

**BIOACTIVE POTENTIAL OF CATECHIN AND EPICATECHIN FROM ACACIA  
CATECHU WILD. A PHARMACOLOGICAL APPROACH**Harshit Mishra<sup>1</sup>, Ankur Kapil<sup>2\*</sup>, Manoj Sharma<sup>2</sup>, Ankit Singh Tomar<sup>3</sup>, Yogesh Yadav<sup>2</sup> and Sanskar Bhardwaj<sup>2</sup><sup>1</sup>Divine International Group of Institutions, Gwalior, MP 474001.<sup>2</sup>School of Studies in Pharmaceutical Sciences, Jiwaji University, Gwalior, Madhya Pradesh, India 474011.<sup>3</sup>Department of Pharmacy, Birla Institute of Technology and Science, Pilani, Rajasthan-333031.**\*Corresponding Author: Ankur Kapil**

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**ABSTRACT**

Catechin and epicatechin are natural compounds found in the heartwood of *Acacia catechu*; a plant Extensively used in traditional medicine. These compounds possess several beneficial pharmacological activities, including antioxidant, antimicrobial, anti-inflammatory and anticancer effects. As antioxidants, catechin and epicatechin safeguard cells from harm caused by potentially damaging molecules known as free radicals. This makes them valuable in preventing diseases linked to oxidative stress, such as heart disease and diabetes. Their anti-inflammatory properties result from their ability to reduce substances in the body that cause swelling and pain, which could help manage conditions such as arthritis. These compounds also show strong activity against bacteria and fungi, making them useful in treating infections. Moreover, catechin and epicatechin have been studied for their ability to fight cancer by stopping the growth of cancer cells and triggering their destruction. This review highlights the multiple health benefits of catechin and epicatechin and their potential as natural treatments for various diseases. Additional research is required to gain a clearer understanding how they work and to develop methods that enhance their effectiveness for medical use.

**KEYWORDS:** *Acacia catechu*, Catechin, Epicatechin, Flavonoids.**INTRODUCTION**

For many years, Ayurveda has made extensive use of *Acacia catechu* (L.f.), a deciduous tree belongs to the Fabaceae family, for the therapeutic options and prevention of a broad array of illnesses and/or ailments. In Hindi, it is known as Kahir, in English as the Cutch tree, and in Sanskrit as Khadira.<sup>[1]</sup> "Kachu," which is made by boiling the heart wood, has many phenolics and is chewed with betel leaves. Nesting grounds for granivorous birds such as Munias (*Lonchura* spp.) are found on dense, thorny branches. The catechin component of litter inhibits the development of soil fauna and bacteria. Protein-rich seeds used as "paan" ingredients. The majority of people drink boiled *A. catechu* (khair) water. This plant's heartwood yields a highly strong medicinal substance called Katha, which has numerous potential therapeutic uses. Katha, a component of paan (betel leaf mastication), gives saliva a crimson color. It is made up of concentrated extracts from 10- to 20-year-old *A. catechu* trees.

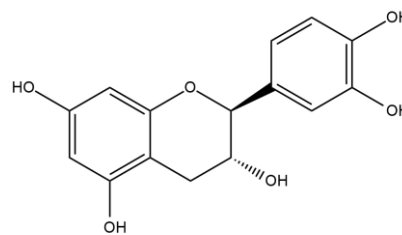
The Austronesians have been using *Acacia Catechu* L. (Fabaceae) in large quantities for thousands of years as holistic medicine. Analgesic, antidiabetic, wound

healing, antitumor, immunological booster, antioxidant, anti-inflammatory, antibacterial, antifungal, astringent, and anthelmintics are just a few of the many medical benefits that the entire *A. Catechu* plant possesses.<sup>[2]</sup> The leaves of *A. catechu* contain steroids, carbohydrates, saponins, flavones, alkaloid, glycosides, tannins, and phenolic substances.<sup>[1]</sup> The ethanolic extract of *Acacia catechu* (Fabaceae) leaves yielded ten compounds whose structures were identified as follows: ellagic acid; the nine flavonoids (+)-catechin, (-)-epicatechin, (+)-afzelechin, (-)-epiafzelechin, kaempferol, quercetin, quercetin 3-methyl ether (+)-mesquitol, and caryatin; and ellagic acid. The chemical structures of these compounds were identified via spectroscopic techniques (mass spectrometry, 1D and 2D nuclear magnetic resonance, and comparisons with values from the literature). This is the first time that the isolation of caryatin from the *Acacia* genus has been reported.<sup>[3]</sup> The bark of the plant<sup>[4]</sup> contains catechin, maclurin, Irisfloreantin, kaempferol, quercetin, rutin, gallic acid, epigallocatechin, Epigallocatechin afzelechin, Epiafzelechin, naringenin, isoquercetin, diosmetin, chrysin, and myricetin. The heartwood contains gallic acid, quercetin, 3-rhamnoside,

quercetin 3-glucuronide, protocatechuic acid-4-glucoside, and epicatechin.<sup>[1]</sup>

