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Pharmacological Potential Of *Terminalia Catappa*: A Comprehensive Review Of Bioactive Compounds And Therapeutic Applications

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Abstract: Terminalia Catappa, commonly known as the tropical almond, is a widely distributed plant with significant pharmacological potential. This review aims to provide a comprehensive analysis of its bioactive compounds and therapeutic applications. The plant's phytochemical constituents, including flavonoids, tannins, and phenolic acids, exhibit diverse pharmacological activities, such as antioxidant, anti-inflammatory, antimicrobial, and hepatoprotective effects. This article highlights the current advancements in research and identifies potential areas for future exploration.

Keywords: Anticancer, Antidiabetic, Antioxidant, Hepatoprotective, Terminalia Catappa, etc.

I. Introduction

Terminalia Catappa, commonly known as Indian almond or tropical almond, is a large tropical tree belonging to the Combretaceae family that has garnered significant attention in the field of pharmacology due to its diverse therapeutic potential. The plant's various parts, including leaves, bark, and fruits, have been extensively studied for their pharmacological activities, which encompass a wide range of properties such as antioxidant, anti-inflammatory, antimicrobial, hepatoprotective, anticancer, antidiabetic, wound healing, cardiovascular protective, analgesic, and neuroprotective effects. These activities are attributed to the presence of bioactive compounds, including phenolics, flavonoids, and tannins, which have been identified in different parts of the plant. [1]

The extensive research conducted on T. Catappa has revealed its potential applications in treating various health conditions. For instance, its antioxidant properties may help combat oxidative stress-related disorders, while its anti-inflammatory effects could be beneficial in managing inflammatory conditions. The plant's antimicrobial activity suggests potential use in treating infectious diseases, and its hepatoprotective effects may offer liver protection against various forms of damage. Additionally, the anticancer potential of T. Catappa extracts has been demonstrated through antiproliferative and cytotoxic activities against various cancer cell lines. [2,3] The plant's antidiabetic properties, wound healing capabilities, cardiovascular protective effects, analgesic properties, and neuroprotective potential further underscore its versatility as a potential source of therapeutic agents. However, it is important to note that while these findings are promising, further research, including clinical trials, is necessary to fully elucidate the mechanisms of action and establish the efficacy and safety of T. Catappa-derived treatments in human subjects. [4,5]

II. Synonyms [6]

Plant can be called with different names like; Sea Almond, Ketapang, Tropical Almond Christian, Pacific Almond, Singapore Almond, Indian Almond, Bastard Almond, Telisai, Jelawai Ketapang in their respective regions

III. Botanical description:

The *Terminalia Catappa* tree can grow up to 35 meters tall with a straight trunk and a balanced, symmetrical crown. Its branches spread out horizontally in distinct layers. The tree has large, dark green, glossy, and leathery leaves, measuring about 15-25 cm in length and 10-14 cm in width. It is monoecious, meaning both male and female flowers grow on the same tree. These flowers are small, about 1 cm in diameter, white to greenish in color, and lack petals. The tree produces a drupe-shaped fruit, which is initially green, then turns yellow, and finally red when fully ripe. Inside the fruit, there is a single seed that becomes edible when mature. [Figure 1]

Image no. 1- Terminallia Cattapa

IV. Phytoconstituents & bioactive compounds of *T. Cattapa:*

The T. Catappa plant contains various phytochemicals in its fruits, seeds, and bark. The fruit comprises 1.95 g of protein, 12.03 g of carbohydrate, and 1.21 g of ash, with significant amounts of β-carotene (2,090 µg) and vitamin C (138.6 mg). Sun-dried fruit mesocarp, containing ash, protein, glucose, moisture, tannin, carbohydrate, and oil, has a calorific value of 3,434.5 kcal/kg, contributing to its nutritional importance. The seed consists of 51.2% fixed oil, 54% olein, and 46% stearin. Seed composition includes 4.13% moisture, 4.94% crude fibre, 23.78% crude protein, 4.27% ash, 51.80% fat, and 16.02% carbohydrate, with a total calorific value of 548.78 kcal. The bark contains glycoside, cardiac tannins, volatile oils, saponin, steroid, glycosides, and phenols. The oils, categorized in the oleic-linoleic acid group, are rich in unsaturated fatty acids, particularly oleic (up to 31.48%) and linoleic (up to 28.93 %) recently identified punicalagin (a polyphenol), its derivatives, and other compounds in T. Catappa leaves. [7] T. catappa leaves contain various compounds including 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 are rich in nutrients such as 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 . Shikhamandloi et al.[8] identified quercetin in T. catappa leaves. The traditional use of this plant may be attributed to phytoconstituents such as flavonoids, carotenoids, and phenolic compounds.

