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Catechin as a potential source of phytomedicine and nutraceutical: present and future

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Abstract

Catechins, natural chemicals found in plants, have garnered attention for their therapeutic potential, including preventing atherosclerosis, modulating angiogenesis, mitigating cerebral ischemia, and providing organ-specific protection. Found in dietary sources like green and black tea, catechins are readily absorbed and retain their bioavailability, making them valuable additions to diets. However, despite their promise, catechins face challenges with bioavailability due to factors like oxidative degradation, gastrointestinal instability, and low permeability. Innovative strategies such as hydroxyl group protection and novel delivery systems aim to overcome these obstacles, turning catechins into potent medicinal compounds for drug development. Chemical evidence supports catechins' bioactivity, with studies elucidating their molecular mechanisms and pharmacological effects in vivo and in vitro. Understanding these processes sheds light on how catechins interact with biological systems and exert therapeutic effects.

In conclusion, catechins offer diverse health benefits, but addressing their bioavailability issues requires creative solutions. Incorporating catechins into food and nutraceuticals underscores their importance not only as therapeutics but also for overall well-being.

Keywords: Catechin; Phytochemistry; Pharmacology; Bioavailability; Formulations.

Introduction

Throughout history, natural products have been vital for healing human ailments, with nature still a primary source for drug development today, despite compound complexity (Kaushik, Ahlawat, Singh, & Singh, 2021; K. Singh, Aggarwal, Singh, & Ahlawat, 2022)

One such class of natural metabolite is flavonoids, mainly found in fruits, vegetables, and grains. Catechin is in the flavanoid group of secondary metabolites, a polyphenolic compound present mainly in various foods and beverages. Chemically, they are a group of flavan-3-ol and are mainly attributed to their antioxidant activity.

Among the various sources, fruits such as apricots and strawberries are known for their high catechin content, whereas epicatechin concentrations are highly correlated with apples and blackberries. Both black and green tea contain significant amounts of epigallocatechin, epicatechin gallate, and epigallocatechin gallate (Monobe, Ema, Tokuda, & Maeda-Yamamoto, 2014). The use of catechins in recent advances in therapeutic claims mainly for anticancer, cardioprotective, atherosclerosis (Mankovskaia, Levesque, & Prakki, 2013), phagocytosis (Gu et al., 2013), dental caries (Mereles & Hunstein, 2011), angiogenesis, etc. (Sutherland, Rahman, & Appleton, 2006) has received great attention. However, all of these catechins suffer from poor bioavailability, poor permeability, and instability (in alkaline media), which hinders their development into drug-like molecules despite their great potential. The most promising catechin is epigallocatechin gallate, and increasing its bioavailability will be difficult (Rinaldo et al., 2010). The review summarizes the natural sources of catechin, the chemical arrangement for its bioavailability, therapeutic claims, mechanism of action, nutraceuticals aspects, prospective formulation, bioavailability challenges and complications, and solutions to become a druglike candidate.

1. Natural Sources of Catechin

The main source of catechins has been mainly green tea, which accounts for 25% to 35% of their dry weight. A detailed list of different types of isolated catechins and their natural sources is shown in Table 1.

1.1 Tea Catechins in meat preservation

Due to their high fat content, red meat and poultry are often vulnerable to lipid oxidation. The amount of fat in meat varies depending on the type, age and sex of the animal, as well as the type of tissue used. Studies have shown that tea catechins, which are natural antioxidants, may extend the shelf life of various types of meat by preventing lipid oxidation. The addition of tea catechins at a level of 300 mg/kg was demonstrated in a study by Tang, Kerry et al., to significantly inhibit

lipid oxidation in red meat and poultry patties. However, concentrations of tea catechins higher than 300 mg/kg were required for the inhibition of lipid oxidation in samples with high levels of highly unsaturated lipids, such as fish. (Mc Carthy, Kerry, Kerry, Lynch, & Buckley, 2001; Tang, Kerry, Sheehan, Buckley, & Morrissey, 2001; TL, Kerry, Kerry, Lynch, & Buckley, 2001).

