857. Doi: 10.7439/ijpp.v15i1.5857 Available from: https://ssjournals.co.in/index.php/ijpp/article/view/5857

1. Introduction

Helminth infections are one of the most prevalent diseases in developing and developed countries [1]. Globally, an estimated 2 billion people are infected by intestinal nematodes [2]. Anthelmintic drugs are used for the control of parasitic infections caused by helminths T [3].

Hedemands for new and effective anthelmintic is immense, as the drugs currently employed in the control of helminths is expensive and most of them lose their efficacy in 20 years due to the problem of resistance [4-5]. It is extremely hard to eradicate helminthiasis because of the close association between these diseases and poverty. The clinical development of these common and ubiquitous infections is such that they are generally neglected until they become manifested [6]. They are more frequent in hot climates and in places with poor sanitary conditions, the presence of large water tanks and carriers of parasites and contaminated food and water [7-8]. This does not mean, however, that good economic conditions constitute a complete safeguard against such infections [9]. Moreover, individuals from more affluent countries might well acquire such infections during travel to more endemic regions. Until such time as effective vaccines can be discovered, anthelmintic chemotherapy is the only effective, practical and inexpensive way of keeping such infections under control [10-12]. Helminth infections resulting to diseases such as ascariasis, hookworm infection and schistosomiasis constitute the bulk of the 13 diseases classified as neglected tropical diseases (NTDs) by the WHO. The search for novel anthelmintics has traditionally involved two approaches, the empirical and the selective methods [13]. The empirical approach involves the screening of large numbers of chemicals, quite unrelated to each other, possessing no

known anthelmintic activity and screened that one or more of them may exhibit sufficient activity to constitute a chemical lead. This method is most commonly used in large-scale drug development programs [14]. The selective approach involves biological investigation of the activity of chemicals allied structurally to those known to possess activity against a particular organism. The major objective of this approach is increased activity or decreased toxicity through chemical modification of the parent compound. This approach has recently been used in a drug development program funded by a Primate Foundation

Parasitic worms or helminths cause chronic and sometimes deadly diseases that have a major socio-economic impact worldwide. In humans, the disease caused by the parasitic worms is about 14 million globally, also called neglected tropical diseases (NTD) [15-16]. In agricultural animals, diseases caused by parasites led to losses of about billions of dollars per year throughout the world. Gastrointestinal nematodes (GI), such as hookworms, whipworms, and roundworms affect under 15 years most [17]. Approximately more than 10% of the population is infected by GI nematodes worldwide. As of now, no vaccines are available in the market, so, control of helminths lies on the sum of effective drugs, called anthelmintics, but their inadequate use causes serious drug resistance problems worldwide, so, urgent need is required for isolating, identifying new anthelmintic drugs, for humans, it lies on chemotherapy [18-19]. Parasitic nematodes in human are of two types: intestinal nematodes and tissue or blood nematodes [20].

Interest in traditional medicines is not new but has been spurred in recent years by methodological advances in ethno botanical and pharmacological studies [21-22]. However, on practical grounds herbal medicines present with problems like misleading botanical identification, adulteration, variability in the application of common standardization procedures and above all limited studies towards ascertaining the correct origin of the drug [23]. Hence, scientific evaluation of herbal drugs with promising therapeutic use is highly essential [24-25]. The observation, identification, and experimental investigation of the ingredients and the therapeutic effects of indigenous drugs are all interdisciplinary fields of research [26-27]. A number of plants/extracts are reported to have anthelmintic activity. Most of the studies reported *in vitro* activity and only few studies report *in vivo* activity [28]. Therefore, further research is necessary to investigate the molecular mechanism of action of the reported anthelmintic plants and extracts. Additionally, there is a need to either modify existing anthelmintic agents or explore new molecular targets to develop next-generation anthelmintic agents [29].

Now a days novel anthelmintic targets like lysine deacetylases, KDAC inhibitors, kinase inhibitors are explored. Modification of chemical structure and combination of known anthelmintics is also one of the ways to combat this challenge. Drug repurposing is also an emerging trend in anthelmintic drug discovery.

The present work has been taken up to investigate the anthelmintic potential of extracts of crude drugs which have been mentioned in traditional texts and establish a correlation between the phytochemical andpharmacological profile, which has not yet been carried out for aforesaid activities. Hence efforts have been made to assign Pharmacognostic, phytochemical and pharmacological standards on a scientific basis.

