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Protective Effect of *Terminalia arjuna* Against DBTC Induced Pancreatic Cancer in Male Wistar Rats

Kadiyala Harshitha[1] and Uma Sankar Gorla[2*]

[1]Pharmacology Division, University College of Pharmaceutical Sciences, Andhra University, Visakhapatnam, Andhra Pradesh, 53003- India.
[2]College of Pharmacy, KoneruLakshmaiah Education Foundation, Vaddeswaram, Andhra Pradesh, 522502-India.

Authors' contributions

This work was carried out in collaboration between both authors. Author KH designed the study, literature survey, wrote the protocol, and wrote the first draft of the manuscript. Author USG managed the analyses of the study, revised the draft and performed the statistical analysis. Both authors read and approved the final manuscript.

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ABSTRACT

Aims: To study the protective effect of hydroalcoholic bark extract of *Terminalia arjuna* against DBTC induced pancreatic cancer in male wistar rats.
Study design: Healthy male Wistar Albino rats weighing 150-200 g were segregated into four groups (n=6). Group I was considered as normal control, received normal saline (0.9%w/v, 1 ml/kg body weight, orally). Group II rats were treated with DBTC (6 mg/kg body weight, i.p.) which served as negative control. Group III and IV received *Terminalia arjuna* Linn bark hydroalcoholic extract at doses of 250 mg/kg body weight, per oral and 500 mg/kg body weight, per oral respectively.
Place and Duration of Study: University College of Pharmaceutical Sciences, Andhra University, Visakhapatnam, Andhra Pradesh, India, between May 2020 and July 2020.
Methodology: The experimental animals were segregated into four groups of six rats each. According to acute toxicity data, 250 mg/kg as low dose and 500 mg/kg as high dose of the test compound have been chosen for administration. All the drugs were given for 28 consecutive days to all the respective groups with standard pellet diet and water *ad libitum*. The assessment of

**Corresponding author: E-mail: umasankargorla@gmail.com;*

serum parameters such as α-Amylase, Lipase and blood glucose levels were carried out on 1st day, 14th day and 28th day to the respective groups.

Results: Pretreated groups of *Terminalia arjuna* Linn bark hydroalcoholic extract (250 mg/kg and 500 mg/kg body weight, orally) showed significant ($^{\#}p<0.001$) decrease in the levels of α-Amylase, Lipase and glucose in the blood when compared to DBTC (6 mg/kg body weight, i.p.) induced group which served as negative control.

Conclusion: This study suggests that *Terminalia arjuna* may have a protective role against DBTC induced pancreatic cancer in male wistar rats and further investigation may be required to confirm its therapeutic potentials clinically.

Keywords: Terminalia arjuna; DBTC; Pancreatic cancer; α-Amylase; Lipase.

1. INTRODUCTION

Cancer is a major public health issue worldwide and is the second leading cause of death in the United States [1]. Generally, cancer rates are highest in countries where the populations have the highest life expectancy, education level, and standard of living [2]. In 20th century, death rate of cancer has fallen from its peak in 1991 through 2018, for a total decline of 31%, due to early detection and treatment. Worldwide in 2020, there were 18.1 million new cases and 9.5 million cancer-related deaths (International agency for research on cancer). Pancreatic cancer is one of the most lethal of known cancers and the only treatment is surgery. It is the 7th most common cause of cancer related deaths in western countries. Pancreatic ductal adenocarcinoma (PDAC) constitutes more than 90% of all pancreatic cancer cases [3]. Some risk factors are known to increase the risk of pancreatic cancer namely diabetes over weight chronic pancreatitis, family history, diet such as red and processed meat (American cancer society) [4].