1.2 Catechins in animal feed supplement

Tea catechins are added to feed to preserve the quality of the meat in pigs and chickens. Tea catechins have shown in vivo antioxidant activity. However, adding tea catechins to a cattle's diet does not improve the meat quality but variations in the types or quantities of tea catechins used in feedstuffs, along with modifications to digestive systems, could result in differences in efficacy. (Frisby, Raftery, Kerry, & Diamond, 2005; Yilmaz, 2006).

1.3 Catechins as Antimicrobial agent

To prevent the development of infections or slow down the deterioration of food, antimicrobial compounds may be naturally occurring in food or added to it. Many studies have been conducted to evaluate the antibacterial potency of phenolic antioxidants in meals. As an example, tannins, which are flavanol polymers, have been shown to inhibit the growth of *Clostridium botulinum, Vibrio, Klebsiella, Shigella, Enterobacter, C. perfringens, Aeromonas, Bacillus, Proteus, Staphylococcus aureus, Streptococcus, and Pseudomonas* (Chung, Wei, & Johnson, 1998). Epigallocatechin-3-gallate (EGCG) and epicatechin had an inhibitory impact on the development of *H. pylori*, but EGCG had superior inhibitory efficacy compared to epicatechin (Yuk-Kei Yee, 2001).

1.4 Functional food

According to a study, catechin (-)-epicatechin gallate is 7.8 times more effective than trolox, an analogue of vitamin E. The study suggests that catechins may enhance human health by protecting cellular redox balance. (Grzesik, Naparło, Bartosz, & Sadowska-Bartosz, 2018).

2. Catechin as dietary supplements

From ancient times, ancient societies have used the therapeutic benefits of tea (*Camellia sinensis L.*), the second most consumed beverage in the world (after water), and it is widely consumed in unfermented (green tea), semifermented (oolong teas), and fermented (black and pu-erh or red) forms. About 76-78% of the tea produced and consume globally is the black tea, followed by 2% oolong tea and 20-22% green tea (Cabrera, Giménez, & López, 2003). Recent research has shown that tea polyphenols may also help people lose weight; therefore, they are now a common ingredient in weight loss products (Saper, Eisenberg, & Phillips, 2004).

Green tea dietary supplements (GTDS) are available commercially in two forms: those solely based on green tea extracts (GTEs) and those combining GTEs with other botanical extracts. There are limited publications on comparisons of tea product quality and the relationship between label claims and actual phytochemical levels (Henning et al., 2003). The presence and levels of caffeine in GTDS are important due to the well-known stimulatory, psychotropic, neurological, and weight loss consequences of caffeine usage as well as the broad consumer preference for decaffeinated products (Dórea & da Costa, 2005). The dietary items made from oolong tea were also shown to be particularly beneficial in helping obese persons to lose weight. It has been discovered that green tea catechin EGCG is helpful for obesity. Tea catechins aid in weight control, and human body weight significantly decreases after consuming green tea catechins (Suzuki et al., 2013).

3. **Tea Catechin as nutraceuticals**

Nutraceuticals are now being researched for the prevention and treatment of many illnesses, including cancer, diabetes, cardiovascular disease, and others (Chanda, Tiwari, Kumar, & Singh, 2019). Many bioactive substances in tea, including polyphenols, polysaccharides, vitamins, amino acids, and others with therapeutic benefits, may be used as food additives for creating nutraceuticals (Y. Wang & Ho, 2009). There is an excellent chance that tea's bioactive components will be exploited as food additives that have medical or health benefits for illness prevention and treatment, opening the door for the creation of nutraceuticals (K. W. Lee, Lee, & Lee, 2002).

Tea polyphenols provide prospective nutraceuticals for a number of type 2 diabetes mellitus complications. Daily black or green tea consumption helps prevent diabetic cataracts and reduce blood glucose levels. Similar to this, oolong tea has a significant impact on the management of type 2 diabetes (Chongde Sun, 2020).