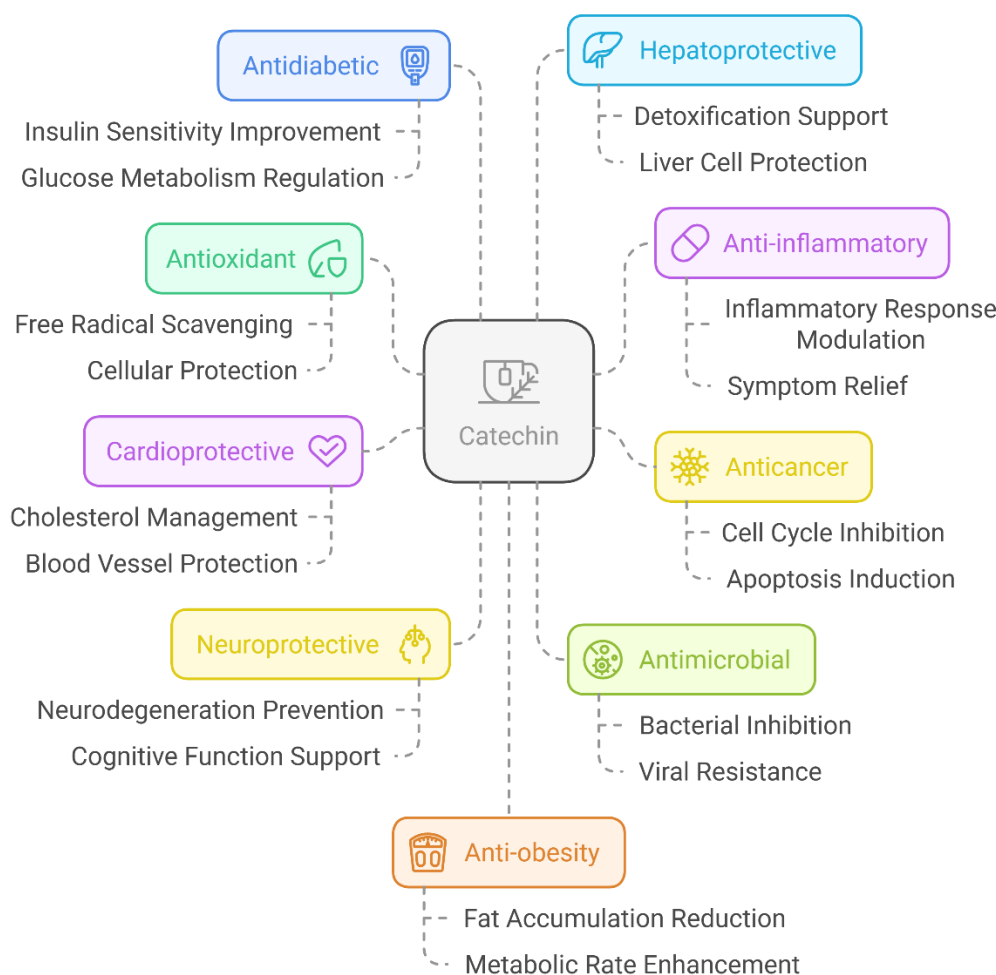
### Catechin

Catechin is a secondary metabolite from plants that belongs to the flavonol family. The word catechin comes from an extract of *Acacia catechu* L.<sup>[5]</sup> Catechin can be found in many foods, dietary fibers, plants, green tea, wine, and coca, including various herbs.<sup>[6]</sup> It has two steric forms of catechin (3,3',4',5,7-pentahydroxyflavan): an enantiomer and (+)-catechin (Figure 1).<sup>[7]</sup> Two benzene rings and a dihydropyran ring make up catechin, which has a hydroxyl group bonded to carbon 3. The presence of two chiral centers at carbons number 2 and 3 is responsible for diastereoisomer formation.<sup>[5]</sup> Catechins have numerous benefits for human health, such as anti-inflammatory, anti-oxidant, antidiabetic, anticancer, and antarthritic effects, including bactericidal, memory-enhancing, and hepatoprotective properties.<sup>[8]</sup>



**Figure 1: Chemical structure of (+)-catechin.**

In vitro investigations have shown that catechins protect against degenerative diseases and are strongly inversely proportional to the chance of death due to chronic heart disease. According to some reports Compared to gram-negative bacteria, catechins are more efficient against gram-positive bacteria in terms of antibacterial activity.<sup>[9]</sup> Research on animals has shown that green tea catechins prevent the progression of cancer in the skin, lungs, esophagus, stomach, liver, small intestine, bladder, prostate, and mammary glands.<sup>[10]</sup>



**Figure 2: Pharmacological effects of catechin.**

### Pharmacological activity of catechin

#### Anti-diabetic activity

The effects of catechin on blood glucose control and obesity in people with type 2 diabetes have been studied in clinical studies. The consumption of beverages high in

catechins helps individuals with type 2 diabetes avoid obesity, recover their ability to secrete insulin, and maintain low hemoglobin A(1c) levels. In a separate investigation, administering catechins resulted in the return of modified glycogen synthase, glucose-6-

phosphatase, glucokinase, and glycogen phosphorylase levels to practically normal levels. In addition, after catechin administration, GLUT4 mRNA and protein expression increased. Additionally, the insulin-mimetic action of catechins has been noted.<sup>[11]</sup> Administration of catechins also stops the progression of diabetes. Diabetes mellitus-induced vascular endothelial dysfunction is prevented by catechin therapy, which also stops the activation of the endothelial PI3K signal when eNOS and nitric oxide synthesis are activated. Furthermore, there is defense against type 2 diabetes erythrocyte damage caused by oxidation. Insulin grafted with catechin suppressed the activity of glycolytic enzymes, specifically glucosidase and amylase.<sup>[12]</sup>

#### **Inhibition of bone resorption**

In one study, pretreating embryonic mouse calvaria with catechin resulted in a culture that was resistant to the effects of bone-resorbing drugs. This effect might result from the ability of catechins to stabilize collagen.

#### **Antihyperlipidemic effects**

An irregularity in the metabolism of fats leads to the onset of hyperlipidemia. There appears to be a risk to this scenario as cardiovascular disease advances. Moreover, atherosclerotic plaques develop as a result of high triglyceride, cholesterol, phospholipid, and fatty acid levels. Catechins may decrease triglyceride and cholesterol levels by increasing the level of LDL receptor protein. Catechin protects endothelial function, which prevents the harmful effects of dyslipidemia on the biomechanical characteristics and wall structure of cerebral arteries, hence facilitating the recovery of cerebral blood flow.