Thus, in the present study phytochemical investigation of *Artocarpus altilis* and screening for anthelmintic potential was performed.

2. Materials and Methods:

2.1 Collection of Plant Samples:

Artocarpus altilis fruit was obtained locally from Bhopal. Fruits were carefully and mechanically separated washed with water. After drying in shade, they were powdered and stored. The fruits were extracted using Soxhlet successively with ether, chloroform and ethanol for 24 hours. The extract obtained was stored in airtight container in a desiccator. Preliminary phyto-chemical analysis was carried out on the ethanolic extract of *Artocarpus altilis* to assess the presence of alkaloids, glycosides, saponins, flavonoids and steroids.

2.3 Animals:

Earthworms (*Pheretimaposthuma*) were randomized and allocated into different groups (5 per group). Pheretimaposthuma were kept at a temperature of 24 ± 2oC and relative humidity of 30-70%. A day with a 12:12 light: dark cycle with free access to rodent feed and water.

2.4 Preliminary Phytochemical Screening:

The preliminary phytochemical screening was carried out on the petroleum ether, chloroform and ethanolic extracts of *Artocarpus altilis* for qualitative identification. Tests for common phytochemicals were carried out by standard methods described in Practical Pharmacognosy.

2.5 Acute Toxicity Study:

The acute toxicity studies were carried out for ethanolic extract of *Artocarpus altilis* using fixed dose method according to OECD guidelines no. 425.

2.6 In vitro anthelmintic activity:

2.6.1 Adult motility assay:

A total of about 6-8 adult Pheretimaposthuma were used to assess the anthelmintic effect of extracts

against mature Pheretimaposthuma on adult motility assay (AMA), according to the method described by Sharma *et al*. Each plant extract was tested on different concentrations (10, 5, 2.5, and 1.25 mg/ml) prepared in PBS respectively.

The assay was conducted in six groups.

Group I and Group II received crude ethanol extract from the fruits of *Artocarpus altilis*, respectively.

Group III and IV received 0.25 mg/ml of Albendazole (positive control) and PBS respectively.

Inhibition of motility was taken as an indication of worm mortality/paralysis. To assess the motility inhibition effect of the extracts, the observations were taken at regular time intervals until the 7th hour after treatment.

Worms not showing any motility were taken out and placed in lukewarm PBS for 10 minutes and in case of revival in motility, the observed worms were counted as alive; otherwise, they were counted as dead.

2.6.2 Egg hatch test (EHT):

In the current study, the egg hatch test (EHT) has been evaluated as an *in vitro* technique to detect Albendazole (ABZ) resistance in Fasciola hepatica. The intra- and inter-assay variations of the EHT were measured by means of the coefficient of variation in different fluke isolates and over time; then, the results of the EHT were compared with the ―gold standard‖ controlled efficacy test, to assess the in vivo anthelmintic efficacy.

The EHT was used later to evaluate the intra-herd variability regarding the level of ABZ resistance in calves infected by the same fluke isolate. Finally, several factors of the initial protocol were modified to improve the simplicity of the assay, including the incubation time of eggs with the drug and the use of eggs collected from faeces. The greatest uniformity between results within the assay and over time until 8 weeks after gallbladder collection (the deadline proposed for egg analysis) was obtained with an ABZ concentration of 0.5 µm. The length of exposure to ABZ was shown to be critical, as prolonged incubation (15 days) led to a change of ovicidal activity. The ABZ concentration of 0.5 µm is suggested as a possible discriminating dose to predict ABZ resistance, due to the close agreement between the results of the EHT at an ABZ concentration of 0.5 µm and those of the in vivo assays.

2.6.2.1 Egg Hatch Test:

The in vitro EHT described in the current study was based on a previous study (Alvarez *et al*., 2009). In brief, eggs of different fluke isolates were collected from gallbladders of infected animals by suctioning bile with a 10 ml syringe and a 19G needle. After collection, the bile was washed several times using tap water and eggs were recovered by sedimentation. The eggs were identified and stored at 4 ºC in darkness until required.

Working solutions of ABZ were prepared by dissolution of ABZ (≥99 % purity, Sigma–Aldrich, St. Louis, MO, USA) in pure methanol to reach final concentrations of 500, 50 and 5 µM.