4. **Interaction of catechins with enzymes/drug substance**

Catechins are converted to theaflavins and thearubigins by the enzyme’s polyphenol oxidase and peroxidase (Abudureheman, Yu, Fang, & Zhang, 2022; Dasgupta & Klein, 2014; Komatsu et al., 1993). Black tea's theaflavins prevent DNA damage, which is a significant factor in the development of cancer. Tea polyphenols' ability to bond with carcinogens and facilitate metabolism is linked to their anti-carcinogenic function. The research on black tea and its polyphenols in human leukaemia cells provides evidence for the beverage's ability to prevent cancer. Black tea may save immune cells from apoptosis brought on by tumours (Feng et al., 2002; Kundu, Dey, Roy, Siddiqi, & Bhattacharya, 2005). Catechins react with proteins and

caffeine to generate precipitates that cause the cream to develop, making the solution hazy (Marcel, M., & Penders, 1998). Moreover, catechins produce precipitate when they interact with certain enzymes, including lipoxygenase, α-amylase, pepsin, trypsin, and lipase, which then prevents these enzymes from doing their function (McDougall, Kulkarni, & Stewart, 2008). Compared to catechins without an ester link, those having an ester bond, including EGCG and ECG, are more able to precipitate with the enzymes (Afzal et al., 2022; Sekiya, Kajiwara, Monma, & Hatanaka, 1984). Moreover, tea's chemical composition might hinder the absorption of iron from meals; however, lemon-infused green tea lessens this impact. They are both highly efficient in healing wounds, so green tea and honey have been used for centuries (Chacko, Thambi, Kuttan, & Nishigaki, 2010; V. Sharma, 2005).

Variations in antioxidant activity, polyphenol bioaccessibility, and protein digestibility of protein-polyphenol complex beverage models are likely influenced by competitive interactions between proteins, polyphenols, and digestive enzymes during gastrointestinal processing. (Bhagat et al., 2019; Lamothe, Azimy, Bazinet, Couillard, & Britten, 2014).

5. Chemical evidence to bioactivity

Catechins consist of a three-ring hydroxylated system, with rings A and B resembling benzene rings attached to a central dihydropyran ring (ring C). Unlike other flavonoids, catechin lacks a double bond between positions 2 and 3 or a keto group at position 4 of ring C. With four diastereoisomers due to two chiral centers, green tea contains these stereoisomers. (Figure – 1) *viz.*:

1. Catechin and Epicatechin.
2. Epigallocatechin (EGC) and Gallocatechin (GC).
3. Catechin gallate (CG) and Epicatechin gallate (ECG).
4. Epigallocatechin gallate (EGCG) and Gallocatechin gallate (GCG).

The structures of these stereoisomers are shown in in Figure – 1, and also summarized in Table - 2 (Alam et al., 2011; Kemberling, Hampton, Keck, Gomez, & Selman, 2003)

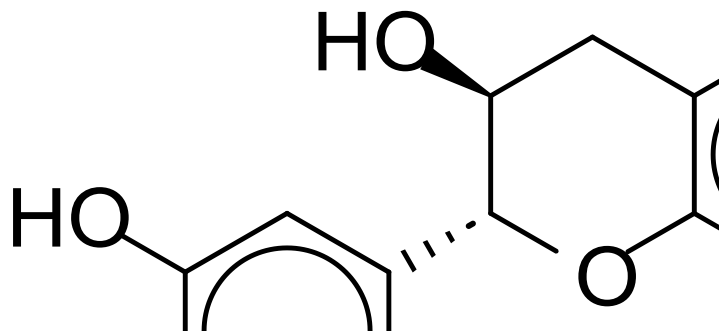

Figure – 1: Structures of four pairs of stereoisomers

Table 2: Sterioisomers of Catechin

Flavan-3-ol	R_1	R_2	R_3
(+)-Catechin (C)	H	H	OH
(+)-Catechin-3-gallate (CG)	H	H	Gallate
(-)-Epicatechin (EC)	H	OH	H
(-)-Epicatechin-3-gallate (ECG)	H	Gallate	H
(-)-Epigallocatechin (EGC)	OH	OH	H
(-)-Epigallocatechin-3-gallate (EGCG)	OH	Gallate	H
(+)-Gallocatechin (GC)	OH	H	OH
(+)-Gallocatechin-3-gallate (GCG)	OH	H	Gallate