Despite of many challenges, novel treatment strategies currently in clinical trials including PEGPH20 (pegylated recombinant human hyaluronidase for stromal modulation) [5]. Ruxolitinib (JAK/STAT inhibitor) [6] and ibrutinib (Bruton's tyrosine kinase inhibitor) [7]. However, Natural medicine has been used in traditional medical system for thousands of years. Considering the significance of natural compounds as a source of medicine even today dried powdered bark of *Terminalia arjuna* have been selected because it has traditionally been used to treat a variety of illnesses [8]. *Terminalia arjuna* is a sacred medicinal plant commonly called as Thella Maddi belongs to Combretaceae family. It contains pale yellow flowers, grey and soft bark with abundance of phytochemicals such as hydrolysable tannins, glycosides, flavonoids and phenolics [9] which are used to treat plethora of diseases. Pharmacological investigations of *Terminalia arjuna* have been reported for the treatment of endothelial dysfunction, [10] antioxidant property, nitric oxide inhibitory activity, [11] anti-hypertensive property, [12] improves cardio-vascular endurance, [13] antidiabetic property, [14] and antifungal property. [15] Research evidences revealed that the hydroalcoholic extract of *Terminalia arjuna* have anti-colitis activity [16] and improves proinflammatory cytokines, cardiac and apoptotic indicators in myocardial infarction. [17] However, *Terminalia arjuna* has been less explored for its varying pharmacological properties, hence an attempt has been made to assess its anticancer activity in DBTC induced pancreatic cancer in male Wistar albino rats.

2. MATERIALS AND METHODS

2.1 Collection of Plant Material

The fresh bark of *Terminalia arjuna* was collected from Kambalakonda wild life sanctuary, Visakhapatnam, Andhra Pradesh, India in June 2020, identified and authenticated by Department of Botany, Andhra University, Visakhapatnam, Andhra Pradesh, India. The fresh bark was collected, properly cleaned, shade dried about one month at room temperature, powdered mechanically, sieved and stored in air tight container for further study.

2.2 Preparation of Hydroalcoholic Extract

Terminalia arjuna bark powder was weighed, packed in Soxhlet column and extracted with (70:30) ethanol and water by using Soxhlet extraction method for 48 hours. [18] The extracted liquid was concentrated for a period of 120-180 minutes by using distillation unit and desiccated overnight at room temperature. The

final extract was stored in stock vials, labelled and kept in refrigerator at 3±1℃ for further studies.

2.3 Experimental Animals

For the current study, healthy male wistar albino rats weighing 150-200 g were used. The rats were housed in polypropylene cages and were kept in standard laboratory conditions at 21±2°C temperature, 45-50% Humidity and 12 hr light / dark cycles. They were habituated to hygienic laboratory environment for 10 days on a standard pellet diet and water. The Institutional Animal Ethical Committee (IAEC) of A.U. College of Pharmaceutical Sciences, Andhra University under registration number No. 516/01/A/CPCSEA, approved the study protocol and all the research work were performed with the guidelines and regulations of IAEC and CPCSEA.

2.4 Acute Toxicity Study

The *Terminalia arjuna* bark extract was evaluated for acute oral toxicity in rats according to OECD guideline No. 425. [19] Prior to dosing, the rats were fasted overnight and the dosage was adjusted based on the fasted body weight. Single doses of 2000 mg/kg of *Terminalia arjuna* bark hydroalcoholic extract was administered to the rats orally by gavage using a suitable intubation cannula. Food was withheld for another 3-4 hr after treatment and observed continuously for any toxic symptoms. The animals were under continuous monitoringfor2weeks for any mortality, weight, physiological and psychological changes.

2.5 Study Protocol and Dosage Regimen

The experimental animals were segregated into four groups of six rats each. According to acute toxicity data, 250 mg/kg as low dose and 500 mg/kg as high dose of the test compound have been chosen for administration. In Group I, the rats were treated with normal saline (0.9%w/v, 1 ml/kg body weight, orally) to serve as normal control. Group II rats were treated with DBTC (6 mg/kg body weight, i.p.) which served as negative control. In Group III, rats were simultaneously treated with *Terminalia arjuna* Linn bark hydroalcoholic extract (250 mg/kg body weight, orally) and DBTC (6 mg/kg body weight, i.p.) dissolved in three parts of glycerol which serves as a low dose treatment group. In Group IV, rats were simultaneously treated with *Terminalia arjuna* Linn bark hydroalcoholic extract (500 mg/kg body weight, orally) and DBTC (6 mg/kg body weight, i.p.) dissolved in three parts of glycerol which serves as high dose treatment group. All the drugs were given for 28 consecutive days to all the respective groups with standard pellet diet and water *ad libitum*.