Table 2: Chemical constituents present in different parts of *Terminalia Catappa*

Sr no:	Parts	Chemical constituents
1.	Fruits	Phenolic acids: Gallic acids, ellagic acids, corilagin, brevifolin carboxylic acid
		Flavonoids: kaemferol, quercetin
		Terpenoids: ursolic acid
		Plant sterols: Beta-sitosterol
		Fatty acid: oleic acid, linoleic acid
		Tannins: Ellagitannin, punicalagin
		Carotenoid: Beta carotene
2.	Leaves	Phenolic compounds: Gallic, chebulagic, genistic acid
		Flavonoids: Quercetin, kaemferol
		Triterpenoids: beta-amyrin, Lupeol
		Tannins: ellagitanins
		Saponins: Oleanolic acid
		Steroids: beta-setosterol
		1-degalloy eugenin
3.	Bark	Phenolic acid: Gallic, ellagic, protocatechuic acid
		Flavonoids: quercetin, arjunilic acid, rutin
		Triterpenoid: Oleanolic acid
		Tannins: punicalagin, Ellagitannin
		Saponins: Arjun glycoside, arjunic acid
		Sterols: Beta-sitosterol, stigma sterol
		Alkaloid: Indole, triterpenoid
4.	Seeds	Phenolic compounds: Gallic acid, ellagic acid
		Flavonoids: Quercetin, kaemferol, luteolin
		Saponins: Quinovic acid glycosides.

V. Pharmacological Activities of *Terminalia catappa:*

Anti-inflammatory, pain relieving & modulatory effect:

Aimola et al.[09] discovered a new compound in T. Catappa leaves that induces fetal hemoglobin production. This compound works in harmony with other components and is believed to have a dual regulatory impact on natural red blood cell formation. Research by Ratnasooriya et al.[10] demonstrated that the extract from young leaves possesses both anti-inflammatory and analgesic properties without impacting the estrous cycle or causing sedation, regardless of the dosage. Wound-healing Properties A wound occurs when living tissues lose their cellular and functional capabilities. The development of synthetic antimicrobial agents for wound treatment has been hindered by drug resistance and toxicity. Many plants with effective pharmacological properties may provide better alternative wound treatments. Prasanthi Daram et al[11]

Antidiabetic Effects

Nagappa et al.[12] assessed the antidiabetic potential of T. Catappa fruits using various extracts (aqueous, methanol, and petroleum ether) on fasting blood sugar levels and serum biochemical parameters in alloxan-induced diabetic rats. All three extracts showed significant antidiabetic activity at one-fifth of their lethal doses. Histopathological examination of the pancreas revealed notable regeneration with aqueous and methanolic extracts in tissues previously damaged by alloxan. Both aqueous and cold extracts of fresh, young T. Catappa leaves can lower elevated blood glucose and lipid levels in alloxan-induced animal models. Histopathological studies further support its antidiabetic potential. T. Catappa fruit extract and fallen dry leaf decoction have also been shown to have cholesterol-lowering effects in rats. The methanolic extract of T. Catappa leaves exhibits a dose-dependent increase in inhibitory effects on α-glucosidase (up to 73.2%) and α-amylase (up to 54.04%) enzymes. Abdul Vahab A et al [13]

Antimicrobial Activity

Harmful microorganisms cause numerous diseases and deaths. While many medicines are available, they often have adverse side effects. Natural sources offer potential solutions to this problem.

Taganna et al.[14] discovered that T. catappa leaves are rich in tannins and can inhibit certain phenotypic expressions of quorum sensing (QS) in some test strains. L V Giang et al.[15] investigated the antimicrobial l activity of T. catappa leaves at different stages using water extracts against various harmful microorganisms. The results indicate that T. catappa leaves possess the ability to combat various organisms effectively.