There are several hydroxyl groups in ring B that are mainly attributed to antioxidant activity. The literature reveals that the substitution of the hydroxyl group for the methoxy group reduces its antioxidant activity. On the other hand, methylated catechin has a greater lipid lowering effect

compared to nonmethylated catechin. Although additional galloyl groups in gallate derivatives did not result in an increase in activity, the galloyl group and its derivatives, such as Alkyl Mono and Bis-Gallate and Gallamide derivatives, demonstrated strong antiproliferative activity against human leukemia HL-60 cells.(Braicu, Pilecki, Balacescu, Irimie, & Neagoe, 2011; Seeram & Nair, 2002) The inhibition of lipid peroxidation activity increases with the number of hydroxyl groups in ring B. Ring A has a lower level of reactivity to pyroxyl radicals than ring B (Vyas, Sharma, Sharma, & Singh, 2007). However, the 8th position substitution results in increased free radical activity (Es-Safi, Beauhaire, Guerneve, & Ducrot, 2007). Lipid peroxidation activity could be stopped by making a change at the third position of ring C. For example, galloyl substitution at position 3 of ring C decreased inhibitory activity. The gallate of epigallocatechin (EGCG), epigallocatechin (EGC), catechin (C), and epicatechin (EC) were examined, and it was discovered that the gallate catechins are more potent at inducing apoptosis and antiproliferative activity, with IC50 values ranging from 15.81 to 326 M when tested for time- and dose-dependent effects in the breast cancer cell line (Hagerman, Dean, & Davies, 2003).

O-acyl derivatives of partially purified catechins from green tea show 85% survival rate as compared to O-acyl-substituted (–)-ECG prodrugs against for 7,12-dimethylbenzanthracene/12-O-tetradecanoylphorbol-13-acetate (DMBA/TPA)-induced skin carcinogenesis in Swiss albino mice (Hu, Toda, Okubo, Hara, & Shimamura, 1992). Epigallocatechin gallate (EGCG) and related products are less damaging to the biological protein system than epigallocatechin (EGC), which is a more potent protein-precipitating agent (Wan et al., 2005). Further examination of various catechins revealed that galloyl group was found to enhance maximum B-cell proliferation (Dell'agli et al., 2005). Due to the presence of ester carbon, EGCG should have proteasome-inhibiting properties (Vyas et al., 2007).

The gelatinolytic activity of matrix metalloproteinase-9 (MMP-9) is modulated by (+/-)-gallocatechin-3-gallate and (+/-)-catechin-3-gallaten resulting in inhibition of nuclear factor kappa B-driven transcription (Rinaldo D, 2010). Research data supports the enhancement of its antioxidant activity by substitution at the C-8 position of ring A (Es-Safi et al., 2007). The presence of the pyrogallol structure and the galloyl group in the B ring is attributed to biological activities (Fujimura, Umeda, Yamada, & Tachibana, 2008; Ishikawa et al., 1997).

Such biological properties are related to the presence or absence of the hydroxyl group or the presence of the galloyl group associated with intra-inter hydrogen bonding and also depend on the solvent interface used (Botten, Fugallo, Fraternali, & Molteni, 2015).

It has been seen that only ring B is linked to pro-oxidant activity. This is because quinone is formed when ring B is oxidized. Further it was came to knowledge that pyrogallol pattern contributing to the formation of protein carbonyl in Human Serum Albumin, thus act as prooxidant (Ishii et al., 2010).

