Antitumor and antioxidant status of *Terminalia catappa* against Ehrlich ascites carcinoma in Swiss albino mice

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**ABSTRACT**

**Objective:** The present study was undertaken to evaluate the antitumor and antioxidant status of ethanol extract of *Terminalia catappa* leaves against Ehrlich ascites carcinoma (EAC) in Swiss albino mice.

**Materials and Methods:** The leaves powder was extracted with Soxhlet apparatus and subjected to hot continuous percolation using ethanol (95% v/v). Tumor bearing animals was treated with 50 and 200 mg/kg of ethanol extract. EAC induced in mice by intraperitoneal injection of EAC cells 1 × 10^6 cells/mice. The study was assed using life span of EAC-bearing hosts, hematological parameters, volume of solid tumor mass and status of antioxidant enzymes such as lipid peroxidation (LPO), reduced glutathione (GSH), superoxide dismutase (SOD) and catalase (CAT) activities. Total phenolics and flavonoids contents from the leaves extract were also determined.

**Results:** Total phenolics and flavonoids contents from the leaves extract were found 354.02 and 51.67 mg/g extract. Oral administration of ethanol extract of *T. catappa* (50 and 200 mg/kg) increased the life span (27.82% and 60.59%), increased peritoneal cell count (8.85 ± 0.20 and 10.37 ± 0.26) and significantly decreased solid tumor mass (1.16 ± 0.14 cm^2) at 200 mg/kg as compared with EAC-tumor bearing mice (*P* < 0.01). Hematological profile including red blood cell count, white blood cell count, hemoglobin (11.91 ± 0.47 % g) and protein estimation were found to be nearly normal levels in extract-treated mice compared with tumor bearing control mice. Treatment with *T. catappa* significantly decreased levels of LPO and GSH, and increased levels of SOD and CAT activity (*P* < 0.01).

**Conclusion:** *T. catappa* exhibited antitumor effect by modulating LPO and augmenting antioxidant defense systems in EAC bearing mice. The phenolic and flavonoid components in this extract may be responsible for antitumor activity.

**KEY WORDS:** Antioxidant, Ehrlich ascites carcinoma, flavonoids, *Terminalia catappa*, total phenolic

**Introduction**

Carcinogenesis is the process characterized by the uncontrolled growth and multiplication of abnormal cells that invade surrounding and distant tissues. Epidemiology studies have revealed that the incidence of most cancers increase exponentially with age. [1] *Terminalia catappa* Linn. (Combretaceae) is found throughout the warmer parts of India. The various extracts of leaves and bark of the plant have been reported to have anticancer, antioxidant, [2] anti-human immunodeficiency virus reverse transcriptase [3] and hepatoprotective, anti-inflammatory, genoprotective and aphrodisiac activity. Silibinin, a polyphenolic flavonoid isolated from milk thistle has shown to inhibit the lung cancer metastasis. [4,5] The present study was undertaken to evaluate the antitumor and antioxidant status of *T. catappa* against Ehrlich ascites carcinoma (EAC) cells in mice.

**Materials and Methods**

**Plant and Extraction**

Leaves of plant *T. catappa* were collected in the month of October and authenticated by Dr. Jawahar Raveendran,
Botanist, Bangalore, Karnataka, India and which have been deposited in the Department of Pharmacology (Specimen No: FRLHT/Plant authentication/65/2009, Dated: 05/08/2009). The leaves were shade dried and made core powder. The powder was then packed into Soxhlet apparatus and subjected to hot continuous percolation using ethanol (95% v/v) as a solvent. The extract (yield: 48.56%) was concentrated under vacuum evaporator. The preliminary phytochemical screening of ethanol extract was carried out by chemical tests.  

Animals
Swiss albino mice (20-25 g) were obtained from the National Institute of Mental Health and Neuro Science, Bangalore. Mice were housed in polypropylene cages at controlled environment (temperature 25 ± 2°C and 12 h dark/light cycle) and provided standard mice pellets and water was allowed ad libitum. Experimental protocol was approved by Institutional Animal Ethical Committee (Protocol No: IAEC/P’iology/12/09-10).

Chemicals
1-Chloro 2, 4-dinitro benzoic acid, 5,5-dithio-bis-2-nitrobenzoic acid (DTNB), reduced glutathione (GSH) an GSH, gallic acid, quercetin, Folin-Cioclateau reagent were purchased from Sigma Aldrich, USA. Thiobarbituric Super Religare Laboratories, Bombay, India and other chemicals were AR grade. All other chemicals used were of analytical grade.