Antioxidant and free radical neutralizing capacity

The body's antioxidant defence system can only function effectively when free radicals are at normal levels. Significant research has been conducted to identify natural plant-based antioxidants using available experimental methods. Wangui Clement Mwang et al [16] Their findings suggest potential benefits in both preventing and treating various life-threatening conditions. Pretreatment of CHO-K1 cells with T. catappa leaf aqueous extract significantly reduces mitomycin C-induced micronuclei formation. It also decreases lipid peroxidation and hydrogen peroxide production caused by TPA in human mononuclear leukocytes in a concentration-dependent manner.

Research by Lin et al.[17] demonstrated that T. catappa aqueous extracts showed hepatoprotective effects against CCl4-induced toxicity in rats. The crude extract exhibited antioxidant properties in FeCl2-ascorbic acid-induced lipid peroxidation in liver homogenate. Furthermore, electron spin resonance and spin trapping techniques revealed that T. catappa effectively scavenges superoxide radicals and provides hepato protection.

Ko et al.[18] identified squalene in T. catappa leaves and seeds using gas chromatography-mass spectrometry and high-performance liquid chromatography spiking analyses in supercritical CO2. T. catappa leaf extracts demonstrated strong DPPH scavenging and antioxidant activities. In contrast, seed extracts only showed significant inhibition of conjugated diene hydroperoxide formation and minimal DPPH scavenging activity. Annegowda et al.[19] discovered that T. catappa leaf extract obtained through 40 minutes of sonication contained higher polyphenolic content compared to 20 and 60 minutes of sonication and control. Antioxidant assays also indicated that the 40-minute sonicated extract had significantly higher vitamin C equivalent values than other sonication intervals and control. The polyphenolic content may be responsible for this activity. T. catappa has been shown to possess concentration-dependent antioxidant activity through DPPH assay, nitric oxide assay, reducing power assay, and H2O2 assay

Hepatoprotective activity

The liver, as the body's primary metabolic powerhouse, is the main target for most toxins entering the system. It plays a crucial role in metabolizing and eliminating toxicants and other chemicals. T. catappa suppresses the excessive expression of the interleukin-6 (IL-6) gene in the liver of mice exposed to Chemokine (C-C motif) ligand 4 (CCl4) and reverses alanine aminotransferase (ALT) activity. Moreover, it effectively reduces histological changes such as inflammatory cell infiltration and hepatocyte swelling in affected mice. Tang et al.[20] extracted 2alpha, 3beta, 23-trihydroxyursane-12-en-28-oic acid (DHUA) from T. catappa leaves and assessed its superoxide radical scavenging and antimitochondrial swelling properties in vitro. DHUA (50-500 μmol/L) inhibits Ca2+-induced mitochondrial swelling and demonstrates dose-dependent superoxide radical scavenging activity. Oral administration of T. catappa leaves (20 mg/kg/d, 50 mg/kg/d, and 100 mg/kg/d for 7 days) normalizes elevated ALT and aspartate aminotransferase (AST) serum levels and significantly reduces morphological alterations in D-galactosamine-induced animal models. Furthermore, T. catappa leaves reduce mitochondrial sensitivity to exogenous Ca2+ stimulation.

Anticancer activity

In 2007, cancer was responsible for 13% of global deaths Cancer progression involves uncontrolled DNA replication and abnormal cell division, leading to metastasis of tumors that invade nearby tissues, blood, and the lymphatic system. Ko et al. [21] found that supercritical CO2 leaf extracts of T. catappa did not induce mutagenicity (at 0.5 mg/plate) but exhibited strong antimutagenic effects. These extracts also showed higher cytotoxicity towards human hepatoma cells compared to normal liver cells.

