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A Review

The pharmacological potential of catechin

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The contemporary scientific community has presently recognized flavonoids to be a unique class of therapeutic molecules due to their diverse therapeutic properties. Of these, catechin, also, has been explored for a number of pharmacological effects. The present review aims to document the therapeutic potential of catechin. Tea leave, catechu, and much more possess catechin as one of the active constituents. Today, catechin has been observed for its nutraceutical effect. The objective of this review is to examine the evidence of the effectiveness and pharmacological effects of catechin. Preclinical, as well as randomized controlled clinical trials pertaining to studies of catechin,are included in the study. Chemical properties of catechin and its structure-activity relationship about various biological activities have also been documented. The review revealed protective effects of catechin on functions and integrity of liver, kidney, heart , and age-related memory impairment. Catechin demonstrated the antimicrobial, anticancer, antihypertensive, anticoagulant , and antiulcer effect. The present review highlights the current information and the health-promoting effects of catechin. Along with this, the chemotherapeutic potential of the same has also been discussed.

Keywords: Anticancer, Antidiabetic, Antimicrobial, Organ protection, Polyphenol

Introduction

Tea from *Camellia sinensis* is the second most consumed beverage worldwide. Chinese traditional medicine documents its use to cure many ailments possibly due to the presence of catechin. Catechin is a plant-derived secondary metabolite widely found in nature belonging to flavonols family. The word ‘catechin’ is originated from catechu, obtained from the boiled extract of *Mimosa catechu*[1]. Sources of catechin include green tea Korean tea, matcha tea, black tea, coconuts onion, grape seeds and much more (Fig. 1).

Catechin contains two benzene rings (A ring, B ring) along with dihydropyran (C ring) onto which the hydroxyl group is attached to carbon 3. The presence of two chiral centres molecule at carbon 2 and 3 is accountable for the generation of diastereoisomers. Two isomers with trans configuration are termed as ‘catechin’; while the other two with cis configuration are known as ‘epicatechin’. These isomers can be distinguished by chiral chromatography[2]. The uptake of these polyphenols (Table 1) by the biological system makes it an important molecule to be explored for therapeutic and pharmacological effects. The present review focuses on the pharmacological potentials as studied in various experimental models.

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Abbreviations: AIDS, Acquired immuno deficiency syndrome; ALP, Alanine phosphatase; CCl_4, Carbon tetrachloride; GLUT4, Insulin-regulated glucose transporter; H+-K+-ATPase, Hydrogen potassium proton pump; Hemoglobin A(1c), Glycosylated hemoglobin; HIV, Human immunodeficiency virus; LDL, Low density lipoprotein; MAPK, Mitogen-activated protein kinases; Na^+K^+ATPase, Sodium potassium proton pump; NF, Nuclear factor; PI3K, Phosphatidylinositol 3-kinase; TBARS, Thiobarbaturic acid reacting substances; TNF, Tumor necrosis factor

Pharmacological effects

Endocrine effects

Antidiabetic activity

Diabetes mellitus is one of the critical public health problem observed in developed and developing nations. It is amongst the seventh cause of death worldwide. It is a metabolic disorder that is characterized by the absence or lack of insulin along with ‘chronic hyperglycemia’. This condition is also observed by increased ‘lipid metabolism’.

Catechin has been tested clinically to determine its effects on obesity and blood glucose control in patients with type 2 diabetes. Catechin rich beverage intake resulted in the prevention of obesity along with the recovery of insulin secretory ability and, as a mode to

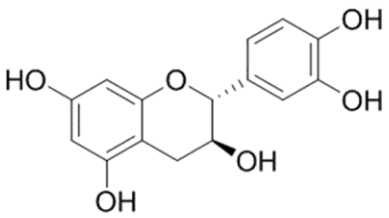

Fig. 1 — Structure of Catechin

Table 1 — Pharmacokinetics of Catechin

Absorption	Oral	39
Distribution	Widely distributed	39,40
Metabolism	Hydroxylation	41
Excretion	Urine	42
Active metabolite	Taxifolin	41,43

maintain low haemoglobin A(1c) levels in type 2 diabetic patients. In another independent study, treatment with catechins caused restoration in altered levels of glucokinase, glucose-6 phosphatase, glycogen synthase and glycogen phosphorylase levels nearly normal. Along with this, GLUT4 mRNA and protein expression were augmented after treatment with catechins. The Insulino-mimetic activity was also observed[3]. Phospholipase A2 and lipid peroxidation were also reduced[4]. Catechin administration also delays the progression of diabetes. Catechin treatment prevented diabetes mellitus-induced vascular endothelial dysfunction along with 'activation of the endothelial PI3K signal following activation of eNOS and nitric oxide generation. There was also protection against oxidation-induced damage of type 2 diabetic erythrocytes. Catechin grafted insulin caused inhibition of glycolytic enzymes *viz* amylase and glucosidase[5].