Table 1 Natural source of different catechins

Plant	Plant Part	Catechins	Reference
Camellia sinensis (L.) Kuntze (Theaceae)	Leaf	(-)-Epicatechin (EC,), (-)-epigallocatechin (EGC), (-)-epicatechin-3-gallate (ECG), and (-)-epigallocatechin-3-gallate (EGCG)	(Yinzhe Jin, Jin, & Ho Row, 2006; Li, Wang, Liu, & Chen, 2010)
Withania somnifera L. (Dunal) (Solnaceae)	Root, Fruit and Leaf	Gallic, syringic, benzoic, p-coumaric and vanillic acids, catechin, kaempferol and naringenin	(Yamazaki, Okuyama, Matsudo, Takamaru, & Kaneko, 1987)
Acacia catechu L.f. (Willd) (Leguminosae)	Heart wood	Kaempferol, quercetin,3,4',7-trihydroxyl-3',5-dimethoxyflavone, catechin, epicatechin , afzelechin, epiafzelechin, mesquitol, ophioglonin, aromadendrin and phenol	(Tamura et al., 2013)
Artocarpus integra Merr (Moraceae)	Leaf	Catechin, epicatechin, epigallocatechin, epicatechin gallate, & epigallocatechin gallate	(C. F. Huang et al., 2011)
Arachis hypogaea L. (Fabaceae)	Seed	Epicatechin, catechin	(Kofink, Papagiannopoulos, & Galensa, 2007)
Nelumbo nucifera Gaertn (Nymphaeaceae)	Leaf	Quercetin, and catechin	(Danila, Kotani, Hakamata, & Kusu, 2007)
Theobroma cacao L. (Malvaceae)	Seed	(-)-Epicatechin and (+)-catechin	(Y. Jin, Jin, & Row, 2006)
Fagopyrum esculentum Moench (Polygonaceae)	Seed	Rutin, catechin, epicatechin, and epicatechin gallate	(Ban, Jeon, Bae, Song, & Seong, 2006)
Smilacis chinae (Liliaceae)	Rhizome	Catechin and epicatechin	(Takano, Tanaka, Tsukamoto, Yahagi, & Fushiya, 2003)
Red wine	-	Trans-resveratrol, (+)-catechin, (-)-epicatechin and quercetin	(Ogawa, Hisada, & Inagaki, 1972)
Actinidia argute var. arguta (Actinidiaceae.)	Stems	(+)-Catechin and (-)-epicatechin	(Matsuo, Hanamure, Shimoi, Nakamura, & Tomita, 1994)
Enkianthus nudipes (Honda) Kitam. (Ericaceae)	Leaves	Catechins	(Haslam, 1969)
Psidium guajava L. (Myrtaceae)	Leaves	(+)-Gallocatechin	(Roux & Maihs, 1960)
Bergenia ciliata Sternb. and *Bergenia ligulata* Wall. (Saxifragaceae)	Rhizome	(+)-Catechin-3-gallate	(Roux, 1957)
Acacia mearnsii De Wild. (Fabaceae)	Leaf and stem bark	(-)-7:3':4':5'-tetrahydroxyflavan-3-ol, (+)-catechin and (+)-gallocatechin	(M. H. Chen, Tsai, Hsu, & Lu, 2014)

Casuarina equisetifolia Linn (Casuarinaceae)	Bark	d-Gallocatechin	(Abd El-Aziz, Mohamed, Pasha, & Abdel-Aziz, 2012)

8.Therapeutic claims

8.1 Atherosclerosis

Hyperhomocysteinemia is one of the important factor affecting premature atherosclerosis. A murine model of hyperhomocysteinemia was used to evaluate endothelial dysfunction. The expression of endothelial dysfunction biomarkers and plasma homocysteine levels were both positively impacted by catechin and epicatecchin. Both the substance were found to be helpful on the expression of proinflammatory cytokines, with catechin demonstrating an even better effect (Monobe et al., 2014).