#### **Antithyroid potential**

Upon the administration of catechins, there was a notable increase in thyroid sodium and potassium ATPase activity, a decrease in thyroid peroxidase activity, and notable hyperplasia of the follicles. TSH levels were elevated in conjunction with a notable decline in T3 and T4 levels. All of these findings support the antithyroid impact of catechins and it was observed that consuming large amounts of catechins may increase the risk of thyroid function changes. Additionally, aromatase inhibition was noted.<sup>[13]</sup>

#### **Antihypertensive effects**

A clinical trial revealed that consuming 120–599 mL of green tea per day decreased the risk of developing hypertension by 46%. Catechin-rich oil palm has vasodilatory effects that are mediated by pathways dependent on the endothelium. Furthermore, there was no indication of cardiotoxicity. It was previously believed that the antioxidant activity of catechin mediated its antihypertensive effect.

#### **Anticoagulant antiplatelet effects**

Micromolar concentrations of catechin inhibited platelet adherence to collagen and aggregation generated by

collagen. The activity was mediated by phospholipase C activation and decreased hydrogen peroxide generation, which inhibited platelet function.<sup>[14]</sup>

#### **Antiepileptic effects**

An assessment of the antiepileptic efficacy of catechin was conducted. In the ipsilateral cortex, superoxide dismutase activity increased and TBARS production decreased after catechins were administered. The antioxidant effect is believed to act as a mediator of this effect.<sup>[15]</sup>

#### **Anti-anxiety effects**

After getting daily catechins during a course of treatment with the stress hormone corticosterone, subjects demonstrated a marked decrease in immobility in the forced swimming test and increase in open-arm exploration activity in the elevated plus maze test. The central noradrenergic system's inflexion is most likely what led to the improvement in helplessness behavior that was observed. Thus, catechin may help reduce anxiety and depression.<sup>[16]</sup>

#### **Anti-Parkinson effects**

In addition to preventing cerebral ischemia/reperfusion damage, catechin has been demonstrated to prevent age-related cognitive decline. In cases of encephalomyelitis, catechin has been shown to reduce "brain inflammation" and protect neurons from degeneration.<sup>[17]</sup>

#### **Anti-Alzheimer effect**

Treatment with the green tea catechin resulted in a significant decrease in behavioral impairment, Wnt protein levels, A $\beta$ -42 generation,  $\gamma$ -secretase activity, APP-C99/89 expression and MAPK activation. The levels of some enzymes, such as  $\alpha$ -secretase, neprilysin, and Pin1, increased. Overall, there was a positive and defensive effect of green tea catechins against Alzheimer's disease.<sup>[16]</sup>

#### **Anti-Inflammatory Activity**

This study examined the combined anti-inflammatory properties of quercetin and catechin in RAW 264.7 macrophages activated with lipopolysaccharide (LPS). These findings indicate that catechin and quercetin have combined anti-inflammatory properties that may be explained by their ability to inhibit the TLR4–MyD88-mediated NF- $\kappa$ B and mitogen-activated protein kinase signaling pathways.<sup>[18]</sup>

The in vivo anti-inflammatory efficacy of catechin was evaluated in a carrageenan-induced rat paw edema model, while the in vitro anti-inflammatory effect of catechin (10, 50, and 100  $\mu$ M) was evaluated by measuring COX-2 enzyme inhibition via detection of the PGE2 concentration and NO production inhibition in LPS-treated RAW 264.7 macrophages. In vivo and in vitro protocols had strong anti-inflammatory effects. These findings, along with the pharmacokinetic profile, point to catechin as a potential strong contender for an

herbal anti-inflammatory formulation. Additionally, catechin can be taken in addition to currently available anti-inflammatory medications to lessen microbial resistance to medication and adverse effects.<sup>[19]</sup> Chronic inflammation increases TNF- $\alpha$  production, which, alongside TNFR, amplifies the inflammatory response. This triggers JNK phosphorylation, initiating apoptosis and caspase activation. Catechin and EGCG administration curbed TNF- $\alpha$  release and TLR4 expression, mitigating neuronal inflammation and cell death.<sup>[20]</sup>

#### **Analgesic activity**

This study investigated how catechin functions in the neuroprotective properties of the chronic constriction injury model. Seemingly, male adult Sprague–Dawley rats are in good health. These findings demonstrated that catechin alleviated neuropathic pain symptoms. Moreover, it reduced the concentrations of TNF- $\alpha$  and IL-6, IL- $\beta$  in the brains of the rats. Therefore, catechin holds a lot of promise for treating and managing neuropathic pain by reducing the levels of NF- $\kappa$ B-regulated inflammatory cytokines in a model of chronic constriction injury.<sup>[21]</sup>

#### **Anti-osteoporotic and anti-osteopenic effects**

In mouse bone marrow mesenchymal stem cell line, tea catechins exhibited increased osteogenic gene activity in addition to increased mRNA expression of the core binding factors  $\alpha$ 1 (Cbfa1/Runx2), osteocalcin, osteon and ALP. Oil palm leaf extracts high in catechins have been shown to increase the calcium content of bones. After extract treatment, the calcium content increased, as did the bone density and structure. Additionally, the total mineral content and ALP levels significantly increased.<sup>[22]</sup>

#### **Stimulation of bone growth**

In an osteoblastic MC3T3-E1 cell study, catechins increased both alkaline phosphatase activity and cell viability. Together with osteoblast apoptosis, catechin also reduces the synthesis of tumor necrosis factor  $\alpha$  and interleukin-6. Following catechin therapy, there was an enhance in osteoblastic activity and suppression of the osteoclast differentiation. Catechins also reduce the resorption of bone. It appears that catechin helps control bone remodeling.<sup>[23]</sup>