Research shows that when T. catappa is administered orally, it significantly decreases the number of aberrant crypt foci per colon per rat and β-catenin accumulated crypts per centimeter per rat compared to the control group. Additionally, the colonic proliferating cell nuclear antigen-labeling index is notably reduced. These findings suggest that T. catappa exhibits potent short-term chemo preventive effects on various biomarkers of colon carcinogenesis induced by the carcinogen azoxymethane. This effectiveness may be linked to the inhibition of aberrant crypt foci and β-catenin accumulated crypts development. Morioka et al [22] Studies on cultured CHO cells demonstrate that pretreatment with T. catappa leaf water extract and its primary tannin component, punicalagin, prevents gene mutations and suppresses intracellular free radical generation in response to bleomycin-induced genotoxicity. Pin-Shern Chen et al [23] found that Both T. catappa and punicalagin inhibit the proliferation of H-ras-transformed NIH3T3 cells in a dose-dependent manner, while only moderately affecting non-transformed NIH3T3 cells, indicating selectivity. Treatment with these compounds reduces anchorage-independent growth, possibly due to cell cycle arrest at the G0/G1 phase. Punicalagin treatment decreases intracellular superoxide levels and the levels of phosphorylated c-Jun N-terminal kinase 1 (JNK1) and protein kinase38 , supporting its chemo preventive effect. Pin-Shern Chen et al [24] studied that In tumour-bearing rats, blood, liver, and kidney levels of total cholesterol, triglycerides, and very-low-density lipoprotein (VLDL) cholesterol are elevated, while high-density lipoprotein (HDL) cholesterol is reduced. Administration of T. catappa (500 mg/kg) significantly normalizes these lipid levels, demonstrating both antitumor and antilipidemic properties. Naitik B. Pandya et al [25] Research indicates that T. catappa suppresses the transcription of nuclear factors SP-1 and NF-κB, while also reducing the phosphorylation of the ERK1/2 pathway, thereby inhibiting u-PA effects. These findings suggest that targeting u-PA expression could be an effective strategy in T. catappa's suppression of HCC metastasis. Chao-Bin Yeh at al [26] evaluated The ethanolic extract of T. catappa contains 354.02 mg/g of total phenolics and 51.67 mg/g of flavonoids. When administered at 50 mg/kg and 200 mg/kg, the extract enhances peritoneal cell count and extends lifespan. At 200 mg/kg, it significantly reduces solid tumour mass compared to EAC-tumor-bearing mice. Blood parameters remain normal in treated mice. T. catappa boosts SOD and CAT levels while lowering LPO and GSH. The antitumor activity of T. catappa, attributed to its phenolic and flavonoid components, is likely due to its ability to alter LPO levels and antioxidant defence mechanisms. Pandya Naitik, et al [27] studied that T. catappa leaf treatment has been shown to decrease the expression of MMP-2, MMP-9, and urokinase-type plasminogen activator, as well as their endogenous inhibitors, tissue inhibitor of MMP-2 and plasminogen activator inhibitor-1, in a dose-dependent manner. In vivo studies further demonstrate its inhibitory effect on both growth and metastasis of LLC cells. Shu-Chen Chu et al [28] evaluated that Ethanolic leaf extracts of T. catappa significantly reduce the migration and invasion capabilities of SCC4 cells. The extract inhibits MMP-2, MMP-9, and u-PA activities and protein levels. Additionally, it suppresses the phosphorylation of JNK1/2, ERK1/2, and Akt, while also inhibiting the expression of nuclear proteins NF-κB, c-Fos, and c-Jun. Furthermore, T. catappa reduces the DNA-binding activity with AP-1 and NF-κB Given these findings, T. catappa shows promise as a potent chemo preventive agent against cancer.

Antihypertensive activity

Felix Abayomi Dada et al [29] We investigated the effect of extracts from the leaf (ALE) and stem bark (ABE) of Almond tree on activities of some crucial enzymes [angiotensin-1 converting enzyme (ACE), arginase, acetylcholinesterase (AChE), phosphodiesterase-5 (PDE-5), adenosine deaminase (ADA), superoxide dismutase (SOD), catalase], and thiobarbituric acid reactive species (TBARS) associated with hypertension in normal adult male Wistar albino rats and Cyclosporine A (CsA)-stressed rats. The result revealed that CsA stressed rats treated with captopril and extracts (ALE and ABE) had lowered ACE, arginase, AChE, PDE-5, ADA activities, and TBARS level, coupled with improved SOD and catalase activities compared with untreated CsA-stressed rats, which had reversed these biochemicals compared to normal rats. This suggests that the extracts could be explored to suppress hypertension and other cardiac injury known with CsA treatment; the potentials that could be linked with the constituent polyphenols. However, further studies including blood pressure should be determined to ascertain this claim.

VI. **Conclusion**

The pharmacological studies conducted on T. catappa demonstrate the plant's significant potential for treating various ailments. Further research and clinical trials are essential to develop products that will enhance the utilization of T. catappa for upcoming generations.

These pharmacological activities highlight the potential of Terminalia catappa as a source of bioactive compounds for various therapeutic applications. However, further research, including clinical trials, is needed to fully understand the efficacy and safety of these potential applications in humans.

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