Determination of Total Phenolic Compounds

Total phenolic compounds present in the ethanol extract were determined with the Folin-Cioclateau reagent method.  

1 ml of sample solution mixed with 1 ml of Folin-Cioclateau reagent. After 3 min, 3 ml 35% NaOH was added to the mixture followed by the addition of 7 ml of distilled water. The reaction mixture was kept in the dark for 90 min and absorbance was measured at 725 nm. The concentration of total phenolic compound in the sample was determined as milligram gallic acid equivalents/gram extract.

Determination of Total Flavonoid Concentration

Flavonoid concentration was determined by the method Park et al.  

1 ml of extract was diluted with 80% of aqueous ethanol containing 0.1 ml of 10% aluminum nitrate and 1 M of aqueous potassium acetate. After 40 min, the absorbance was measured spectrophotometrically at 414 nm. Total flavonoid concentration was calculated using quercetin as standard. Absorbarance = 0.002108 μg of quercetin = 0.01089 (R²: 0.9999); R² = Coefficient of determination

Tumor cell
EAC cells were obtained through the courtesy from Department of Radiology, Kasturba Medical College, Manipal, India. The EAC cells were maintained in Swiss albino mice, by intraperitoneal (i.p.) transplantation of 1 × 10⁶ cells/mouse after every 10 days.

Effect of T. catappa on Survival Time of EAC Bearing Mice
Swiss albino mice were divided into four groups (n = 10). All groups were injected with EAC cells 1 × 10⁶ cells/mouse (0.1 ml of EAC cell/10 g body weight i.p.). This was taken as day 0.

Group I: EAC control and received 0.9% normal saline orally.
Group II: EAC (1 × 10⁶ cells) treated with 50 mg/kg of T. catappa extract orally.
Group III: EAC (1 × 10⁶ cells) treated with 100 mg/kg of T. catappa extract orally.
Group IV: EAC (1 × 10⁶ cells) treated with standard 5-fluorouracil 20 mg/kg, orally.

All treatments were given for 9 days. The body weight and mean survival time (MST) of each group, consisting of 10 mice was noted. The antitumor efficacy of T. catappa was compared to that of 5-fluorouracil. The percentage increase life span of each group was calculated by using the following equation.

Increase in lifespan = (T − C)/C × 100

Where T = number of days the treated animals survived and C = number of days control animals survived.

Effect of T. catappa on Normal Peritoneal Cells
Swiss albino mice were divided into six groups of six animals each, were used for the study. Group I was served as control (0.9% normal saline orally). Group II and Group III was treated with 50 and 200 mg/kg, p.o. of T. catappa only once for a single day. Group IV and Group V was treated the same treatment (50 and 200 mg/kg, p.o.) for two consecutive days. Group V was treated with 5-fluorouracil (20 mg/kg, p.o.) for two consecutive days. Peritoneal exudate cells were collected after 24 h of treatment by repeated i.p. wash with 0.9% normal saline and counted by using Neubauer chamber in each of the treated groups and compared with the control group.

Effect of T. catappa on Hematological Parameter of EAC Bearing Mice
Swiss albino mice were than divided into five groups (n = 6). All groups were injected with EAC cells (1 × 10⁶ cells/mouse) i.p. except the normal group. This was taken as day 0. On the 1st day, 1 ml/kg of normal saline was administered in group I (Normal group). normal saline, 1 ml/kg/day, was administered in group II (EAC control). T. catappa extract at different doses (50 and 100 mg/kg day) and the standard drug 5-fluorouracil (20 mg/kg) were administered in groups III, IV and V respectively for 14 days orally. After the last dose and 18-h fasting, mice from each group were sacrificed for the study of hematological and liver biochemical parameters.

Hematological Studies
Blood was drawn from each mouse by retro orbital plexus method and hemoglobin (HB) content, red blood cell (RBC) and white blood cell (WBC) counts were measured. Differential leukocyte count of WBC was carried out from Leishman stained blood smears. of normal, EAC control, T. catappa and 5-fluorouracil treated groups, respectively.