#### **Antiulcer effects**

Catechin, an antioxidant in green tea, protects against peptic ulcers in animal studies by inhibiting ethanol- and stress-induced ulcer formation, reducing oxidative stress markers, and blocking stomach acid production as a noncompetitive inhibitor of H<sup>+</sup>-K<sup>+</sup>-ATPase. It also defends against ischemia–reperfusion-induced gastric ulcers by increasing mucus production and increasing antioxidant activity. These findings suggest potential benefits for humans, pending further clinical research confirmation.<sup>[24]</sup>

#### **Age-related memory loss and benefits of neuroprotection**

Long-term catechin use prevents memory decline by reducing number of A $\beta$ 1-42 oligomers and increasing the number of proteins associated to synaptic plasticity in the hippocampus. In a study on a mouse model of brain aging, catechin intake, even in early adulthood, suppressed cognitive decline and partially improved brain structure and function.<sup>[25]</sup> Additionally, improvements in the ability to learn spatial cognition were noted.<sup>[26]</sup>

#### **Cardioprotective effects**

The cardioprotective effects of catechin were evident at a daily dose of 1.7 mg per mouse over 14 weeks, which halted atherosclerosis progression. Combining catechins with vitamin C mitigated idarubicin-induced cardiotoxicity, restoring cardiac contractility and body weight. Histopathological findings revealed preserved essential cardiac structures, with only minor sarcoplasmic reticulum dilation.<sup>[27]</sup>

#### **Hepatoprotective Effect**

Studies executed in vitro and in vivo have shown the protective benefits of catechins on liver integrity. In HepG2 cells, catechin at 1 mg/mL exhibited hepatoprotective properties. In vivo, catechin reduced hepatic lipid accumulation from chronic ethanol consumption by repairing ethanol-induced changes in the redox state of the liver. Compared with control rats, CCl<sub>4</sub>-treated rats presented reduced lipid peroxidation and increased hepatic antioxidant enzyme activity when inulin was grafted with catechins.<sup>[28]</sup> There is a chance of adverse effects associated with dosage, such as an increase in liver function marker enzymes. This noticeable increase in AST and ALT levels at high doses.<sup>[29]</sup>

#### **Anti-cataractogenic effects**

Catechin had an antiapoptotic effect on cataracts caused by N-methyl-N-nitrosourea. The lens epithelium presented increased Bcl-2 and Bax expression as well as prevention of apoptotic cell death.<sup>[30]</sup>

#### **Nephroprotective effects**

Gentamicin is the primary antibiotic for gram-negative infections, but its nephrotoxicity restricts its application. Catechin, which have been studied experimentally, shows nephroprotective effects. At 50 mg/kg daily orally, catechin significantly prevents glomerular and tubule degeneration, restoring depleted renal glutathione levels, mainly by its antioxidant activity.<sup>[31]</sup> Additionally, catechins have renoprotective effects against renal injury caused by ischemia–reperfusion. Catechin likely has renoprotective benefits through its antioxidant and radical scavenging properties.<sup>[32]</sup>

#### **In utero effects**

Catechins can cross the placenta, where they accumulate in fetal organs. A study in which 550 mg/kg green tea

extract was administered to expectant mothers on the fifteenth gestation day revealed catechins in fetal organs, notably the brain, eyes, lungs, heart, kidneys, and liver, with concentrations approximately ten times higher than those in other organs. Another study revealed that catechin concentrations in maternal plasma were 50–100 times higher than those in the fetus and approximately ten times higher than those in the placenta.<sup>[33]</sup>

#### Autoimmune myocarditis

When artificial autoimmune myocarditis is induced by a porcine cardiac myosin vaccination, Lewis rats showed improved cardiac function after receiving tea catechins. Notably, NF-B and ICAM-1 were suppressed.<sup>[34]</sup>

#### Sjogren's syndrome

The hallmark of Sjogren's syndrome is a deterioration of the secretory capacity of these glands as a result of lymphocytic penetration of the lacrimal and salivary glands. Tea polyphenols have been shown to shield normal human salivary acinar cells from the cytotoxicity caused by TNF- $\alpha$ .<sup>[35]</sup>

#### Respiratory disorders

Frequent catechin doses have positive effects on asthma and chronic pulmonary disease.<sup>[36]</sup>

#### Antiallergic effects

Catechin has been shown to be anti-allergenic. class IV allergy caused by oxazolone following percutaneous administration.<sup>[37]</sup>

#### Immunological insufficiencies

Research on AIDS has explored catechin and its analogs. In one study, the synergistic effect of retinoic acid and catechin in a mustard oil emulsion formulation on immunological responses against the HIV-1 gp120 protein (CN54) was examined. Administering this novel nutritional immune-enhancing delivery method significantly increased systemic and local antibody levels and cytokine responses, with implications for vaccine development and modern pathogen design, including HIV-1.<sup>[38]</sup>

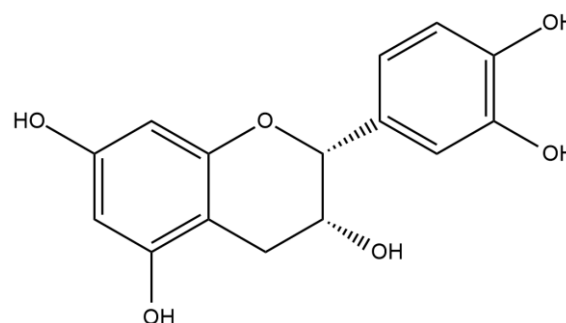
#### Antimicrobial effects

Using the microbroth dilution method, the *in vitro* antibacterial activity of catechin was assessed against a wide range of gram-positive and negative cultures. The results revealed that the MIC ranged from 1.25 to 10.0 mg/ml. A neutropenic rat thigh infection model was used to assess the *in-vivo* antibacterial activity and results

demonstrated considerable antibacterial effects.<sup>[19]</sup> A lower level of free radical scavenging activity was demonstrated by epicatechin gallate and (+) catechin. The results indicated that whereas catechin gallate and (+)-catechin shows reduced activity against microorganisms, the epimerized form of gallocatechin gallate had a high antagonistic effect on both tested strains, followed by epigallo catechin. Pyrogalllic acid is one of the phenolic acids with most antibacterial action.<sup>[39]</sup>