Fluke eggs (approximately 200) in 1 ml of water were incubated at 25 ºC in darkness for a 12 h period with ABZ, at concentration of 5, 0.5 or 0.05 nmol/ml.

10 µl of each working solution or methanol was added to the egg suspension, reaching a final methanol concentration of 1% (v/v).

In each assay, between 3 and 5 replicates were used for each drug concentration. Control eggs were incubated only with 10 µl of methanol in 1 ml of water.

After incubation, all eggs were washed gently with tap water three times to facilitate drug removal, and kept in darkness at 25 ºC for 15 days. After this period, eggs were exposed to light for 2 h to stimulate the hatching of miracidia. Immediately afterwards, 1 ml of 10% (v/v) buffered formalin was added to each tube in order to prevent further hatching of eggs.

Hatched and unhatched (undeveloped) eggs were evaluated using an optical microscope (DM IL, Leica, Germany). The term ―hatched eggs‖ includes hatched and embryonated eggs.

In all tests, embryonated eggs represent not more than 10 % of total-hatched eggs‖.

Approximately 90-110 eggs were counted to estimate the proportion of hatched eggs in each tube.

The percentage of eggs hatched is presented as the arithmetic mean ± standard deviation (SD).

The ovicidal activity, expressed as a percentage, was estimated for each dose using the following formula:

$$\textit{Ovicidal activity}\ (\%) = \frac{(\%\,eggs\ \text{hatched in control}) - (\%\ eggs\ \text{hatched after drug incubation}) \times 100}{\%\ eggs\ \text{hatched in control}}$$

To compare several EHT results, a parametric test (Student's t-test or ANOVA + Tukey) was carried out using the Instant 3.0 Software (Graph Pad Software, CA, USA).

A value of $P < 0.05$ was considered to be statistically significant.

2.6.2.2 Egg recovery:

The ability of the extracts to inhibit egg hatching was conducted according to the procedure described by Coles *et al.*

Eggs were washed thrice with distilled water and adjusted to a concentration of 100-200 eggs/ml using the McMaster technique.The suspension was centrifuged for 5 minutes at 1500 rpm and the supernatant was discarded.Approximately 100 eggs in 200 μl of distilled water were pipetted into each well of a 48-well micro titer plate.To each of the test wells, 200μl of each plant extract at

concentrations of 0.1, 0.25, 0.5, and 1 mg/ml was added to a final volume of 400 μl per well. Similarly, 200μl of Albendazole (99.8% pure standard reference) at a concentration of 0.25 mg/ml was used as a positive control, while distilled water (200 μl) was used as a negative control. The experiment was conducted in duplicates for each concentration and replicated three times. In this assay, all plates were incubated at 37°C for 48 hr. A drop of Lugol's iodine solution was added to each well to stop further hatching, and all the unhatched eggs and L1 larvae in each well were counted under a dissecting microscope. Finally, percent inhibition of egg hatching was calculated: Percent inhibition = $100(1 - P_{test}/P_{control})$, where P = number of eggs hatched in EHIA.

2.6.2.3 Test Procedure:

Egg hatch test was conducted by the method described by Coles *et al*., 1992. Egg suspension of (0.2 ml; 100 eggs) was distributed in a 24 well multi-well plate (Flow Laboratories) and mixed with the same volume of different concentrations (0.25 to 8 mg /ml) of plant extract. The positive control wells received different concentrations (0.09 to 3.0 µg/ml) of oxfendazole (Systamex—ICI Pakistan, Ltd., 2.265%, w/v) in place of the plant extracts, while the negative control wells contained the diluent and the egg solution. The eggs were incubated in this mixture at 27°C. After 48 hours, two drops of Lugol's iodine solution were added to stop the eggs from hatching. All the eggs (dead and embryonated) and hatched larvae in each well were counted. There were three replicates for each treatment and control.