Antihyperlipidemic effects

Hyperlipidemia arises as a consequence of anomaly in the metabolism of lipids. This situation seems to be jeopardy in the progression of 'cardiovascular disease'. Further, increase in the levels of cholesterol, phospholipids, fatty acids and triglycerides resultin the development of 'atherosclerotic plaques'. Catechins promote lowering cholesterol and triglyceride concentrations in possibly due to increased LDL receptor protein level. By safeguarding 'endothelial function', catechin retarded harmful effect of 'dyslipidemia' on cerebral artery wall structure and associated biomechanical properties thus aided in the restoration of cerebral blood flow[6].

Antithyroid potential

Flavonoids are known to show health benefits, yet they are observed to demonstrate the antithyroid effect. Administration of catechins resulted in remarkable hyperplasia of follicles along with a reduction in the activity of thyroid peroxidase, 5′-deiodinase I and increase in thyroidal Na^+K^+ATPase activity. There was a significant decrease in the levels of T3 and T4 together with an increase in TSH levels. All these results demonstrated the antithyroid effect of catechins, and it was concluded that intake of the high amount of could predispose to 'alteration in thyroid function'. Aromatase inhibition was also observed[7].

Inhibition of bone resorption

In a study, pretreatment with catechin caused embryonic mouse calvariainaculture resistant to the action of bone resorbing agents. The effect could be due to the collagen-stabilizing properties of catechins[8].

Cardiovascular effects

Anti-hypertensive effects

According to a clinical study, daily consumption of '120–599 mL of green tea' is reported to reduce the chances of budding hypertension by 46%. Catechin rich oil palm demonstrated vasodilatory effects mediated *via* '*via* endothelium-dependent mechanisms'. Along with this, there was no sign of cardiotoxicity. Antihypertensive effect of catechin was thought to be mediated due to antioxidant effect[9].

Anticoagulant Antiplatelet effects

Catechin in micromolar amounts caused inhibition of collagen-induced platelet aggregation and platelet adhesion to collagen. The activity was mediated due to inhibition of platelet function by reducing the production of hydrogen peroxide along with phospholipase C activation[10].

Gastrointestinal effects

Antiulcer effects

Peptic ulcers are the results of an imbalance between 'aggressive' and 'protective' factors at the luminal surface of thegastricepithelium. Catechin has demonstrated anti-ulcer effects on the experimental animal. Oral administration of catechins caused dose-dependent inhibition of ethanol-induced ulcers and restraint plus water immersion stress-induced acute gastric mucosal injury. There was a reduction in levels of thiobarbituric acid-reactive substances in catechins treated group. The protective effect was augmented due to antioxidant activity and gastric mucus-increasing actions[11].Catechin has been proven to be non-competitive inhibitors of H^+-K^+-ATPase Catechin showed a protective effect on gastric mucosa

against ischaemia-reperfusion-induced gastric ulcers due to antioxidant activity and mucus protection[12].

Bone growth

Bone growth promotion

In a study onosteoblastic MC3T3-E1 cells, catechins caused increase cell survival along with increment in alkaline phosphatase activity. Catechin also causes a decrement in Tumour necrosis factor-alpha and interleukin-6 production along with osteoblast-apoptosis. An increase in osteoblastic activity and inhibition of osteoclast differentiation was observed after treatment with catechins. Bone resorption was also inhibited by catechins. Catechin seems to be beneficial in regulating bone remodelling[13].

Antiosteoporotic & antiosteopenic effect

A study in Europe revealed are duction in hip fracture in habitual tea drinkers. In another study, it was observed that the bone mineral density of habitual tea drinkers and post-menu pause women with the habit of regular tea intake was higher as compared to non-tea drinkers.

Tea catechins demonstrated increased activity of osteogenic genes along with an increase in mRNA expression of core binding factors a1 (Cbfa1/Runx2), osterix, osteocalcin, and ALP in murine bone marrow mesenchymal stem cell line. Catechin-rich oil palm leaf extract has demonstrated in enhancement in bone calcium content. Treatment with extract increased bone density and structure including an increase in calcium content. There was also a significant increment in ALP levels and total mineral content[14].

Organ protective effects

Age-relatedmemory impairment and neuroprotective effects

Someplant-derived polyphenols have demonstrated beneficial consequences on memory and learning and are helpful in protecting against detrimental effects on memory, learning, and neuro-cognitive performance. When absorbed, flavonoids and their associated metabolites are capable of crossing blood brain barrier. This could be a reason for the exertion of neuropharmacological effects of flavonoids. On reaching the brain, they influence 'signalling pathway', 'expression of genes' and 'protein function'.