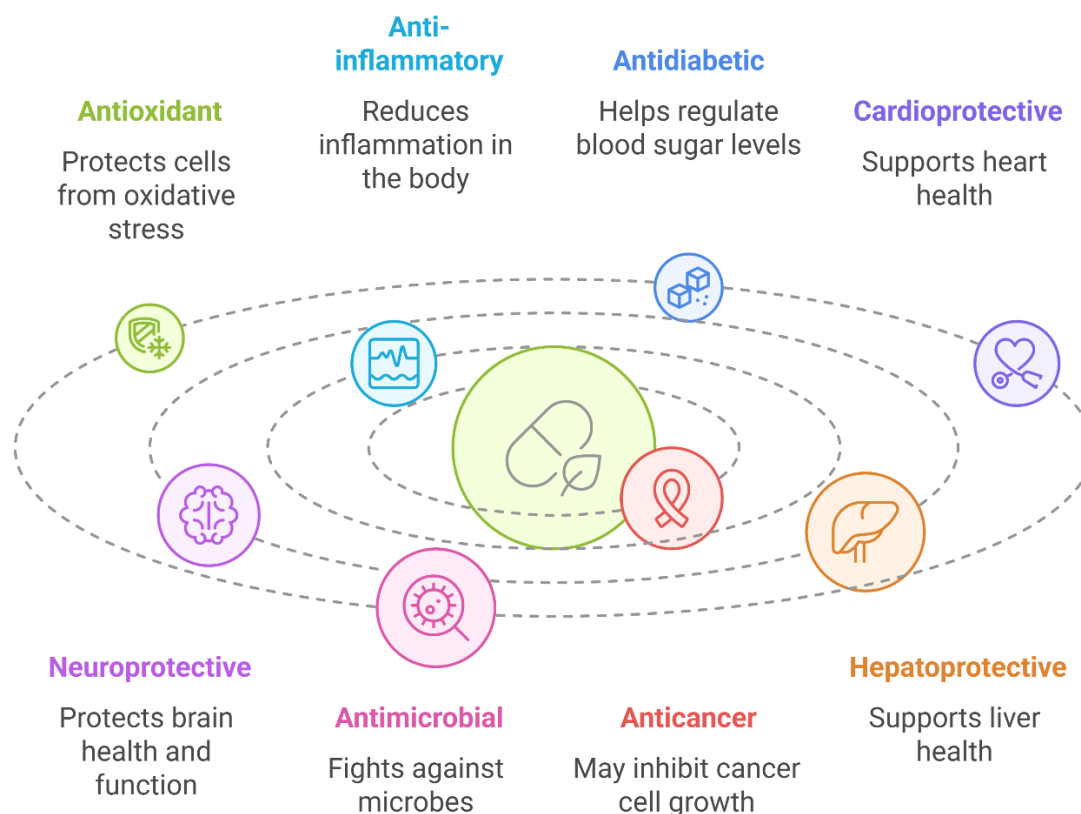
#### Epicatechin

Epicatechin (EC) (Figure 2) is a plant secondary metabolite and one of the most common polyphenols in the human diet.<sup>[40]</sup> Epicatechin is present mainly in tea, coca, grapes, apples, catechus, and green tea.<sup>[41]</sup> Epicatechin is widely known for its excellent antioxidant properties. In the human body, epicatechin metabolites are found in the plasma and accumulate in the kidney, colon, heart, liver, and brain, and other organs. As a result, epicatechin might be advantageous for many human body tissues and organs.<sup>[42]</sup>



**Figure 3: Chemical structure of (-)-Epicatechin.**

According to recent research, certain types of food containing (–)-epicatechin may be able to reduce blood pressure. The mechanism that explains the activity of (–)-epicatechin have been related to the prevention of endothelial dysfunction and oxidative damage, both of which have been linked to hypertension and specific brain illnesses.<sup>[43]</sup> Epicatechins have various medicinal properties such as anti-inflammatory, antidiabetic, antioxidant and anticancer activity. Additionally, epicatechin is neuroprotective, enhances muscle performance and helps for the therapy of cardiovascular disease.<sup>[41]</sup>



**Figure 4: Pharmacological effects of epicatechin.**

### Pharmacological activity of epicatechin

#### Anti-diabetic activity

A test for oral glucose tolerance was conducted using 10 mg/kg doses of rutin, catechin, and epicatechin to study their effects on blood glucose levels. Analysis revealed that a combination of 25% epicatechin and 75% rutin was optimal for reducing hyperglycemia and hypoglycemia. This combination was confirmed to be effective in diabetic mice after 28 days. Catechin, epicatechin and rutin exhibited strong antihyperglycemic effects.<sup>[44]</sup> Epicatechin, an active ingredient, acts similar to insulin, increasing glycogen content and glucose uptake in the rat diaphragm. It inhibits lipolysis, increases oxygen uptake in fat cells, and does not compete with insulin for binding sites. It is insulinogenic and insulin-like, showing promising effects.<sup>[45]</sup>

#### Anti-hypertensive activity

In spontaneously hypertensive rats (SHRs), dietary supplementation with (-)-epicatechin (3 g/kg) decreased blood pressure by 27- and 23-mm Hg on days 2 and 6, respectively in albeit modestly, compared with the blood pressure in SHRs receiving only drinking water.<sup>[23]</sup> (-)-Epicatechin may therefore influence blood pressure via NO in the vasculature because (-)-epicatechin administration increased the activity of nitric oxide synthase in the aorta by 173% on day 6. In addition, vascular smooth muscle cell function was intact in all the groups used.<sup>[46]</sup> Epicatechin is a bioactive substance found in cocoa and flavanol-rich foods and beverages. In both human and animals, it has been demonstrated to

enhance endothelium function. In salt-sensitive animal models of hypertension, epicatechin reduces blood pressure and end-organ damage. Nitric oxide (NO) appears to be involved in antihypertensive and anti-endothelial dysfunction as a key signaling molecule.<sup>[47]</sup>

