An updated review of *Terminalia catappa*

Arumugam Vijaya Anand, Natarajan Divya[1], Pannerselvam Punniya Kotti[2]

Departments of Science and Humanities and [1]Biochemistry, MIET Engineering College, Tiruchirappalli, [2]Department of Biochemistry, Kanchi Shri Krishna College of Arts and Science, Kancheepuram, Tamil Nadu, India

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ABSTRACT

Terminalia catappa Linn. is known for its nutritional fruit and possesses medicinal benefits as well. This is a comprehensive review of the phytoconstituents and pharmacological benefits. *T. catappa* has been recognized for its medicinally essential phytoconstituents, such as phenol, flavonoid, and carotenoid. Numerous pharmacological investigations have confirmed this plant's ability to exhibit antimicrobial, anti-inflammatory, antidiabetic, antioxidant, hepatoprotective, and anticancer activities, all of which support its traditional uses.

Key words: Anticancer, antidiabetic, antioxidant, hepatoprotective, *Terminalia catappa*

INTRODUCTION

Terminalia catappa Linn. (Combretaceae) is native to Southeast Asia. The generic name originates from the Latin "*terminalis*," referring to the leaves teeming at the ends of the shoots. It is a large tree that grows well in subtropical and tropical climates. It is widely planted throughout the tropics. This tree is grown for its ornamental purposes and its edible nuts. The nut kernel can be eaten raw.

T. catappa is a well-recognized herb in Ayurveda. The juice of its fresh leaves is used in the preparation of medicinal lotion for leprosy and scabies, and it is taken internally for stomachache and headache. Scientific studies on the medicinal benefits of *T. catappa* began untimely and the reports uphold a tradition of repeating the data for each decade. It is necessary to develop a system to use the plant continuously for the most effective health care purposes. This review focused on the phytochemical and pharmacological benefits of *T. catappa* from the Internet database PubMed and the most relevant articles were considered for review [Table 1].

Address for correspondence:
Dr. A. Vijaya Anand, Department of Science and Humanties,
MIET Engineering College, Gundur,
Tiruchirappalli - 620 007, Tamil Nadu, India.
E-mail: avamiet@yahoo.com

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BOTANICAL DESCRIPTION

The tree grows to a height of 35 m with an upright, symmetrical crown and horizontal branches. Its branches are characteristically arranged in tiers. The leaves are large, 15-25 cm long and 10-14 cm broad, ovoid, glossy dark green, and leathery. The trees are monoecious, with distinct male and female flowers on the same tree. Both are 1 cm in diameter, white to greenish, and inconspicuous with no petals. The fruit is a drupe 5-7 cm long and 3-5.5 cm broad, green at first, then yellow, and finally red when ripe, containing a single seed. The seed within the fruit is edible when fully ripe [Figure 1].

Phytochemistry

Gao *et al.*[1] identified various phytoconstituents from the fruits, seeds, and barks of the *T. catappa*. The fruit has 1.95 g of protein, 12.03 g of carbohydrate, and 1.21 g of ash. β-carotene (2,090 μg) and vitamin C (138.6 mg) are present in high amounts. The mesocarp of fruits dehydrated by the sun having ash, protein, glucose, moisture, tannin, carbohydrate, and oil with 3,434.5 kcal/kg calorific value is very essential for its nutritive value. The seed is composed of fixed oil (51.2%), olein (54%), and stearin (46%). The seeds yield 4.13% moisture, 4.94% crude fiber, 23.78% crude protein, 4.27% ash, 51.80% fat, and 16.02% carbohydrate; the total calorific value is 548.78 kcal. The bark contains glycoside, cardiac tannins, volatile oils, saponin, steroid, glycosides, and phenols. Classified in the oleic-linoleic acid group, the oils contain huge levels of unsaturated fatty acids, exclusively oleic (up to 31.48%) and linoleic (up to 28.93%). More recently, Mininel *et al.*[2] isolated punicalagin (polyphenol), its derivatives, and other several compounds in the leaves of *T. catappa*.