Long-term administration of catechin prevented spatial learning and memory impairment. The effect was mediated due by decreasing A β1-42 oligomers and upregulating synaptic plasticity-related proteins in the hippocampus. In another study, mouse, a model of 'brain senescence' along with 'short life', 'cerebral atrophy' and 'cognitive dysfunction' was used as n experimental model to study the effect of tea catechins administration. Catechin, even when ingested during the early adult stage caused repression of brain dysfunction. Intake of catechins caused partial improvement in morphologic and functional changes in the brain[15]. Improvement in spatial cognition learning ability was also observed[16].

Cardioprotective effects

Catechin is extensively studied for cardioprotective effects. Catechin in an average dose of 1.7 mg catechin/day/mouse for 14 weeks offered cardio protection. During the study, the development and progression of atherosclerosis was also prevented. Catechin combination with vitamin C caused amelioration of idarubicin-induced cardiotoxicity. Administration of this dynamic combination caused restoration of body and heart weight, recovery of cardiac contractility. Histopathological evidence suggested only slight dilatation of the sarcoplasmic reticulum with the preservation of other vital histo-architecture[17].

Hepatoprotective effect

In vitro and *in vivo* studies have demonstrated a protective effect of catechins on liver integrity and liver protection. Catechin in dose (1 mg/mL) exhibited hepatoprotective effects on HepG2 cells. Catechin, in an *in vivo* study, caused inhibition of hepatic lipid accumulation as a result of chronic ethanol ingestion. Such an effect is mediated due to the correction of 'ethanol-induced alterations' in 'hepatic redox state'. Similarly, in another study, catechin grafted inulin augmented hepatic superoxide dismutase, glutathione peroxidase, glutathione reductase, catalase, glutathione and total antioxidant capacity along with decrement in lipid peroxidation in CCl_4 treated animals[18]. Chances of dose related untoward effects (raise in liver function marker enzyme) are seen. In high dose a significant increase in AST and ALT levels was seen[19].

Nephroprotective effects

Gentamicin seems to be a 'gold standard' antibiotic against gram-negative bacterial infections. However, nephrotoxicity associated with it appears to be a limiting factor for its use. Catechin has been experimentally studied for nephroprotective effects. Catechin (50 mg/kg/day, per os) administration

prevented the degeneration of glomeruli and tubules to a major extent. Along with this, the restoration of renal-reduced glutathione to normal levels was observed. The antioxidant mechanism of catechins played a significant role in mediating nephroprotective effect[20]. Catechins also demonstrated a renoprotective effect against ischemia-reperfusion-induced renal injury[21].

Anticataractogenic effects

Catechin demonstrated a protective effect against apoptosis against N-methyl-N-nitrosourea-induced cataract. The increment in Bcl-2 and Bax expression along with inhibition of apoptotic cell death in the epithelium of the lens was observed[22].

In utero effects

A study demonstrated the capability of catechins to cross and accumulate in the placenta. Green tea extract was administered to pregnant dams (550 mg/kg) on 15.5 days of gestation day of pregnancy. Fetal organs were studied for the presence of polyphenols. Catechins were observed in organs like the brain, eyes, lungs, heart, kidneys and liver. The concentration of catechins was about ten times higher than other organs. In another study, maternal plasma concentrations of catechin were about ten times more than in the placenta and 50-100 times greater than in the fetus[23].

CNS Effects

Antiepileptic effects

The antiepileptic effect of 'β-catechin' was evaluated. The administration of catechins caused a decrement in TBARS formation and augmentation of superoxide dismutase activity in the ipsilateral cortex. The activity was thought to be mediated through antioxidant effect[24].

Anti-parkinson effects

Catechin has shown a protective role against an age-related decline of cognition along with prevention of cerebral ischemia/reperfusion injuries. Reduction in 'brain inflammation' along with the prevention of neuronal damage in encephalomyelitisis observed with catechin[75].

Anti-Alzheimereffect

Green tea catechin treatment caused a significant reduction in behavioural impairment, γ-secretase component, Aβ-42 production, APP-C99/89 expression, γ-secretase activity, Wnt protein levels, and MAPK activation. There was an increase in levels of enzymes like enzyme activities α-secretase, neprilysin, and Pin1. Over-all green tea catechins showed abeneficial and protective effect against Alzheimer's disease[27].

Anti-anxiety effects

Daily administration of catechins pretreated with a stress hormone 'corticosterone' caused a significant reduction in immobility in forced swimming test and an increase in open arm exploratory behaviour in elevated plus maze test. Improvement in helplessness behaviour was observed probably due to the inflexion of central noradrenergic system. Catechin, thus, could be useful in alleviation of anxiety and depression[27].