Estimation of In Vivo Antioxidants
After the collection of blood samples, the mice were sacrificed by cervical dislocation. The liver was excised, rinsed in ice-cold normal saline solution and kept on ice and subsequently blotted on filter paper, weighed and homogenized in chilled sodium phosphate buffer (0.1 M, pH 7.4). A 10% w/v homogenate was prepared in chilled sodium phosphate buffer (0.1 M, pH 7.4). Homogenization procedure was performed as quickly as possible under completely standardized conditions. The homogenates were centrifuged at 10,000 g speed for 20 min at 4°C in cooling centrifuge and supernatant obtained from 10%
(w/v) homogenate of tissue was used for the estimation of lipid peroxidation (LPO), reduced GSH, superoxide dismutase (SOD), catalase (CAT) and total protein.

**Effect of T. catappa on LPO**

The level of thiobarbituric acid reactive substances (TBARS) in the liver was measured by the method of Ohkawa et al.\[^{[10]}\] as a marker for LPO. The liver homogenate (0.2 ml) was treated with 20% of 1.5 ml of acetic acid (pH 3.5), 1.5 ml of 0.67% thiobarbituric acid and 0.2 ml of sodium dodecyl sulfate (8.1%), volume is made up to 5 ml with distilled water. The mixture was then heated at 100°C for 60 min. The mixture was cooled and 5 ml of n-butanol-pyridine mixture (15:1) was added and shaken vigorously. After centrifugation of the mixture at 4,000 g for 10 min, the absorbance of the organic layer was measured at 532 nm. The rate of LPO was expressed as nm of TBARS reactive substance formed/h/mg protein and MDA as nm/g wet tissue.

**Effect of T. catappa on Reduced GSH**

The tissue GSH was determined by the method of Ellman,\[^{[11]}\] virtually all the non-protein sulphydryl groups of tissues are in the form of reduced GSH. 0.2 ml of tissue homogenate was mixed with 1.8 ml of EDTA solution. To this 3.0 ml precipitating reagent (1.67 g of metaphosphoric acid, 0.2 g of EDTA disodium salt, 30 g sodium chloride in 1000 ml of distilled water) was added, mixed thoroughly and kept for 5 min before centrifugation. A total volume of ml of the filtrate, 4.0 ml of 0.3 M disodium hydrogen phosphate solution and 1.0 ml of DTNB reagent were added and read the absorbance at 412 nm. The results were expressed as nM DTNB oxidized/min/mg of protein.

**Effect of T. catappa on SOD**

The activity of SOD in tissue was assayed by the method of Kakkar et al.\[^{[12]}\] Added 0.1 ml of liver homogenate to 1.2 ml of sodium pyrophosphate buffer (pH 8.3) followed by the addition of 0.1 ml phenazine methosulphate, 0.3 ml nitroblue tetrazolium sodium pyrophosphate buffer (pH 8.3) followed by the addition of 0.1 ml phenazine methosulphate, 0.3 ml nitroblue tetrazolium and 0.2 ml nicotinamide adenine dinucleotide. Reaction mixture was incubated for 90 s at 30°C and the reaction was stopped by the addition of 0.1 ml of glacial acetic acid. It was stirred vigorously and shaken with 4.0 ml of n-butanol and centrifuged at 4,000 g for 10 min. Absorbance of the organic layer was measured at 560 nm. Control was prepared using 0.1 ml of distilled water instead of 0.1 ml of homogenate.

**Effect of T. catappa on CAT activity**

CAT activity was assayed by the method of Claiborne.\[^{[13]}\] Changes in absorbance were recorded at 240 nm. CAT activity was calculated in terms of nM H2O2 consumed/min/mg protein using molar extinction coefficient of 0.36 × 10⁻³ M/cm.

**Estimation of Total Protein**

The protein concentration of liver homogenate was determined by the method of Lowry et al.\[^{[6]}\] by using span diagnostic kit.

**Effect of T. catappa on Volume of Solid Tumor**

Mice were divided into four groups of six mice each. EAC cells (1 × 10⁶ cells/mouse) were injected into the right hind limb (thigh) of all animals intramuscularly. Group I severed as EAC-bearing control. Groups II and III was treated with as T. catappa (50 and 200 mg/kg) orally for 5 alternate days. Group IV was treated with 5-fluorouracil (20 mg/kg). Tumor mass was measured from the 15th day of tumor induction. The measurement was carried out every 5th day for a period of 30 days. The volume of tumor mass was calculated using the formula \( V = \frac{4}{3} \pi r^3 \) where \( r \) is the mean of \( r_1 \) and \( r_2 \) which are two independent radii of the tumor mass.\[^{[13]}\]

**Statistical Analysis**

The data was statistically analyzed by one-way analysis of variance followed by Dunnett test. \( P < 0.05 \) was considered statistically significant.

