

# 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  $1 \times 10^6$  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 ( $8.85 \pm 0.20$  and  $10.37 \pm 0.26$ ) and significantly decreased solid tumor mass ( $1.16 \pm 0.14$  cm<sup>2</sup>) 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 ( $11.91 \pm 0.47$  % 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.<sup>[1]</sup>

*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,<sup>[2]</sup> anti-human immunodeficiency virus reverse transcriptase<sup>[3]</sup> and hepatoprotective, anti-inflammatory, genoprotective and aphrodisiac activity. Silibinin, a polyphenolic flavonoid isolated from milk thistle has shown to inhibit the lung cancer metastasis.<sup>[4,5]</sup> 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,

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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.<sup>16</sup>

#### 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  $25 \pm 2^\circ\text{C}$  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'ology/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-Ciocalteu 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-Ciocalteu reagent method.<sup>17</sup> 1 ml of sample solution mixed with 1 ml of Folin-Ciocalteu reagent. After 3 min, 3 ml 35%  $\text{Na}_2\text{CO}_3$  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.*<sup>18</sup> 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.

Absorbance =  $0.002108 \mu\text{g}$  of quercetin - 0.01089  
( $R^2$ : 0.9999);  $R^2$  = 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  $1 \times 10^6$  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  $1 \times 10^6$  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 ( $1 \times 10^6$  cells) treated with 50 mg/kg of *T. catappa* extract orally.

Group III: – EAC ( $1 \times 10^6$  cells) treated with 100 mg/kg of *T. catappa* extract orally.

Group V: – EAC ( $1 \times 10^6$  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.

$$\text{Increase in lifespan} = \frac{T - C}{C} \times 100$$

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 in to 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 VI 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 ( $1 \times 10^6$  cells /mouse) i.p. except the normal group. This was taken as day 0. On the 1<sup>st</sup> 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,<sup>19</sup> 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  $4^\circ\text{C}$  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.*<sup>[10]</sup> 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.<sup>[11]</sup> virtually all the non-protein sulfhydryl 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.*<sup>[12]</sup> 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 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.<sup>[13]</sup> Changes in absorbance were recorded at 240 nm. CAT activity was calculated in terms of nM H<sub>2</sub>O<sub>2</sub> consumed/min/mg protein using molar extinction coefficient of 0.36 × 10<sup>-3</sup> M/ cm.

**Estimation of Total Protein**

The protein concentration of liver homogenate was determined by the method of Lowry *et al.* by using span diagnostic kit.<sup>[14]</sup>

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

Mice were divided into four groups of six mice each. EAC cells (1 × 10<sup>6</sup> cells/mouse) were injected into the right hind limb (thigh) of all animals intramuscularly. Group I served 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 15<sup>th</sup> day of tumor induction. The measurement was carried out every 5<sup>th</sup> day for a period of 30 days. The volume of tumor mass was calculated using the formula  $V = 4/3 \pi r^2$  where r is the mean of r<sup>1</sup> and r<sup>2</sup> which are two independent radii of the tumor mass.<sup>[15]</sup>

**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:**

**Effect of *T. catappa* extract on body weight, mean survival time and life span of EAC bearing mice and on normal peritoneal cell count in normal mice**

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 × 10 <sup>6</sup>
EAC bearing control (1 × 10 <sup>6</sup> cells/mouse)	28.04±0.14	17.00±0.71	—	Normal mice	5.18±0.16
EAC+ <i>T. catappa</i> (50)	26.19±0.15	21.73±0.64	27.82	<i>T. catappa</i> treated once in a day (50)	6.21±0.19*
EAC+ <i>T. catappa</i> (200)	24.12±0.19#	27.30±0.39#	60.59	<i>T. catappa</i> treated once in a day (200)	7.72±0.32**
EAC+5-Fluorouracil (20)	21.11±0.13#	32.50±1.65#	91.17	<i>T. catappa</i> treated once for 2 days (50)	8.85±0.20**
—	—	—	—	<i>T. catappa</i> 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  $5.13 \times 10^6$  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