The results obtained from this study confirmed that N, as NOX; H<sup>+</sup>, as a Na<sup>+</sup>/H<sup>+</sup>-exchanger; O, as MT dodecyl sulfate; and F, as formamide (outside EC as an endothelial cell) are essential for transgenesis by cellular liquidators and toxicity detection in hypertensive and normotensive patients and that they are able to cause more oxidation than normal individuals. Conclusion (-) Epicatechin exerts a protective effect on MDA and protein carbonyls and modulates the redox state through an increase in GSH and the number of membrane -SH groups present in hypertension. Thus, (-) epicatechin functions as a powerful intracellular antioxidant for cells.<sup>[48]</sup> Chronic epicatechin administration improves blood pressure, endothelial function, and oxidative status in hypertension caused by deoxycorticosterone acetate (DOCA)-salt. For 5 weeks, the rats were given either 2 or 10 mg kg<sup>-1</sup> day<sup>-1</sup> (-)-epicatechin. Both the rise in systolic blood pressure and the proteinuria were decreased by the high dose of epicatechin caused by DOCA-salt.

#### Anticoagulant antiplatelet effects

Human plasma samples (from 12 healthy individuals) were incubated with increasing concentrations of epicatechin. The absorbance was read at 405 nm to

quantify the turbidity of the fibrin clot. Fibrin clot nanostructure was quantified by scanning spectrometry (wavelengths ranging from 500 to 800 nm), and the average fibrin fiber size was assessed via electron microscopy. The permeability of the fibrin clot was measured as an index of its functional properties. The fibrin clot structure was found to be less tight and more open when the samples were treated with epicatechin.<sup>[44]</sup>

Epicatechin reduced platelet aggregation induced by various agents at 100  $\mu$ M (ADP: -39%, TRAP: -48%, epinephrine: -30%, and collagen: -30%). At concentration of 1  $\mu$ M, the thrombin potential significantly reduces ( $1332 \pm 230$  versus  $1548 \pm 241$  nM for the control) ( $p < 0.01$ ), and fibrinolysis increased, reducing the clot lysis time by 16% and 33% at 10 and 100  $\mu$ M, respectively, in comparison with that of the control ( $1271 \pm 775$  s). This results suggest that epicatechin has antiplatelet, anticoagulant and pro-fibrinolytic effects, highlighting its potential for preventing cardiovascular diseases.<sup>[49]</sup>

#### Anti-inflammatory activity

Effect of epicatechin on the production of inflammatory mediators in Raw264.7 cells stimulated by LPS. Epicatechin at doses of 5, 25, and 50  $\mu$ M significantly ( $p < 0.05$ ) inhibited the production of pro-inflammatory mediators such as nitric oxide (NO) and prostaglandin E2 (PGE2), as well as proinflammatory cytokines such as tumor necrosis factor (TNF)-alpha and interleukin (IL)-6, in LPS-induced Raw 264.7 macrophages.<sup>[50]</sup>

EC reduces TNF- $\alpha$ -induced inflammation and prevents low-level inflammation in patients with metabolic syndrome. EC inhibits TNF- $\alpha$ -triggered NF- $\kappa$ B signaling and blocks RelA nuclear transport. NF- $\kappa$ B-DNA binding decreases inflammation as well as inflammatory bowel disorders associated with diabetes mellitus by inhibiting TNF- $\alpha$  activity in intestinal barrier permeability dysfunction.<sup>[51]</sup>

Studies on flavanol-rich foods suggest potential cardioprotective effects, but the impact of individual flavanols such as epicatechin on reducing diet-induced atherosclerosis associated with cardiovascular risk factors (e.g., dyslipidemia and inflammation) remains unclear. Our investigation confirmed reduced lesional neutrophil content and inhibited NF $\kappa$ B activity in epicatechin-treated NF $\kappa$ B-luciferase reporter mice. Epicatechin also reduces the level of circulating inflammatory markers (e.g., SAA and human-CRP) and has local anti-inflammatory effects on vessel walls.<sup>[52]</sup>

ECG showed strong anti-inflammatory effects in a model of paw edema caused by carrageenan, as evidenced by reduced levels of proinflammatory mediators (PGE2, TNF- $\alpha$ , IL-1 $\beta$ , and IL-6) in plasma across treatment groups.<sup>[53]</sup>

#### Analgesic activity

The antinociceptive effects of epicatechin were blocked by the intraperitoneal administration of methiothepin (5-HT1/5 receptor antagonist), WAY-100635 (5-HT1A receptor antagonist), SB-224289 (5-HT1B receptor antagonist), BRL-15572 (5-HT1D receptor antagonist), SB-699551 (5-HT5A receptor antagonist), naloxone (opioid receptor antagonist), CTAP ( $\mu$  opioid receptor antagonist), nor-binaltorphimine ( $\kappa$  opioid receptor antagonist), and 7-benzylidenenaltrexone ( $\delta$ 1 opioid receptor antagonist) in the formalin test. Similarly, inhibitors of NO synthase (l-NAME), neuronal NO synthase (7-nitroindazole), guanylyl cyclase (ODQ), and various potassium channels (glibenclamide, 4-aminopyridine, and iberiotoxin) also blocked the effects of epicatechin, indicating the involvement of the NO-cyclic GMP-K<sup>+</sup> channel pathway, 5-HT1A/1B/1D/5A serotonergic receptors, and  $\mu/\kappa/\delta$  opioid receptors in its mechanism of action.<sup>[54]</sup>