**Results**

The phytochemical screening result showed the presence of alkaloid, flavonoids, resins, saponins, steroids, sugars and tannins in the ethanol extract. Total phenols (gallic acid equivalents) and flavonoids (quercetin equivalents) contents from the ethanol extract of leaves were found 354.02 and 51.67 mg/g extract.

The present investigation indicates that the T. catappa showed significant antitumor and antioxidant activities in EAC-bearing mice. T. catappa (50 and 200 mg/kg) treated mice showed significant increase (\( P < 0.01 \)) in MST as compared to EAC treated control group. Single day treatment and two consecutive treatments groups with T. catappa (200 mg/kg) enhanced peritoneal cells significantly as compared to normal mice (\( P < 0.01 \)) [Table 1].

**Table 1:**

| Treatment and dose (mg/kg, p.o.) | Body weight (g) | Mean survival time (in days) | Increased in life span (%) | Treatment and dose (mg/kg, p.o.) | No of peritoneal cells/mouse × 10⁶ |
|---------------------------------|-----------------|-----------------------------|---------------------------|---------------------------------|----------------------------------|
| EAC bearing control (1 x 10⁶ cells/mouse) | 28.04±0.14 | 17.00±0.71 | — | Normal mice | 5.18±0.16 |
| EAC+T. catappa (50) | 26.19±0.15 | 21.73±0.64 | 27.82 | T. catappa treated once in a day (50) | 6.21±0.19 |
| EAC+T. catappa (200) | 24.12±0.19* | 27.30±0.39* | 60.59 | T. catappa treated once in a day (200) | 7.72±0.32 |
| EAC+5-Fluorouracil (20) | 21.11±0.13* | 32.50±1.65* | 91.17 | T. catappa treated once for 2 days (50) | 8.85±0.20* |
| — | — | — | — | T. catappa treated once for 2 days (200) | 10.37±0.26* |
| — | — | — | — | 5-Fluorouracil treated once for 2 days (20) | 14.18±0.21* |

Data are expressed as the mean±SEM (n=10). *\( P<0.01 \), when compared with the EAC bearing control group. **\( P<0.05 \) and ***\( P<0.01 \) when compared with normal mice. Data analyzed using one way analysis of variance followed by Dunnett test. EAC=Ehrlich ascites carcinoma, T. catappa=Terminalia catappa.
RBC cells count and HB content in EAC bearing control group was significantly decreased compared to saline control group (P < 0.01). Treatment with *T. catappa* at 200 mg/kg significantly increased the RBC count and HB content compared with EAC bearing mice (P < 0.05 and P < 0.01). The total WBC count and total protein was found to be increased significantly in the EAC bearing control group when compared to normal control (P < 0.01). Administration of *T. catappa* extract in EAC bearing mice significantly (P) reduced the WBC count and total protein as compared with EAC bearing control group. *T. catappa* treated group changed altered parameters to the normal values. However, the change was marginal at 50 mg/kg dose [Table 2].

*T. catappa* treated group significantly (P) reversed the altered enzymes levels as compared with EAC bearing control group [Figure 1].

A markedly reduction in the tumor mass of *T. catappa* treated mice was observed with 200 mg/kg [Figure 2].

**Discussion**

In EAC bearing mice, a regular rapid increase in ascites tumor volume was noted. Ascites fluid is the direct nutritional source for tumor cells and a rapid increase in ascites fluid with tumor growth would be a means to meet the nutritional requirement of tumor cells. [16] Treatment with extract of *T. catappa* inhibited the tumor masses and the reliable criteria for judging the value of any anticancer drug are the prolongation of the life span of animals. The extract of *T. catappa* decreased the ascites fluid masses and increased the percentage of life span. *T. catappa* by decreasing the nutritional fluid volume and arresting the tumor growth finally increased the life span of tumor bearing mice. [17]

The effect of *T. catappa* treatment on the peritoneal cells of normal mice was an indirect method of evaluating its inhibitory effect on tumor cell growth. Normally, a mouse contains about 5.13 x 10^6 peritoneal cells, 50% of which are macrophages. The extract of *T. catappa* treatment was found to enhance the peritoneal cells count. These results demonstrate that indirect inhibitory effect of *T. catappa* on EAC cells, which is probably mediated by the enhancement and activation of macrophages. [18]

Usually, in cancer chemotherapy the major problems encountered are myeloid-suppressor and anemia due to reduction in RBC or HB content. [19] Treatment with *T. catappa* brought back the HB content, RBC and WBC count more or less to normal levels. This indicates that extract of *T. catappa* possesses protective action on the hemopoietic system.