The leaves of *T. catappa* contain 1-degalloyl-eugeniin, 2,3-(4,4',5,5',6,6'-hexahydroxy-diphenoyl)-glucose, chebulagic acid, gentisic acid, corilagin, geraniin, granatin B, kaempferol, punicalagin, punicalin, quercetin, tercatain, tergallagin, terflavin

A, and terflavin B. The seeds contain carbohydrates, protein, fat, fiber, iron, ascorbic acid, arachidic acid, β-carotene, linoleic acid, myristic acid, oleic acid, palmitic acid, palmitoleic acid, stearic acid, phosphorus, potassium, niacin, riboflavin, thiamin, and water. The fruit contains glucose, pentosans, corilagin, brevifolin carboxylic acid, β-carotene, cyanidin-3-glucoside, ellagic acid, gallic acid, and tannin.[3] Shikhamandloi *et al*.[4] identified quercetin in the leaf of *T. catappa*. The phytoconstituents like flavonoids, carotenoids, and phenolic compounds may be responsible for the traditional use of this plant.

Antimicrobial activity

Harmful microorganisms are the agents for many diseases and deaths. Many medicines are available but have some harmful side effects. To overcome this problem, many natural sources are available.

Figure 1: *Terminalia catappa*

The chloroform as well as methanolic extracts show good antimicrobial activity against Gram-positive and Gram-negative microorganisms. The chloroform root extract of *T. catappa* shows antimicrobial activity against *Escherichia coli* and *Staphylococcus aureus* while petroleum root ether extract of *T. catappa* is devoid of antimicrobial activity. The methanolic root extract of *T. catappa* exhibits minimal inhibition concentration (MIC) of 0.065 mg/ml against *Escherichia coli* and the chloroform extract exhibits MIC of 0.4 mg/ml against *Staphylococcus aureus*.[5]

The aqueous and methanolic extracts of the leaves of *T. catappa* show different degrees of activity against *Pseudomonas aeruginosa, Pseudomonas testosteroni, Pseudomonas pseudoalcaligenes, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus subflava, Proteus mirabilis, Proteus vulgaris, Proteus morganii, Bacillus cereus, Bacillus subtilis, Bacillus megaterium, Citrobacter freundii, Micrococcus flavus, Alcaligenes faecalis, Enterobacter aerogenes, Salmonella typhimurium, Klebsiella pneumoniae, Escherichia coli, Streptococcus faecalis, Streptococcus cremoris, Streptococcus agalactiae,* and *Candida tropicalis*. The methanolic extract is significantly more efficient than the aqueous extract in inhibiting the investigated microbial strains.[6] Shikhamandloi *et al*.[4] found that the methanolic extract shows antifungal activity against *Curvularia lunata*, *Aspergillus niger*, *Penicillium chrysogenum*, and *Trichophyton tonsurans*.

Taganna *et al*.[7] found that the leaves of *T. catappa* are rich in tannin components and are able to inhibit certain phenotypic expression of quorum sensing (QS) in some test strains. Akharaiyi *et al*.[8] conducted the work on antibacterial activity of *T. catappa*. Leaves in different stages are extracted by using water and are used against various harmful microorganisms. The results show that *T. catappa* leaves have the capacity to be active against various organisms.

Table 1: Ethnomedical uses of *T. catappa*

Medicinal uses	Extract (used)	Parts (used)	References
Antimicrobial	Chloroform and methanol	Roots	Pawar and Pal, 2002
Antimicrobial	Aqueous and methanol	Leaves	Nair and Chanda, 2008
Antibacterial	Aqueous	Leaves	Taganna *et al*. 2011
Anti-inflammatory	Ethanol	Leaves	Fan *et al*. 2004
Modulatory	Methanol	Leaves	Aimola *et al*. 2014
Analgesic	Ethanol	Leaves	Ratnasooriya *et al*. 2002
Wound healing	Chloroform	Bark	Khan *et al*. 2013
Antidiabetic	Aqueous, methanol, and petroleum ether	Fruit	Nagappa *et al*. 2003
Antidiabetic	Aqueous and cold	Leaves	Ahmed, 2005
Antioxidant	Aqueous	Leaves	Liu *et al*. 1996
Anti hepatotoxic	Aqueous	Leaves	Lin *et al*. 1997
Radical scavenging	Aqueous	Leaves	Lin *et al*. 2001
Antioxidant	Aqueous	Leaves	Lin *et al*. 2001
Hepato protective	Chloroform	Leaves	Gao *et al*. 2004
Anti mitochondrial swelling	Aqueous	Leaves	Tang *et al*. 2004
Radical scavenging activity	Chloroform	Leaves	Tang *et al*. 2004
Hepato protective	Chloroform	Leaves	Tang *et al*. 2006
Hepato protective	Aqueous	Leaves	Kinoshita *et al*. 2007
Anticancer	CO2	Leaves/seed	Ko *et al*. 2002
Antimutagen	Aqueous	Leaves	Chen *et al*. 2000
Anticancer	Ethanol	Leaves	Yeh *et al*. 2012
Anticancer	Ethanol	Leaves	Pandya *et al*. 2013
Anticancer	Ethanol	Leaves	Yang *et al*. 2010
Anti-aging	Aqueous	Leaves	Wen *et al*. 2011