8.2 Phagocytosis

Green tea, catechins mainly (-)-epigallocatechin and (-)-epigallocatechin gallate, accelerate phagocytic function of macrophage-like cells. The H_2O_2-degrading enzyme catalase plays a part in the augmentation of phagocytic activity by EGC/EGCG. Melastatin 2 is a Ca2+ - is associated to boosting the innate immune system and activates transient receptor potential when combined with diphosphate ribose and H_2O_2. When the role of transient receptor potential melastatin 2 was examined, it was discovered that catechins significantly increased phagocytic function (Mankovskaia et al., 2013). The researchers further suggested that the pyrogallol moiety and caspase signalling pathways may be to responsible for the increased phagocytic activity (Monobe, Ema, Tokuda, & Maeda-Yamamoto, 2010).

8.3 Dental caries

Mankovskaia et al (2013) studied that incorporation of epigallocatechin-gallate in resin matrix along with Chlorhexidine (CHX) sustain antibacterial activity and significantly reduced *S. mutans* survival which is similar to the standard drug CHX (Gu et al., 2013). Catechin also shows the anti-inflammatory effect on human dental pulp. The mechanism involved to reduce the expression of IL-6 and IL-8 in pulp cells by epigallocatechin-3-gallate and epicatechin gallate (Nakanishi et al., 2010).

8.4 Angiogenesis

By blocking the expression of HIF-1, NF-B, and VEGF, the natural substance epigallocatechin-3-gallate (EGCG) derived from green tea considerably slows the progression of mouse breast

cancer growth in female immune competent mice. For the aforementioned investigation, E0771, MCF-7, and MDA-MB-231 cells were used (Yang, Yang, Chao, & Chen, 2012).

8.5 Obesity

Obesity is one of the major reasons leading to lifestyle related disorders. The main reasons are more of food intake and less of physical activity. Experimental investigations by Vittorio *et al*. show that drinking tea combined with inulin reduces body weight and fat mass. This combination may be preferable for weight management purposes like in patients with obesity (Vittorio et al., 2012). Methylated catechin showed its lipid lowering activity by lowering the adipose tissue weights, triglycerides level in liver and also by inhibiting the expression of lipogenic genes. Studies have also shown that drinking catechin-containing beverages can prevent diet-related disorders of lipid metabolism (Suzuki et al., 2013).

8.6 Anticancer activity

Catechin and dextran conjugate was prepared by radical grafting reaction and this conjugate was tested for pancreatic cell line (MIA PaCa-2 and PL45). When provided in conjugate form rather than catechin alone, in-vitro testing of exposed cells revealed more significant results. Another study shown that ECG and CG are superior to the green tea compound EGCG in terms of preventing growth and exerting anti-inflammatory effects on pancreatic tumor cells (Bolduc et al., 2012; Kurbitz et al., 2011). Among all catechins, EGCG demonstrated the most antiproliferative effects. The mechanism supposed to be cell cycle arrest in the growth 1 phase and cell apoptosis (Du et al., 2012). But still, it is ambiguous whether catechin suppresses the growth of cancer cell and/or promote apoptosis (Yiannakopoulou, 2014). Epigallocatechin-3-gallate showed its promising role in the skin and prostate cancer. The EGCG act as chemopreventive agent and decreases cell viability and also promote apoptosis in the growth of uncontrolled cell (Johnson, Bailey, & Mukhtar, 2010). The mechanism underlying the anti-cancer effects includes altering protein homeostasis, controlling gene expression, inhibiting the formation of ligand-receptor complexes, and redox homeostasis (Tachibana, 2009). The discovery of the 67-kDa laminin receptor (67LR), which functions as an EGCG receptor on the cell surface. The prevention of cancer is achieved through the receptors' binding properties (Tachibana, 2009).

8.7 Dyslipidemia

It's a condition in which abnormal amount of lipids whether fat or cholesterol gets deposited in the blood. Developed countries are prone to hyperlipidemia type of dyslipidemia. The posterior cerebral arteries (PCA), which were separated from 6-month-old male mice, were studied, and the mice's body weight, plasma lipids, and glucose levels were assessed. Because catechin prevented endothelial dysfunction, the damaging effects of severe dyslipidemia on the cerebral arterial wall were reduced. Prevalence rate **(***P* < 0.05), for catechin was found to be significant against severe dyslipidemia (Ashafaq et al., 2012).