2.6.2.4 Measurements:

Observation of clinical signs and/or death was measured daily. The body weight of the sheep was recorded weekly. Faecal egg counts per gram of faeces (EPG) were performed on each animal on days 0, 3, 6, 9, 12 and 15 post-treatment (PT) and were evaluated for the presence of worm eggs by salt floatation technique (MAFF, 1979). The eggs were counted by the McMaster method (Soulsby, 1982). Egg count percent reduction (ECR) was calculated using the following formula:

ECR (%) = {(pre-treatment EPG – post-treatment EPG)/pre-treatment EPG} × 100

2.9 Statistical analysis:

For egg hatch test, probit transformation was performed to transform a typical sigmoid dose response curve to linear function. The extract concentration required to prevent 50%, i.e., lethal concentration 50 (LC50) of hatching of eggs was calculated from this linear regression (for y = 0 on the probit scale). The data from adult motility assay and in vivo experiments were statistically analyzed using SPSS software. The results were expressed as mean ± standard error of mean (SEM).

4. Results and Discussion

Table 1: Estimation of Phytochemical analysis of *A.altilis* fruit extract

S. No	Chemical test		PEE	CE	EE
1	TestforAlkaloids	Hager'sTest	+ve	+ve	**+ve**
		Mayer'sTest	+ve	+ve	**+ve**
		Dragendroff'sTest	+ve	+ve	**+ve**
		Wagner'sTest	+ve	+ve	**+ve**
2	Testforcarbohydrates	Molisch'sTest	+ve	+ve	**+ve**
		Fehling'sTest	+ve	+ve	**+ve**
		Barfoed'sTest	+ve	+ve	**+ve**
		Benedict'sTest	+ve	+ve	**+ve**
3	Testforcardiacglycosides	Baljettest	+ve	+ve	**+ve**
		Legaltest	+ve	+ve	**+ve**
4	Test for Anthraquinone glycosides	Modified Borntrager'sTest	+ve	+ve	**+ve**
		Borntrager'stest	+ve	+ve	**+ve**
5	Testfor saponin glycosides	Foamtest	+ve	+ve	**+ve**
		Haemolytictest	+ve	+ve	**+ve**
6	Testforfixedoil	StainTest	+ve	+ve	**+ve**
7	TestforProteinsandAmino acids	Million'sTest	+ve	+ve	**+ve**
		BiuretTest	+ve	+ve	**+ve**
		NinhydrinTest	+ve	+ve	**+ve**
8	TestforPhytosterolsandtriterpenoids	Liebermann-BurchardTest	+ve	+ve	**+ve**
		SalkowskiTest	+ve	+ve	**+ve**
9	Testforflavonoids	Shinodatest	+ve	+ve	**+ve**
10	Testfortannin	Leadacetatesolution	+ve	+ve	**+ve**
		5%$FeCl_3$solution	**+ve**	**+ve**	**+ve**

PEE = Petroleum Ether Extract**, CE** =Chloroform Extract**, EE** =Ethanolic Extract

Table 2. Preliminary acute toxicity levels of crude extracts

Group	Extracts DoseLevels(mg/kg)			N	N^0deadPEE	N^0 dead CE	N^0deadEE
	PEE	CE	EE				
Group1	100	100	100	6	0	0	0
Group2	200	200	200	6	0	0	0
Group3	500	500	500	6	0	0	0
Group4	1000	1000	1000	6	0	0	0
Group5	2000	2000	2000	6	1	2	1
Control	1mldH_2O	1mldH_2O	1mldH_2O	6	0	0	0

PEE = Petroleum Ether Extract**, CE =**Chloroform Extract**, EE =**Ethanolic Extract

Table 3: Results of Adult Worm Motility Test

Treatment	Conc. (mg/ml)	15 mins	30 mins	45 mins	60 mins	75 mins	90 mins	105 mins
A. altilis fruit extract	10	4.00 ± 0.58^{cdefa}	5.67 ± 0.33^{defa}	6.67 ± 0.33	7.67 ± 0.33^{efa}	8.67 ± 0.33^{efa}	9.67 ± 0.33^{efa}	10.00 ± 0.00
	5	2.00 ± 0.58	3.33 ± 0.33	4.67 ± 0.33	6.00 ± 0.58	7.67 ± 0.33	9.00 ± 0.00	10.00 ± 0.00
	2.5	1.67 ± 0.33	3.33 ± 0.33	4.67 ± 0.33	6.33 ± 0.67	8.33 ± 0.33	9.33 ± 0.33	10.00 ± 0.00
	1.25	0.33 ± 0.33^{cdefb}	1.00 ± 0.58^{cdefb}	2.00 ± 0.58^{cdeb}	4.00 ± 0.58^{cdeba}	5.00 ± 0.58^{cdba}	6.67 ± 0.33^{cdba}	7.67 ± 0.33^{cdeba}
Albendazole	0.25	4.00 ± 0.58^{cdefa}	5.67 ± 0.33^{defa}	8.33 ± 0.33^{cdefb}	9.67 ± 0.00^{cdefa}	10.00 ± 0.00^{defa}	10.00 ± 0.00^{efa}	10.00 ± 0.00^{efa}
PBS	0.00 ± 0.00	0.00 ± 0.00^{cdefb}	0.00 ± 0.00^{cdfb}	0.00 ± 0.00^{cdefb}	0.00 ± 0.00^{cdefb}	0.00 ± 0.00^{cdefb}	0.00 ± 0.00^{cdeb}	0.00 ± 0.00^{cdeb}