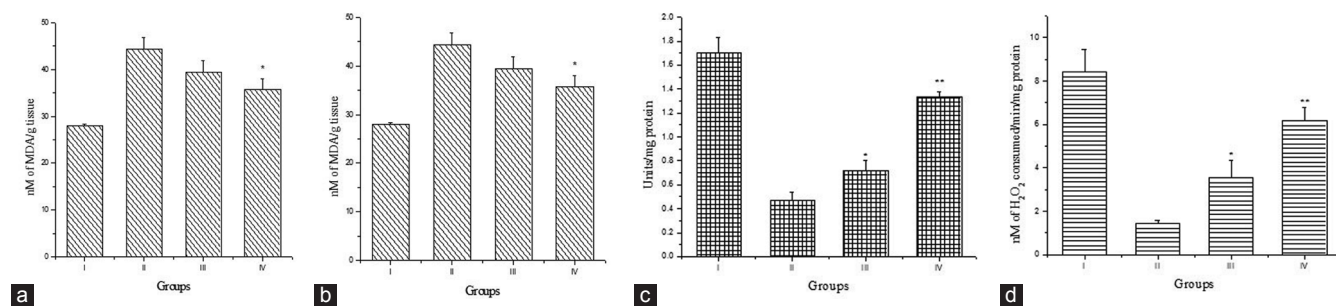
**Table 2:**

**Effect of *T. catappa* extract on hematological parameters of EAC bearing mice**

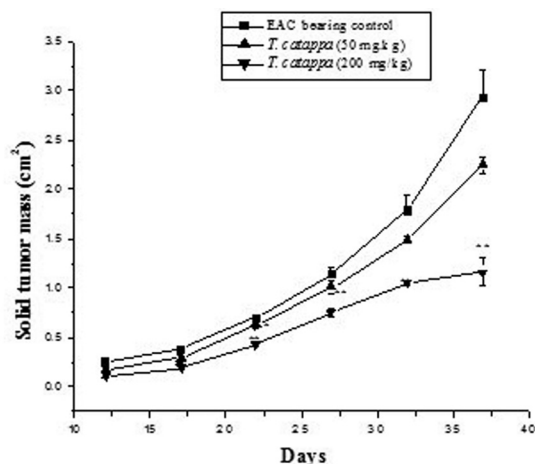
Treatment	Dose (mg/kg, p.o.)	HB (% gm)	RBC (million/mm <sup>3</sup> )	WBC (10 <sup>3</sup> cells/m <sup>3</sup> )	Differential counts (%)			Total protein
					L	N	M	
Vehicle control (normal saline)	0.1 ml/10 g	12.98±0.21	6.28±0.30	11.17±0.28	70.67±1.16	28.16±0.87	1.17±0.40	4.5±0.35
EAC bearing control (1 × 10 <sup>6</sup> cells/ml/mouse) (Normal saline)	0.1 ml/10 g	8.70±0.28 <sup>a</sup>	3.14±0.21 <sup>a</sup>	25.24±0.33 <sup>a</sup>	27.33±1.78 <sup>a</sup>	72.17±1.68 <sup>a</sup>	0.50±0.22 <sup>ns</sup>	14.88±2.1 <sup>a</sup>
EAC+ <i>T. catappa</i>	50	09.99±0.32	3.86±0.81	21.83±1.05 <sup>*</sup>	34.12±1.53 <sup>*</sup>	54.52±1.42 <sup>*</sup>	0.54±0.33	10.14±0.78
EAC+ <i>T. catappa</i>	200	11.97±0.47 <sup>**</sup>	4.30±0.86 <sup>**</sup>	13.19±0.93 <sup>**</sup>	67.16±1.19 <sup>**</sup>	31.67±0.80 <sup>**</sup>	0.67±0.33 <sup>ns</sup>	5.67±0.46 <sup>**</sup>
EAC+5-Flurouracil	20	12.77±0.40 <sup>**</sup>	4.89±0.67 <sup>**</sup>	12.36±0.84 <sup>**</sup>	68.18±1.13 <sup>**</sup>	29.01±0.94 <sup>**</sup>	0.98±0.21 <sup>**</sup>	4.01±0.52 <sup>**</sup>

Values are expressed as mean±SEM (n=6), a=\*\*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

**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 × 10<sup>6</sup> 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/g protein; superoxide dismutase - Units/mg protein; catalase - nM of H<sub>2</sub>O<sub>2</sub> consumed/min/mg protein



**Figure 2:** Effect *Terminalia catappa* extract on solid tumor mass of Ehrlich ascites carcinoma (EAC) bearing mice. (■) EAC bearing control ( $1 \times 10^6$  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  $\pm$  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



various pathological conditions including cancer.<sup>[20]</sup> ROS overproduction induced by different exogenous and endogenous mechanism may exhaust the antioxidant system of cells and contribute to a number of destructive processes and diseases, including cancer.<sup>[21]</sup> Epidemiological studies have suggested that high endogenous level of oxidative adducts and deficiencies in antioxidant levels are likely to be an important risk factors for cancer.<sup>[19]</sup>

LPO, an autocatalytic free radical chain propagating reaction, is known to be associated with pathological conditions of a cell. Malondialdehyde was the end product of LPO was reported to be higher in cancer tissues than in non-diseased organ.<sup>[22]</sup> It was also reported that the presence of tumors in the human body or in experimental animals was known to affect many functions of the vital organs, especially in the liver, even when the site of the tumor does not interfere directly with organ function.<sup>[23]</sup> The *T. catappa* significantly reduced the elevated levels of lipid LPO and GSH content in EAC-treated mice. It has been reported that a decrease in SOD activity in EAC cells and the loss of mitochondria, leading to a decrease in total SOD activity in the liver of EAC bearing mice. GSH is associated with mitogenic stimulation and that GSH may regulate deoxyribonucleic acid synthesis. GSH regulates the onset of tumor-cell proliferation by modulating protein kinase C activity and intracellular pH and that GSH content decreases, during tumor growth *in vivo*, when cell proliferation and the rate of protein synthesis in the tumor decrease. CAT was involved in the free radical scavenging activity. There is a reduction in the levels of the scavengers as a result of tumor growth in disease control animals. Treatment with *T. catappa* brought back the levels of these scavengers and reduced the level of LPO. The findings were compared with that of the standard drug 5-fluorouracil. The free radical hypothesis also support the fact that the *T.*

*catappa* possesses significant antitumor and antioxidant potential against EAC bearing mice.

Over two-third of cancer related death could be prevented through the life-style modification and minimize cancer risk through antioxidant input.<sup>[24]</sup> *T. catappa* contains various polyphenolic and flavonoid compounds recognized as an excellent antioxidant due to their ability to scavenge free radical by a single electron transfer. The content of potential antioxidants compounds like phenolic and flavonoid may responsible for antitumor activity.

## Conclusion

The anti-tumorigenic 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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