2.5.1 Biochemical analysis

Blood samples were collected and serum was separated on 1st day, 14th day and 28th day from the respective groups. Serum biochemical parameters such as α-Amylase, Lipase and blood glucose levels were assessed using standard assay kits (Erba Mannheim) with the help of clinical chemistry analyzer (Erba CHEM-7).

2.6 Statistical Analysis

All findings are expressed as Mean ± Standard Error of the Mean (*n*=6) and assessed by Analysis of Variance (ANOVA) accompanied by Bonferroni post tests for multiple comparative studies using Graph Pad Prism application, version 5.0. The "*P*" value $p<0.001$was considered as statistically significant.

3. RESULTS AND DISCUSSION

Despite recent therapeutic strategies in understanding the molecular mechanisms that contribute to cancer development, novel and effective treatment were always required to maintain this disease under control. [20] In the recent years, phytopharmacological research has been more popular around the world, and a significant data was developed to demonstrate the tremendous potential of phytocompounds used in many traditional systems. [21] In the current investigation, acute toxicity study reported that hydroalcoholic bark extract of *Terminalia arjuna*has LD_{50}>2000 mg/kg body weight. The hydroalcoholic extract of *Terminalia arjuna* bark extract was assessed for effect on serum α-Amylase, Lipase and glucose to understand its protective role in DBTC induced pancreatic cancer in male wistar rats. Pancreatic cancer cell proliferation markedly increases the levels of α-Amylase, Lipase and glucose levels in the blood due to more enzyme secretion.

The effect of administration of *Terminalia arjuna* Linn bark hydroalcoholic extract (250 mg/kg and

500 mg/kg body weight, orally) on serum activity of α-Amylase, Lipase and glucose levels as compared to DBTC (6 mg/kg body weight, i.p.) treated group as shown in Tables 1, 2 and 3. Significant difference were observed in the levels of α-Amylase, Lipase and blood glucose. As shown in Table 1, the DBTC treated group (Group II) showed a significant (*'*p<0.001*) raise in α-Amylase levels as compared to normal control group (Group I) indicating impairment in pancreas. Administration of *Terminalia arjuna* bark extract (250 mg/kg and 500 mg/kg body weight, orally) was found that α-Amylase levels was significantly reduced (*#'p<0.001*) and decreased the effects of DBTC as compared with DBTC alone treated group (Group II) (Fig 1).

Table 1. Effect of hydroalcoholic extract of *Terminalia arjuna* Linn bark on serum alpha amylase of DBTC induced wistar rats

Groups	Treatment	Day 1	Day 14	Day 28
Group I	Normal saline (0.9% W/V, 1 ml/kg)	432.01±0.34	437.3±0.23	433.0±0.51
Group II	DBTC (6 mg/kg)	470.4±1.8*	517.91± 0.65*	543.8±2.061*
Group III	Extract + DBTC (250 mg/kg + 6 mg/kg)	458.21±1.55*#	67.28±2.59*#	491.1± 3.09*#
Group IV	Extract + DBTC (500 mg/kg + 6 mg/kg)	445±2.26*#	453.17±4.4*#	461.27±1.711*#

Results are expressed as Mean±SEM (n=6). SEM = Standard error mean. The statistically significant difference has been determined by ANNOVA accompanied by Bonferroni post tests for multiple comparison and are statistically significant with ''p<0.001 compared with the control group, #'p<0.001 compared with the negative control. ANNOVA = Analysis of variance*