8.8 Cerebral Ischemia

Brain ischemia is a condition with less supply of blood to meet metabolic demand, leading to conditions like stroke. Occlusion of the middle cerebral artery (MCA) is the cause of human ischemic strokes (MCA). On the basis of a rat MCAO (Middle cerebral artery occlusion) model for cerebral ischemia, catechin hydrate was assessed. In MCAO rats, catechin hydrate significantly decreased infarct size, neurological impairments, and downregulated iNOS, GFAP, and NF-kB expression (Wei et al., 2011).

8.9 Cardio protective

Black tea functional drinks include theaflavin and thearubigins, which are beneficial against lipid- and glucose-related disorders, particularly elevated cholesterol and LDL levels (Kuriyama, 2008). Reports assure the promising role of catechin in obesity, high blood cholesterol, diabetes (Samarghandian, Azimi-Nezhad, & Farkhondeh, 2017; Smoak, Burke, & Collier, 2021) which directly or indirectly lead to cardiovascular disease (Ahmad et al., 2015). In the majority of research, EGCG had the highest biological activity among green tea catechins (GTCs) (Suzuki, Pervin, Goto, Isemura, & Nakamura, 2016). Green tea (-)-EFCG decreases body weight in diet-induced obese mice through controlling the expression of many genes in adipose tissue (M. S. Lee, Kim, & Kim, 2009). The collective activities of EGCG and linalool in tea may exert hypolipidemic and antiobesogenic effects by regulating Peroxisome proliferator-activated receptors (PPARs) (S. J. Lee & Jia, 2015). Cardiotoxicity is once again put at risk by oxidative stress and inflammation. Catechin's antioxidant and anti-inflammatory capabilities reduced MDA levels and greatly boosted CAT, GSH-Px, and SOD activities, which had a cardio-protective effect. Success of use of Doxorubicin and Idarubicin in cancer therapy and in leukaemia respectively is counter due to its cardiotoxicity and hepatotoxicity as well. Numerous investigations found that administering the same with catechin reduced cardiotoxicity (Pollock,

Kogan, Thorpe, & Holben, 2011). Anthracycline antibiotic doxorubicin (dox) is frequently used to treat solid tumors. This medication has potentially fatal, dose-dependent adverse effects when used long-term. (Carrasco et al., 2020). Catechin protects against doxorubicin-induced cardiotoxicity (Kozluca et al., 1996). Nano delivery technologies have demonstrated positive outcomes in their absorption by the epithelial system and improved distribution to the target region (Bengaied, Ribeiro, Amri, Scherman, & Arnaud, 2017). Idarubicin-induced cardiotoxicity in rats is greatly decreased by catechin and vitamin (Kalender et al., 2002).

8.10 Osteogenic Effects:

Osteoblastic and osteoclastic mechanism plays an important role in balancing bone growth and development. Imbalance of above will lead to disease like osteoporosis which is most prevalent in elders. Catechin increased calcium deposition without significant cytotoxic effects. Catechin markedly enhanced osteocalcin and Runx2 mRNA expression, calcium deposition, and alkaline phosphatase activity (Otera, Tada, Sakurai, Hashimoto, & Ikeda, 2011).

8.11 Bacteriostatic Effects

Centaurea stoebe Lam. contains racemic mixture of (±)-catechin in its root, when evaluated for bacterial population from Romanian (native range) and Montana (invaded range) soils showed bacteriostatic effect. Bacteriostatic effect was evaluated using Population-Level Inhibition assessing reversibility and bacterial growth kinetics in regard to total culturable and numerous individual bacterial components in above population showing significant effect (Drouin et al., 2011).