Data represent mean ±SD; one-way analysis of variance, ANOVA followed by Tukey's multiple Comparison Test (n=5), Values are compared with control animals, p<0.05.*P<0.01,**P<0.001,***P<0.0001.

3.1 Phytochemical Screening:

Phytochemical evaluation indicated the presence of alkaloids, flavonoids, saponins, cardiac glycosides, triterpenoids, phenolic and tannins in the *A. altilis fruit* extract.

3.2 Acute Toxicity Study:

The acute toxicity study was conducted and the mice were exposed up to a dose of 2000 mg/kg, so that 1/20th, 1/10th and 1/4th (i.e. 100 mg/kg, 200 mg/kg and 500 mg/kg orally) was selected for anthelmintic action. For anthelmintic action of petroleum ether extract, chloroform extract and ethanolic extract of fruit of *A. altilis was* administered in distilled water for oral route of administration.

3.4 Anthelmintic Activity:

3.4.1 Adult Motility Test:

The present study indicated that all concentrations of ethanolic fruit extracts of *A. altilis* produced a relatively comparable anthelmintic activity with the conventional anthelmintic agent, albendazole.

The anthelmintic activity of plant extracts increased with time.

Accordingly, after 7hr exposure of adult Pheretimaposthuma to the highest concentration (10 mg/m) of extracts, both plants produced a significant ($p < 0.05$) mortality of adult Pheretimaposthuma. Albendazole, on the other hand, killed all parasites within 5 hr at a concentration of 0.25 mg/ml. Altilis produced a relatively comparable anthelmintic activity with the conventional anthelmintic agent, albendazole.

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3.4.2 Egg Hatching Inhibition Assay:

Fruits of *A. altilis induced* a significant egg hatching inhibition effect in a concentration-dependent manner. Ethanolic extract of fruit of *A. altilis exhibited* a 98.67% and 88.3% inhibition, respectively, at 1 mg/ml concentration.

Furthermore, the egg hatch inhibitory efficacy profile of *A. altilis* extracts, as percentage of unhatched eggs at the end of the observation period, is as follows:
49.33 and 46.33% at concentration 0.1 mg/ml,
60.67 and 54.33 at 0.25 mg/ml,
72.67 and 68.33 at 0.5 mg/ml, and
94.63 and 90.33 at 1 mg/ml concentration of extracts, respectively.

4. Conclusion

In the current in vitro study, 10 mg/ml concentration of ethanol extract of fruit of *A. altilis* produced a statistically significant anthelmintic activity that is comparable with the conventional anthelmintic agent, Albendazole.This finding is additionally in line with the clinical study that confirmed the efficacy of the plant against nematodes in calves and superior to an in vitro study that reported amoderate level of anthelmintic activity from the rind of *A. altilis*. Moreover, similar to a study done by Prakash *et al*. on the alcoholic extract of *A. altilis* showed a significant anthelmintic activity of the plant as revealed by a concentration-dependent inhibition of transformation of eggs to the larva of Pheretimaposthuma.

The *in vitro* anthelmintic activity of tested plants is characterized by a decrease in hatching and reduced motility of the larvae and adult stage of Pheretimaposthuma.Accordingly, they have the potential to contribute in controlling gastrointestinal parasites of ruminants. Therefore, fractionation of the crude extracts and isolation of compounds to further evaluate the anthelmintic efficacy of these plants involving other parasite developmental stages are warranted.

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