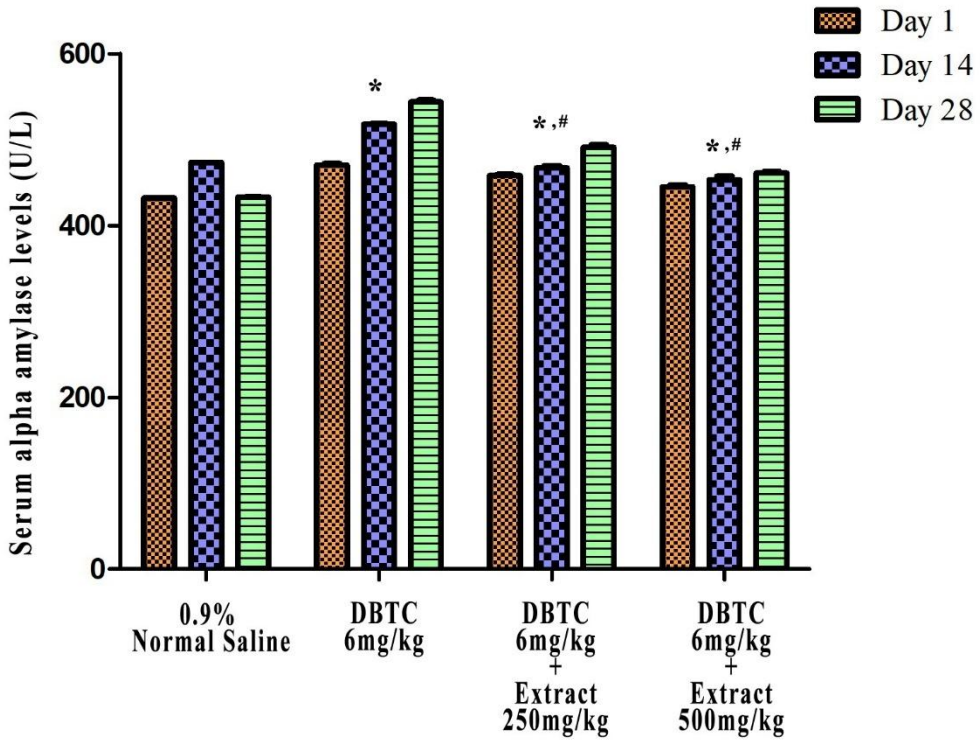

Fig. 1. Effect of *Terminalia arjuna* bark extract on serum alpha amylasein DBTC treated rats
''p<0.001 compared with the control group, #'p<0.001 compared with the negative control.*
Mean ± S.E.M = Mean values ± Standard error of means of six experiments

Administration of DBTC (6 mg/kg body weight, i.p.) significantly (*'*'p<0.001*) increase the serum lipase levels associated with pancreatic cell proliferation (Fig 2). Simultaneous administration of *Terminalia arjuna* bark extract (250 mg/kg and 500 mg/kg body weight, orally) and DBTC (6 mg/kg body weight, i.p.) exhibited significant (*#'p<0.001*) reduction in lipase levels in blood compared with the negative control as shown in Table 2.

Administration of DTBC (6 mg/kg body weight, i.p.) to the rats markedly increases the activity of α-Amylase and Lipase and significantly increases the levels of blood glucose (*'*'p<0.001*) when compared to the normal control as shown in Fig 3.Combined administration of *Terminalia arjuna* bark extract (250 mg/kg and 500 mg/kg body weight, orally) and DBTC (6 mg/kg body weight, i.p.) significantly decreases the glucose levels by inhibiting the effects of DTBC when compared to those administered with DTBC alone (*#'p<0.001*) as shown in Table 3.

Abnormal levels of α-Amylase, Lipase and glucose in the blood indicates pancreatic cell proliferation. The levels were normalized in *Terminalia arjuna* bark extract (250 mg/kg and 500 mg/kg body weight, orally) treated groups when compared with DBTC (6 mg/kg body weight, i.p.) treated group. Furthermore, *Terminalia arjuna* is a rich source of phytochemicals such as tannins, cardenolide, triterpenoid saponins, flavonoids, gallic acid, ellagic acid, phytosterols and minerals like zinc, copper, magnesium and calcium [22]. Many studies reported that *Terminalia arjuna* bark extract arjunoglucoside-I/II/III, arjunoside-I/II/III/IV, arjunic acid, arjunolic acid, earjunone, arjunolone, beta-sitosterol, proanthocayanidins and minerals [23]. The protective effect and antioxidant activity of *Terminalia arjuna* bark extract against N-nitrodiethylamine induced hepatocellular carcinoma in rats may be due to presence of above reported active ingrediants [24]. All the concentration (250 mg/kg and 500 mg/kg body weight, orally) which were studied