Autoimmune state

Autoimmune myocarditis

Tea catechins, when administered to Lewis rats (immunised with porcine cardiac myosin to establish experimental autoimmune myocarditis), caused improvement in cardiac functions. Suppression in NF-κB and ICAM-1was observed[28]

Sjogren's syndrome

Sjogren's syndrome is observed by lymphocytic infiltration of the salivary and lacrimal glands leading to the destruction of secretory functions of these glands. Tea polyphenols demonstrated a protective effect on normal human salivary acinar cells from TNF-α-induced cytotoxicity[29].

Respiratory disorders

Regular administrations of catechins cause beneficial effects against chronic pulmonary disorder and asthma[79].

Antiallergic effects

Catechin demonstrated anti-allergenic effects oxazolone-induced type IV allergy after percutaneous administration[32].

Immunological insufficiencies

Catechin and its analogues have also been studied for AIDS. In a study, retinoic acid along with catechin in mustard oil emulsion formulation has been investigated for a synergistic effect in immune responses against the gp120 protein of HIV-1(CN54). Administration of this new nutritive immune-enhancing delivery system caused significant enhancement of local and systemic antibodies and cytokine responses providing imperative connotations for vaccine and contemporary design for HIV-1 and other pathogens[33].

Antimicrobial effects

Antimicrobial studies of tea date back 100 years ago. Studies revealed that tea extract was able to inhibit

the growth of *Salmonella typhi* and *Brucella melitensis*. Similarly, the antimicrobial effect of *Yersinia enterocolitica* was also documented. In the same way, catechin significantly inhibited the growth of *Bacillus cereus* and *Trypanosoma cruzi*. Catechin inhibited the growth of *Helicobacter pylori*[34], *Trichophyton*, *Candida albicans*, *Chlamydia*, *Mycoplasma*[35]. Primary targets of anticancer effects of catechin include apoptosis induction, cellular cycle arrest, inhibition of proliferation, metastasis, and angiogenesis[36].

Flavonoids are widely studied for their multiple biological effects[37,38]. Catechin has a long history to be used in the treatment of heart disease (revitalizing vascular function)[39-43]. According to available literature, catechin is reported to have unique pharmacological activities *viz*. antihypertensive, antidiabetic, anticancer, antiulcer, hepatoprotective effects[44]. Another phytochemical, hesperidin shares similar pharmacological profile[45]. However, due to variation in its amount in the plant to plant, chances of dose related untoward effects (raise in liver function marker enzyme) are seen. In high dose a significant increase in AST and ALT levels is seen. An attempt has been made to develop a nano-scale formulation of catechin to enhance its bioavailability, but still it is a difficult task as catechin is easily liable to oxidation. In nutshell, this review is aimed to focus on the latest research on catechin with special reference to its pharmacological potential.

Structure-activity relationship

- Availability of 'mono anion form' at catechol B-and resorcinol A-rings is responsible for free radical scavenging activity. The rate of reaction is increased with an increase in electron donating capacity of catechins.
- The presence of the ortho-catechol group in B ring is necessary for the antioxidant effect. The presence of 2, 3 double bond is also necessary to impart antioxidant effect.
- The presence of hydroxyl group at 5 position on B ring and the galloyl group at the 3-position on the C-ring is responsible for DNA polymerase inhibition. Non-competitive type of inhibition is observed.
- The presence of the ortho catechol moiety in the structure is necessary for protection against LOOH-induced cytotoxicity. An increase in activity is observed by adding more electron group.
- In the case of oligomeric derivatives, hydroxylation of 'upper unit of dimer' is necessary for antimicrobial activity. With an increase in substitution of hydroxyl group, a significant increase in antimicrobiual activity is seen.
- The presence of resorcinol in the structure is necessary for inhibition of the COX-1 enzyme. Catechin is peroxidase mediated mechanism-based in activator of COX-1.
- Heat treatment of catechin in the presence of copper sulphate increases antimicrobial activity. This effect might be due to generation of more hydrogen peroxide which is responsible for antimicrobial effect.

Conclusion

Catechin is a polyphenol found abundantly in plants. The benefits of catechu (catechin being an active component of catechu) have been known since ancient times. Among the others, catechuic acid, catechin 7-O-gallate, epicatechin, epigallo catechin gallate and epicatechin gallate are important active compounds. The various pharmacological studies on catechin have demonstrated various valuable, therapeutic and protective effects on organ systems. Owing to its antioxidant and anti-cancer effect, it would be interesting to trace the mechanism by which it modulates cellular system. Thus, as evident from the above facts, catechin is phytochemical with multiple pharmacological activities. Being found in plants, vegetables, and fruits, catechin can be regarded as a 'vital phytochemical' which is needed to be studied extensively to establish adequate safety profile in human to get therapeutic benefits.

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Conflict of Interest

All authors declare no conflict of interest.

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