Anti-inflammatory, analgesic, and modulatory activity

Recently, special importance has been given to the role of inflammation in the pathogenesis of various ailments. Medicinal plants are used worldwide as a remedy for various inflammatory disorders. The various polyphenolic compounds, triterpenoids, and other chemical compounds found in the plants may be responsible for the anti-inflammatory activities.

Ethanolic leaf extracts of *T. catappa* exhibit anti-inflammatory effect on 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced ear edema in both acute and chronic animal models. A bioassay-based fractionation procedure shows that the activity concentrates on the fraction of chloroform and the fraction has ursolic acid (1) and 2alpha, 3beta, 23-trihydroxyurs-12-en-28-oic acid (2) and also exhibits strong anti-inflammatory activities.[9]

Aimola *et al*.[10] isolated a novel fetal hemoglobin-inducing compound (*T. catappa* distilled water active fraction) from the leaves of *T. catappa*, which work synergistically, and recommended a dual modulatory effect on inherent erythropoiesis. Ratnasooriya *et al*.[11] found that the extract form of tender leaves have anti-inflammatory as well as analgesic activities without affecting the estrous cycle, and also found that dosage does not induce sedation.

Wound-healing activity

A wound is the loss or breaking of cellular and functional ability of the living tissues. Resistance to drugs and toxicity of drugs delayed the advancement of synthetic antimicrobial agents to treat wounds. Several plants with effective pharmacological activities may offer healthier alternative treatments for wounds. Khan *et al*.[12] suggested that the application of *T. catappa* ointment on the wound shows 97% reduction in the wound area when compared with control (81%) and betadine ointment as the standard drug. *T. catappa* ointment induces the epithelization faster and this suggests that the bark extracts promote considerable wound-healing activity.

Antidiabetic activity

The prevalence of diabetes is rapidly increasing in both developing and developed countries.[13] Diabetes produces disturbances in carbohydrate, protein, and lipid metabolism. Scientific records recommended that the natural medicines originating in plants could represent culturally relevant complementary or alternative treatments as well as offer good clinical opportunities and also serve in the search for new antidiabetic agents with hypolipidemic potential.

Nagappa *et al*.[14] evaluated the antidiabetic potential of *T. catappa* fruits with different extracts (aqueous, methanol, and petroleum ether) on the levels of fasting blood sugar and various serum biochemical parameters in a diabetic rat induced by alloxan. There is a significant antidiabetic activity shown in all the three extracts at dosage levels $1/5^{th}$ of their lethal doses. Histopathological studies of the pancreas of these animals revealed a notable regeneration with aqueous and methanolic extracts, which were previously necrosed by alloxan. The aqueous and cold extract of fresh and tender leaves of *T. catappa* has the capacity to decrease the high blood glucose level and lipids in alloxan-induced animal models. Simultaneously, histopathologial studies support its antidiabetic potential.[15] *T. catappa* fruit extract and *T. catappa* fallen dry leaf decoction have also been reported to have hypocholesterolemic effects on rats.[16] Methanolic extract of *T. catappa* leaf extract exhibits the dosage-dependent increase in inhibitory effect on α-glucosidase enzyme (up to 73.2%) and α-amylase enzyme (up to 54.04%).[17]

Antioxidant and radical scavenging activity

The antioxidant defense in our body can merely defend itself when the free radicals are within the normal level. Great effort has been made to focus on using the available experimental techniques to identify the natural antioxidants from plants. The results promise benefits in the prevention as well as in the therapy for many life-threatening diseases.