Table 2. Effect of hydroalcoholic extract of *Terminalia arjuna* Linn bark on serum lipase of DBTC induced wistar rats

Groups	Treatment	Day 1	Day 14	Day 28
Group I	Normal saline (0.9% W/V, 1 ml/kg)	26.57±0.29	28.56±0.14	28.74±0.17
Group II	DBTC (6 mg/kg)	36.51±0.62*	44.12±0.46*	47.9±0.26*
Group III	Extract + DBTC (250 mg/kg + 6 mg/kg)	33.53±0.75$^{*\#}$	39.9±0.47$^{*\#}$	44.04±0.38$^{*\#}$
Group IV	Extract + DBTC (500 mg/kg + 6 mg/kg)	30.23±0.40$^{*\#}$	33.74±0.36$^{*\#}$	35.33±1.05$^{*\#}$

Results are expressed as Mean±SEM (n=6). SEM = Standard error mean. The statistically significant difference has been determined by ANNOVA accompanied by Bonferroni post tests for multiple comparison and are statistically significant with "'p<0.001 compared with the control group, #'p<0.001 compared with the negative control. ANNOVA = Analysis of variance*

Table 3. Effect of hydroalcoholic extract of *Terminalia arjuna* Linn bark on serum glucose of DBTC induced wistar rats

Groups	Treatment	Day 1	Day 14	Day 28
Group I	Normal saline (0.9% W/V, 1 ml/kg)	84.53±0.04	84.7±0.21	84.68±0.22
Group II	DBTC (6 mg/kg)	92.56±0.14$^{*\#}$	116.36±0.90*	120.4±0.31*
Group III	Extract + DBTC (250 mg/kg + 6 mg/kg)	89.56±0.21$^{*\#}$	105.13±0.32$^{*\#}$	104.6±0.45$^{*\#}$
Group IV	Extract + DBTC (500 mg/kg + 6 mg/kg)	87.01±0.61$^{*\#}$	88.13±0.30$^{*\#}$	87.63±038$^{*\#}$

Results are expressed as Mean±SEM (n=6). SEM = Standard error mean. The statistically significant difference has been determined by ANNOVA accompanied by Bonferroni post tests for multiple comparison and are statistically significant with "'p<0.001 compared with the control group, #'p<0.001 compared with the negative control. ANNOVA = Analysis of variance*

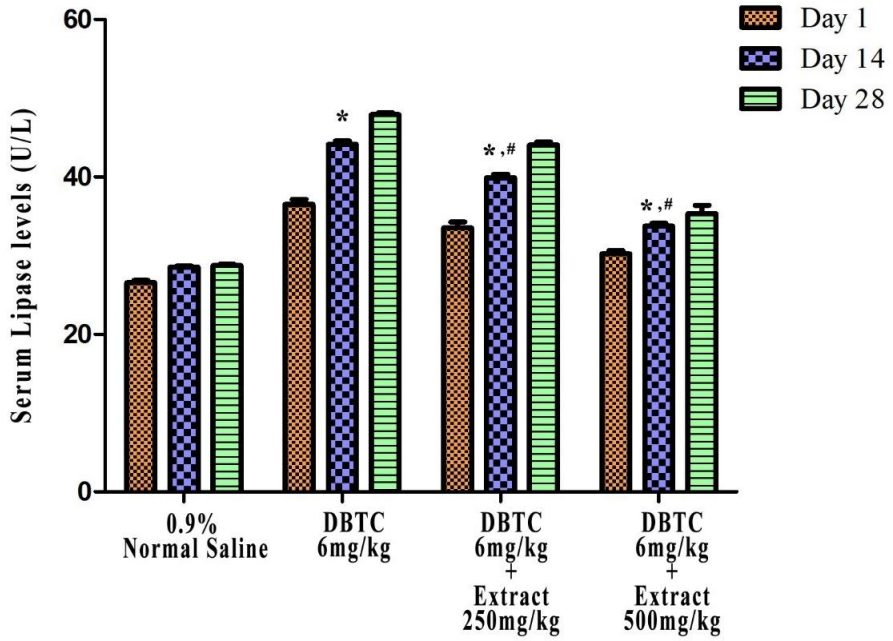

Fig. 2. Effect of *Terminalia arjuna* bark extract on serum lipase in DBTC treated rats