Epicatechin gallate from *Bauhinia hookeri* significantly reduced writhing responses in mice induced by acetic acid ( $p < .001$ ), with percentages inhibition of 32%, 52%, and 62% at the tested dosages compared with those of the positive control. In the hot plate model, ECG significantly increased reaction times ( $p < .001$ ), indicating analgesic effects.<sup>[53]</sup>

#### Bone growth

Epicatechin subacute intramuscular injection alters bone vascularization (greater dosages promote vasoconstriction of blood vessels) but has no discernible effect on compact bone structure.<sup>[55]</sup>

#### Gastroprotective effects

The gastroprotective activity of EC was investigated in gastric ulcers. EC strengthens the mucus barrier and neutralizes gastric juice, resulting in gastroprotection via SH compounds,  $\alpha$  2-adrenoceptors, NO, SOD, and HSP-70.<sup>[56]</sup>

#### Anti-anxiety activity

A high-fat diet (HFD) and obesity may have a negative influence on the brain; however, dietary bioactivity may attenuate these effects. In mice, (-)-epicatechin (EC) has been shown to reduce anxiety-related behaviors generated by a HFD. Using a multigenomic approach, we hope to uncover the molecular underpinnings of EC activities in the hippocampus that underpin its anti-anxiety effects in HFD-fed mice.

#### Anti-Parkinson effects

EC demonstrated neuroprotective effects in a rat model of Parkinson's disease. The neuroprotective effects of ECs are likely due to their antioxidant and anti-inflammatory qualities, making them promising treatment options for Parkinson's disease.<sup>[57]</sup> EC protects against ROT-induced motor and neurochemical impairments in rats by decreasing NO and LPO production while increasing SDH, ATPase, and ETC

enzyme activities as well as striatal catecholamine levels. It also mitigates neuroinflammation and apoptosis, indicating the potential for Parkinson's disease treatment or delay.<sup>[58]</sup> Zhou et al. studied how EC protects substantia nigra neurons against apoptosis and the mTOR/AKT/GSK-3 pathway in rats with 6-dopamine-induced Parkinson's disease. A study on rats with 6-OHDA-induced Parkinson's disease revealed that EC may prevent neuronal cell death in the substantia nigra.<sup>[59]</sup>

#### Anti-Alzheimer effect

Epicatechin protects against A $\beta$  25-35-induced brain injury by reducing lipid peroxidation (LPO) and reactive oxygen species (ROS), thereby improving memory function in Alzheimer's disease models.<sup>[60]</sup> Epicatechin improves memory in AD rats by reducing Tau hyperphosphorylation, lowering BACE1 and A $\beta$ 1-42 expression, and enhancing antioxidant defenses, cognition, and memory function, as evidenced by increased time in the target quadrant.<sup>[61]</sup> Histopathological and DNA fragmentation tests revealed that the combination of vinpocetine and epicatechin significantly reduced aluminum chloride-induced Alzheimer's disease in rats, protecting neurons from AlCl<sub>3</sub>.<sup>[62]</sup>

#### Neuroprotection activity

These findings imply that increased epicatechin consumption activates Akt- and Ca<sup>2+</sup>-mediated signaling pathways that converge on NOS and CREB, resulting in synergistic improvements in neuronal mitochondrial capacity and significant protection against ischemia injury.<sup>[63]</sup>

#### Cardioprotective effects

This study aimed to determine whether epicatechin could interact with and alter myocardial arginase and NOS expression and function. In silico modeling, in vitro activity testing, and a rat model of ischemia/reperfusion injury revealed that epicatechin binds to and acts as a noncompetitive inhibitor of myocardial arginase. Additionally, flavanol reduced I/R-induced nitrosylation of arginase 1 and 2, which is linked to enzyme activation. Epicatechin also decreased elevated levels of the nNOS isoform protein induced by I/R while maintaining eNOS activity, as indicated by phosphorylation levels, suggesting potential cardioprotective effects.

#### Hepatoprotective effect

In a CCl<sub>4</sub>-induced acute liver injury model, EC demonstrated hepatoprotective effects by promoting regeneration of damaged hepatic tissue, as supported by histological evidence. The protective mechanism of EC involves enhancing antioxidant enzyme activity and directly scavenging free radicals, highlighting its potential therapeutic value against liver injury.<sup>[64]</sup>

#### Nephroprotective effects

Pretreatment with epicatechin gallate (5 mg/kg) normalized the oxidative stress, renal function, and histological abnormalities caused by cisplatin. In rats, ECG inhibited MAPK pathway activity while simultaneously reducing inflammation and apoptosis. These findings suggest that ECG reduces cisplatin-induced oxidative stress, inflammation, and apoptosis by inhibiting the MAPK pathway, resulting in improved renal function. Epicatechin was given 8 hours after cisplatin injury was induced in the mouse kidney. Cisplatin caused substantial renal impairment, tubular damage, and increased oxidative stress. Epicatechin therapy dramatically reduces renal and mitochondrial injuries.<sup>[65]</sup>

#### Immunomodulatory activity

Epicatechin-(2 $\beta$ →O→7,4 $\beta$ →8)-entocatechin (EEE) considerably increases splenocyte proliferation when given alone or in combination with concanavalin A (Con A), lipopolysaccharide (LPS), or anti-CD3. EEE significantly increases the cytotoxicity of natural killer (NK) cells as well as macrophage phagocytosis. EEE therapy dramatically increases the amounts of Th1 cytokines, such as IL-2, IL-12, IFN- $\gamma$ , and TNF- $\alpha$ , while decreasing the levels of the Th2 cytokines IL-4 and IL-10. As a result, the Th1/Th2 ratio increases considerably in the presence of EEE. EEE also increased the number of CD4<sup>+</sup> and CD8<sup>+</sup> T cells.