The concurrent pretreatment of the Chinese hamster ovary-K1 (CHO-K1) cells with the aqueous extract of *T. catappa* leaf considerably suppresses mitomycin C-induced micronuclei. It also inhibits lipid peroxidation (LPO) and hydrogen peroxide formation induced by TPA in human mononuclear leukocytes in a dose-dependent manner.[18]

Lin *et al*.[19] found that treatment with the aqueous extracts of *T. catappa* exhibited antihepatotoxic activity against carbon tetrachloride (CCl_4)-induced toxicity in the rat. The crude drug revealed antioxidant property in $FeCl_2$-ascorbic acid-induced LPO in the liver homogenate. In addition, the superoxide radical scavenging effects of *T. catappa* using electron spin resonance and spin trapping technique indicate that *T. catappa* exhibits good superoxide radical scavenger activity and antihepatotoxic activity.

Lin *et al*.[20] stated that the multiple antioxidant effects of the tannin components from *T. catappa* have the capability to prevent LPO, formation of superoxide, and their free radical scavenging activity. Punicalin and punicalagin are the most copious phytoconstituents and have the effective antioxidant activity of *T. catappa*.

Ko *et al*.[21] isolated squalene from the leaves and seed of *T. catappa* by gas chromatography-mass spectrometry and high-performance liquid chromatography spiking analyses in supercritical carbon dioxide (CO_2). The leaf extracts of *T. catappa* show strong 2,2-Diphenyl-1-picrylhydrazyl (DPPH) scavenging and antioxidative activities. Conversely, the seed extracts only exhibited strong inhibition of conjugated diene hydroperoxide formation and very low DPPH scavenging activity.

Annegowda *et al*.[22] found that *T. catappa* leaves extract obtained with 40 min of sonication possessed significant polyphenolic contents when compared with 20 min and 60 min of sonication and control. The antioxidant assays also show that 40 min of the sonicated extract indicate significant vitamin C equivalent values than other different intervals of sonication and control. The polyphenolic content may be responsible for this activity. *T. catappa* has been found to possess the antioxidant activity in

a dose-dependent manner by DPPH assay, nirtic oxide assay, reducing power assay, and H_2O_2 assay.[23]

Hepatoprotective activity

Liver is the metabolic super achiever in the body and it is the main target organ for most of the toxicants that enter the body. It plays a vital role in transforming and clearing the toxicants as well as other chemicals.[24] The reliable liver-protective drugs are explicitly insufficient.[25] Conventional knowledge of medicinal plants has constantly guided the search for new cures. *T. catappa* inhibits the overexpression of interleukin-6 (IL-6) gene in the liver of Chemokine (C-C motif) ligand 4 (CCl_4)-induced mice and the alanine aminotransferase (ALT) activity is reversed. Also, histological alterations such as the infiltration of several inflammatory cells and hepatocyte swelling in injured mice are efficiently lessened by the pretreatment of *T. catappa*.[26]

Tang *et al*.[27] isolated 2alpha, 3beta, 23-trihydroxyursane -12 -en-28-oic acid (DHUA) from *T. catappa* leaves and evaluated the superoxide radicals scavenging activity and antimitochondrial swelling activity by *in vitro*. DHUA (50-500 μmol/L) inhibits Ca^{2+} induced mitochondrial swelling and also shows superoxide radicals scavenging activity in a dose-dependent manner. Oral pretreatment with leaves of *T. catappa* (20 mg/kg/d, 50 mg/kg/d, and 100 mg/kg/d for 7 days) reverses the elevated levels of ALT serum and aspartate aminotransferase (AST), and significant morphological changes are notably lessened in D-galactosamine-induced animal model. Additionally, *T. catappa* leaves decrease the sensitivity of mitochondrial swelling to the exotic Ca^{2+} stimulation. Incubation with *T. catappa* leaves extract in primary cultured hepatocytes of mice may possibly prevent the decrease in cell viability in a dose-dependent manner. It also results in both an increase in AST (1.9 fold) and a decrease in superoxide dismutase (SOD) (48%) activity in supernatant of primary cultured hepatocytes.[28]

Gao *et al*.[1] isolated ursolic acid and asiatic acid from the chloroform extract of the leaves of *T. catappa*. In the acute hepatic damage test, the increased levels of ALT and AST are reversed and significant morphological changes are prevented by pretreatment with 50-100 mg/kg *T. catappa* leaf extract. In the hepatocyte injury experiment, the increase in ALT and AST levels in the medium of primary cultured hepatocytes induced by D-galactosamine are blocked by pretreatment with 0.05 g/L, 0.1 g/L, and 0.5 g/L *T. catappa* leaf extract. In addition, ursolic acid and asiatic acid show superoxide anion and hydroxyl radical scavenging activity in a dose-dependent manner. This can be the mechanism in the protection of mitochondria in the liver and the scavenging action on the free radicals.