''p<0.001 compared with the control group, [#]'p<0.001 compared with the negative control.*
Mean ± S.E.M = Mean values ± Standard error of means of six experiments

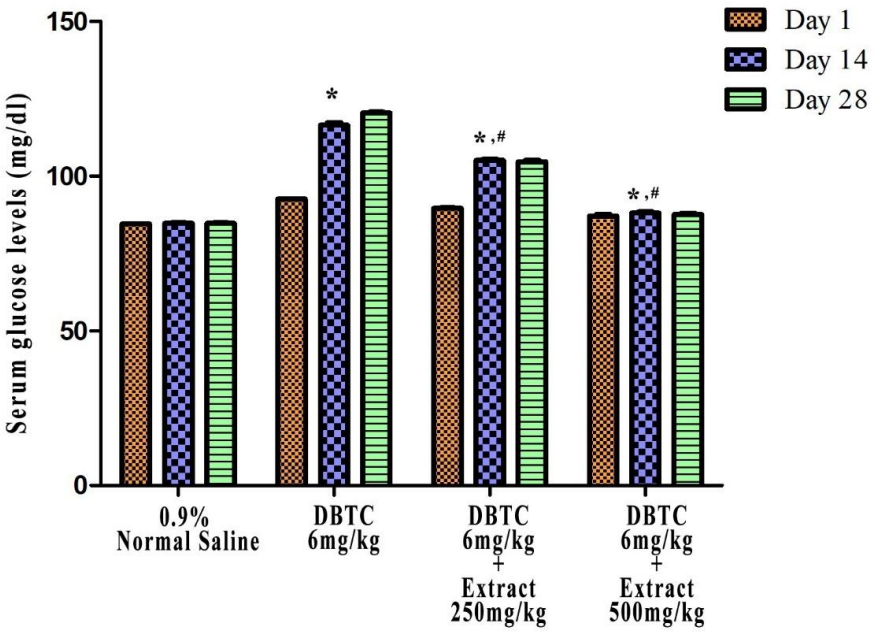

Fig. 3. Effect of *Terminalia arjuna* bark extract on blood glucose in DBTC treated rats

''p<0.001 compared with the control group, [#]'p<0.001 compared with the negative control.*
Mean ± S.E.M = Mean values ± Standard error of means of six experiments

counteracted the elevated levels of α-Amylase, Lipase and glucose in the blood induced by DTBC. The decreased in the levels were observed with increase in concentration (dose dependent manner). The findings clearly indicate the protective role of *Terminalia arjuna* against DBTC induced pancreatic cancer in male wistar rats. It will need further research to pinpoint the precise molecular process that allows to be used in clinical therapy.

4. CONCLUSION

In conclusion, the results indicated that *Terminalia arjuna* bark extract counteracted the elevated levels of α-Amylase, Lipase and glucose in the blood induced by DTBC. As a result, *Terminalia arjuna* might be considered a valuable botanical resource for the management of pancreatic cancer. More studies at molecular level are required to explore the role of *Terminalia arjuna* against pancreatic cancer.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Healthy male wistar albino rats weighing 150-200 g were used. The rats were housed in polypropylene cages and were kept in standard laboratory conditions at 21±2°C temperature, 45-50% Humidity and 12 hr light / dark cycles. They were habituated to hygienic laboratory environment for 10 days on a standard pellet diet and water. The Institutional Animal Ethical Committee (IAEC) of A.U. College of Pharmaceutical Sciences, Andhra University under registration number No. 516/01/A/CPCSEA, approved the study protocol and all the research work were performed with the guidelines and regulations of IAEC and CPCSEA.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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