The results show that epicatechin-(2 $\beta$ →O→7,4 $\beta$ →8)-entocatechin has increased immunomodulatory activity, suggesting that this chemical could be developed as a new immunotherapeutic treatment for cancer and other immune-mediated disorders.<sup>[66]</sup>

#### Respiratory disorders

The effects of epigallocatechin-3-gallate (EGCG) on antigen-induced asthma-like responses in sensitized guinea pigs. EGCG (25 mg/kg b.wt.) or epicatechin (25 mg/kg b.wt.) was given i.p. 20 min before ovalbumin challenge. These findings provide evidence that EGCG can counteract allergic asthma-like reactions in sensitized guinea pigs, most likely by modulating NOS activity, and suggest its potential future use for asthma treatment.<sup>[67]</sup>

Epicatechin (EC) inhibited the generation of reactive oxygen species (ROS) and increased the survival of human bronchial epithelial cells following treatment with cigarette smoke extract (CSE). ECs stimulate ubiquitin-mediated Keap1 degradation by increasing tripartite motif-containing protein 25 (TRIM25) expression and increasing the nuclear localization of the Nrf2 protein. EC significantly suppresses the activation of the NLRP3 inflammasome and decreases CSE-induced pyroptosis, as evidenced by decreased LDH release and the number of caspase-1-positive cells. In a COPD rat model, Nrf2 knockdown reduced the protective effect of EC on human bronchial epithelial cells. Additionally, EC

suppresses the activation of the NLRP3 inflammasome and reduces CS-induced lung inflammation, as shown by decreased interleukin (IL)-1 $\beta$  and IL-18 secretion. EC suppresses the activation of the NLRP3 inflammasome, relieving CS-induced lung inflammation. reduced IL-1 $\beta$  and IL-18 secretion in a COPD rat model. Finally, this study demonstrated the protective impact of EC on experimental COPD rats and described the mechanism by which EC promotes Nrf2 activity, which could provide a unique therapeutic method for COPD.<sup>[68]</sup>

#### Autoimmune myocarditis

The green tea polyphenol epigallocatechin gallate, as a main component, suppresses EAM in rodents. Cacao polyphenols contain epicatechin and oligomeric procyanidins as the main components, which may contribute to EAM inhibition. Epicatechin reduces the lipopolysaccharide-induced increase in proinflammatory cytokines in vitro<sup>32</sup>, and i.p. injection of procyanidins alleviates experimental autoimmune encephalomyelitis. Therefore, epicatechins may have played a major role in EAM inhibition.<sup>[69]</sup>

#### Antimicrobial activity

Epicatechin from loquat leaves was tested for its antibacterial activity against four gram-positive and nine gram-negative bacteria. Epicatechin was found to be efficient against all the tested bacteria. Epicatechin was particularly efficient against three bacterial strains, *Bacillus cereus*, *Listeria monocytogenes*, and *Staphylococcus aureus*, and the antibacterial properties of epicatechin in *Ulmus davidiana* were investigated. The findings of this study indicate that loquat extract and epicatechin can be used as readily available sources of natural antioxidants, as food supplements, or in the pharmaceutical industry.<sup>[70]</sup>

Epicatechin has been explored as a potential antifungal agent. Disc diffusion assays revealed that theaflavin: epicatechin combination had greater antibacterial activity against *C. albicans* NCTC 3255 and NCTC 3179 than did theaflavin alone. Theaflavin had MICs of 1,024  $\mu$ g/ml and 128-256  $\mu$ g/ml when combined with epicatechin. The fractional inhibitory concentration indices were determined, and the synergy between theaflavin and epicatechin against both *C. albicans* isolates was demonstrated. Combinations of theaflavin and epicatechin have considerable potential for use as therapies for *C. albicans* infections.<sup>[71]</sup>

#### CONCLUSION

Over the last few decades, the use of herbal medicines has become a global issue with medical and economic implications. Acacia catechu is a medicinal shrub that is used to cure a variety of ailments in both traditional and modern medicine. This study revealed that A. catechu leaves contain a variety of bioactive chemicals, including polyphenols and flavonoids. Catechin and epicatechin are two of the compounds found in large quantities in this plant. Catechin and epicatechin have been widely

researched for their pharmacological properties. These findings demonstrate that Acacia catechu leaves are potential medicinal plants that might be employed in the development or manufacturing of new medications. Although Acacia catechu has high nutritional and phytochemical value, there is still a paucity of research on its molecular mechanism, as well as chemical examinations and clinical trials to ensure plant safety in the food and pharmaceutical industries.

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#### List of abbreviations

eNOS - Endothelial Nitric Oxide Synthase  
LDL - Low-Density Lipoprotein  
TSH - Thyroid Stimulating Hormone  
TBARS - Thiobarbituric Acid Reactive Substances  
MAPK - Mitogen-Activated Protein Kinase  
COX-2 - Cyclooxygenase-2  
LPS - Lipopolysaccharide  
TNF- $\alpha$  - Tumor Necrosis Factor-alpha  
JNK - c-Jun N-terminal Kinase  
IL-6 - Interleukin-6  
IL- $\beta$  - Interleukin-beta (often refers to IL-1 $\beta$ , Interleukin-1 beta)  
AST - Aspartate Aminotransferase  
ALT - Alanine Aminotransferase  
AIDS - Acquired immunodeficiency syndrome  
Epicatechin (EC) - Epicatechin  
NO - Nitric Oxide  
NOS - Nitric Oxide Synthase  
DOCA - Deoxycorticosterone Acetate  
HFD - High-Fat Diet  
LPO - Lipid Peroxidation  
ROS - Reactive Oxygen Species  
AD - Alzheimer's Disease  
CREB - cAMP Response Element-Binding Protein

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