Treatment with chloroform leaf extracts of *T. catappa* with the concentration of 20 mg/kg, 50 mg/kg, or 100 mg/kg significantly decreases the level of serum ALT, AST, and the level of liver LPO in CCl_4-induced liver damage. Morphological observation also confirms the hepatoprotective effects. In addition, pretreatment with leaf extracts of *T. catappa* effectively prevent the disruption of mitochondrial membrane potential (14.8%), intramitochondrial Ca^{2+} overload (2.1 fold), and suppression of mitochondrial Ca^{2+}-ATPase activity (42.0%). This can suggest a new mechanism of the hepatoprotective effects of *T. catappa*.[29]

Kinoshita *et al*.[30] isolated chebulagic acid and corilagin as the active components from the leaves of *T. catappa*. Both the components exhibit a strong scavenging activity for $O_{(2)}^{(-)}$ and peroxyl radicals and also inhibit the formation of reactive oxygen species from leukocytes, which is stimulated by phorbol 12-myristate acetate. The intraperitoneal administration of leaf extract or corilagin, prior to galactosamine and lipopolysaccharide administration, reduces serum ALT, AST, and glutathione S-transferase (GST) activities. This also decreases the free radical formation and LPO in mitochondria. Moreover, apoptotic events such as DNA fragmentation and the increase in caspase-3 activity in the liver of galactosamine and lipopolysaccharide induce liver injury.

Anticancer activity

In 2007, cancer caused 13% of the deaths worldwide.[31] The uncontrolled replication of DNA and the cellular division of abnormal cells lead to the progression of metastasis of cancerous tumors, which invade and destroy adjacent tissues, blood as well as the lymphatic system. Ko *et al*.[32] observed that supercritical CO_2 leaf extracts of *T. catappa* did not induce mutagenicity (at 0.5 mg/plate), whereas exhibiting strong antimutagenicity effect and they are more cytotoxic to human hepatoma cells than to normal liver cells.

Oral administration of *T. catappa* significantly reduces the number of aberrant crypt foci/colon/rat and β-catenin accumulated crypts/cm/rat when compared to the control group. Colonic proliferating cell nuclear antigen-labeling index is also notably lower than the control. This suggests that *T. catappa* has a potent short-term chemopreventive efficiency on various biomarkers of colon carcinogenesis induced by carcinogen azoxymethane and this efficiency may be related to the inhibition of the development of aberrant crypt foci and β-catenin accumulated crypts.[33]

In the cultured CHO cells, the pretreatment with water extract of *T. catappa* leaf and its major tannin component, punicalagin, prevented gene mutations and also suppressed the generation of intracellular free radicals on bleomycin-induced genotoxicity.[34] *T. catappa* and punicalagin suppressed the proliferation of H-ras-transformed NIH3T3 cells in a dose-dependent manner but moderately affected the nontransformed NIH3T3 cells proliferation that indicates the selectivity of *T. catappa* and punicalagin. *T. catappa* and punicalagin treatment decreased anchorage-independent growth that may have been due to a cell cycle arrest at G0/G1 phase. Punicalagin treatment decreased the levels of intracellular superoxide and also the levels of phosphorylated c-Jun N-terminal kinase 1 (JNK1) as well as protein kinase38 (p38). This will support the chemopreventive effect of punicalagin.[35]

In tumor-bearing rats, the total cholesterol, triglycerides, and very-low-density lipoprotein (VLDL) cholesterol are elevated and high-density lipoprotein (HDL) cholesterol is reduced in

blood as well as in the liver and the kidney. *T. catappa* (500 mg/kg) markedly reverses the lipid levels to normal range and this shows antitumor and antilipidemic activities.[36]