The improper balance between reactive oxygen metabolites (ROMs) and antioxidant defenses results in “oxidative stress,” which deregulates the cellular functions leading to

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**Table 2:**

| Treatment                         | Dose (mg/kg, p.o.) | HB (%) gm | RBC (million/mm^3) | WBC (10^6 cells/m^3) | Differential counts (%) | Total protein |
|-----------------------------------|--------------------|-----------|--------------------|----------------------|-------------------------|--------------|
|                                   |                    |           |                    |                      |                         |              |
|                                   | Vehicle control    | 0.1 ml/10 g (normal saline) | 12.98±0.21          | 6.28±0.30            | 11.17±0.28              | 70.67±1.16   | 28.16±0.87 | 1.17±0.40 | 4.5±0.35 |
|                                   | EAC bearing control | 0.1 ml/10 g (1 x 10^6 cells/ml/mouse) | 8.70±0.28a         | 3.14±0.21a           | 25.24±0.33a             | 27.33±1.78a  | 72.17±1.68b | 0.50±0.22a | 14.88±2.1a |
|                                   | EAC+T. catappa      | 50        | 09.99±0.32         | 3.86±0.81            | 21.83±1.05              | 34.12±1.53a  | 54.52±1.42a | 0.54±0.33 | 10.14±0.78 |
|                                   | EAC+T. catappa      | 200       | 11.97±0.47         | 4.30±0.86            | 13.19±0.93              | 67.16±1.19   | 31.67±0.80 | 0.67±0.33 | 5.67±0.46 |
|                                   | EAC+Flurouracil     | 20        | 12.77±0.40         | 4.89±0.67            | 12.36±0.84              | 68.18±1.13   | 29.01±0.94 | 0.98±0.21 | 4.01±0.52 |

Values are expressed as mean±SEM (n=6), **P<0.01 when compared to vehicle control, *P<0.05 and **P<0.01 when compared with EAC bearing control mice. Data analyzed using one way analysis of variance followed by Dunnett test. L=Lymphocytes, N=Neutrophils, M=Monocytes, EAC=Ehrlich ascites carcinoma, T. catappa=Terminalia catappa, HB=Hemoglobin, RBC=Red blood cell, WBC=White blood cell.

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**Figure 1a-d:** Effect *Terminalia catappa* extract on lipid peroxidation (LPO) and antioxidant enzymes of Ehrlich ascites carcinoma (EAC) bearing mice in liver. Group I: – Vehicle control, Group II: – EAC bearing control (1 x 10^6 cells/mouse), Group III: – EAC + T. catappa (50 mg/kg) and Group IV: – EAC + T. catappa (200 mg/kg). P < 0.05, *P < 0.01 when compared with EAC bearing control mice. Data analyzed using one way analysis of variance followed by Dunnett test. LPO - nm of MDA/min/g tissue; glutathione - nm of 5,5-dithio-bis-2-nitrobenzoic acid oxidized/min/mg protein; superoxide dismutase - Units/mg protein; catalase - nM of H_2O_2 consumed/min/mg protein.
Figure 2: Effect Terminalia catappa extract on solid tumor mass of Ehrlich ascites carcinoma (EAC) bearing mice. (■) EAC bearing control (1 × 10^6 cells/mouse), (▲) EAC + T. catappa (50 mg/kg), (▼) EAC + T. catappa (200 mg/kg), (▼) EAC + 5-Fluorouracil (20 mg/kg). Values are expressed as mean ± SEM (n = 6). *P < 0.05 and **P<0.01 when compared to EAC bearing control mice. Data analyzed using one way analysis of variance followed by Dunnett test.

The anti-tumorogenic effect of T. catappa may be due to the antioxidant and the free radical quenching property of the phytoconstituents of T. catappa.

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