T. catappa leaf extracts inhibit the expression and activities of matrix metalloproteinase-9 (MMP-9) by the assessment of mRNA levels in hepatocellular carcinoma. This inhibition is ensued by upregulating the tissue inhibitor of metalloproteinase-1 (TIMP-1); in addition, it suppresses nuclear translocation and downregulates the DNA binding activity of nuclear factor-kappa B (NF- κB) and activator protein-1 (AP-1) on the MMP-9 promoter in Human hepato cellular carcinoma cell line (Huh 7 cells).[37] In persistence, the treatment of Huh7 cells with *T. catappa* notably decreases the activities of protein levels as well the mRNA levels of urokinase-type plasminogen activator (u-PA). *T. catappa* inhibits the transcription protein of nuclear factors stimulating protein-1 (SP-1), NF-κB, and also inhibits the effects of u-PA by decreasing the phosphorylation of the extracellular-signal-regulated kinase 1/2 (ERK1/2) pathway. These results support that the u-PA expression may be an effective therapeutic target in the *T. catappa* mediated suppression of hepatocellular carcinoma (HCC) metastasis.[38]

The ethanloic extract of *T. catappa* contains total phenolics 354.02 mg/g and flavonoids 51.67 mg/g contents. *T. catappa* extract at two different concentrations (50 mg/kg and 200 mg/kg) increases peritoneal cell count and the life span. It also significantly decreases the solid tumor mass at 200 mg/kg when compared with Ehrlich ascites carcinoma (EAC)-tumor-bearing mice. The red blood cell count, white blood cell count, hemoglobin content, and protein amount are normal in extract-treated mice. *T. catappa* significantly increases the levels of SOD and catalase (CAT), and decreases LPO and reduced glutathione (GSH). *T. catappa* exhibits antitumor activity by changing the LPO levels and the antioxidant defense may be due to the presence of phenolic and flavonoid components.[39]

Treatment with *T. catappa* leaves may reduce the expressions of MMP-2, MMP-9, urokinase-type plasminogen activator and their endogenous inhibitors, specifically tissue inhibitor of MMP-2 and plasminogen activator inhibitor-1, in a dose-dependent manner. Further, *in vivo* studies also show the inhibitory effect on the growth as well as the metastasis of Lewis lung carcinoma (LLC) cells.[40]

Ethanolic leaf extracts of *T. catappa* significantly inhibit the migration of cell and invasion capacities of squamous cell carcinoma4 (SCC4) cells. *T. catappa* inhibits the activities and the levels of protein in MMP-2, MMP-9, and u-PA. Further, *T. catappa* may inhibit the phosphorylation of JNK1/2, ERK1/2, and protein kinase B (Akt) while the expression of nuclear protein NF-κB, c-Fos, and c-Jun are also inhibited. Moreover, *T. catappa* decreases the DNA-binding activity with AP-1 and NF-κB.[41] Therefore, *T. catappa* may provide a powerful chemopreventive substance against cancer.

Antiaging activity

Hydrophilic extract of *T. catappa* shows DPPH-free radical scavenging activity and protects erythrocytes from hemolysis induced by 2,2'-Azobis (2-amidinopropane) dihydrochloride (AAPH). *T. catappa* (10-500 μg/mL) inhibits collagenase activity in a dose-dependent manner (82.3% to 101.0%) but not in elastase activity. Additionally, *T. catappa* inhibits MMP-1 and MMP-9 protein expression at 25 μg/mL and inhibits MMP-3 protein expression at 50 μg/mL. *T. catappa* also promotes the protein expression of type I procollagen. *T. catappa* attenuated the expression of MMP-1, -3, and -9 by inhibiting the phosphorylation of ERK, JNK, and p38. Therefore, it can be used as an antiaging agent.[42]

Toxicology

Azrul *et al*.[43] detected the primary toxicity (by lethal occurrence) and secondary toxicity (by nutritional behavior and physiological observation) of crude aqueous extract *T. catappa* (0.5 g/kg, 1.0 g/kg, and 3.0 g/kg) during 14 days of treatment period. No lethality is observed for the rats in the experimental period. The nutritional behavior is also in normal condition and no abnormalities are detected for physiological aspects of the rats.

CONCLUSION

The pharmacological investigations carried out on *T. catappa* validate the immense potential of this plant in the treatment of numerous diseases. Additional research and clinical trials are needed for the product development to strengthen the use of *T. catappa* for the future generations.

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