8.12 Hypersensitivity pneumonitis

Hypersensitivity pneumonitis leads to inflammation mainly caused by organic dusts of alveoli within the lung. Methicillin-resistant Pneumonia is frequently brought on by *Staphylococcus aureus* (MRSA). Compared to antituberculosis drugs that increased the eosinophil count in the peripheral blood, catechin inhalation lowered the MRSA count in the sputum without causing any noticeable side effects also with low eosinophil infiltration (Bharrhan, Koul, Chopra, & Rishi, 2011).

8.13 Cerebrovascular flow and atherosclerosis

Age-related deterioration in cerebrovascular endothelial function could be slowed down by severe dyslipidemia, oxidative stress, and neuronal loss in the brain. The major causes of stroke include ageing and atherosclerosis, which also contribute to a decrease in NO production and an increase in reactive oxygen species (ROS). Measurements of basal CBF were made, and the

increase in CBF was brought about by whisker stimulation. Utilizing the Morris water maze test model, learning skills were assessed. Catechin improved endothelial function, increased sensitivity to nitric oxide synthase inhibition, decreased cerebral superoxide staining, and prevented learning ability decline (Vasanth Raj et al., 2010).

8.14 Hepatoprotective

Catechin was also found to protect D-Galactosamine induced hepatotoxicity enhancing p53, Bax and down regulation of Bcl-2 mRNA levels in the liver when administered at a dose of 50 and 100 mg/kg b.wt. (Ranjith-Kumar, Lai, Sarisky, & Cheng Kao, 2010; Yu et al., 2010).

8.15 Arrhythmias

When combined with EGCG, a high glucose pre-incubation (30 mM) reduced the protein expression of Cx43 in cardiomyocytes (30mM, 72h). Cardiomyocytes and orderly electrical conduction in the heart also get revived dose- and time-dependent. With induced high glucose, epigallocatechin-3 gallate (EGCG) decreases gap junction downregulation in newborn rat cardiomyocytes (S. M. Lee, Ko, Kim, Kim, & Kang, 2010).

8.16 Immunomodulator

The immune system plays an important role in fighting various pathogens as body's defense mechanism**.** The regulation of RIG-I signaling significantly influences inflammation and viral infection outcomes. When examined in HEK293T cells, epigallocatechin gallate (EGCG) bound RIG-I and inhibited its signaling at low micromolar doses. Additionally, EGCG reduced the ATPase activity of recombinant RIG-I in a dose-dependent manner (Kang, Cheng, Ji, Incardona, & Rampe, 2010).

8.17 Cataract

Catechin demonstrated apoptotic cell death in the lens epithelial and inhibited the development of cataract (Annaba et al., 2010). Epigallocatechin gallate (EGCG) eye drops exhibit potent protection against UVB radiation-induced corneal oxidative damage in mice with increased GSH-Px, GSH-Rd, and GSH activity and decreased TBARS and protein carbonyls in the corneas may be due to the above mechanisms like lipid peroxidation and antioxidant activity (Noll et al., 2013).

8.18 Electrocardiographic

The electrocardiograph plays an important role in providing a general picture of electrical activity within the heart with a series of electrodes attached to the skin surface. An electrocardiogram was evaluated using the Langendorff model for EGCG. Cardiac ion channels

showed protracts PR and QRS intervals reducing QT shifting ST-T-wave segment within PQRST at 30µM concentration (Xu et al., 2009).

8.19 Apical sodium dependent bile acid transporter function (ASBT)

Bile acid reabsorption is carried out via ASBT. When the green tea compound epigallocatechin-3-gallate (EGCG) was examined in human embryonic kidney HEK-293 cells stably transfected with ASBT-V5 fusion protein and intestinal Caco-2 monolayers, it was discovered that EGCG had hypocholesterolemic effects and also maintained the body's cholesterol level (Nagao et al., 2009).

8.20 Anti-angiogenic effect

Angiogenesis play a vital role in growth, recreation and rehabilitation. They play an important role in both neoplasstic and nonneoplastic diseases. Epigallocatechin-3-gallate (EGCG) has a powerful anti-angiogenic effect when evaluated for endometriosis. Endometrial glands and stroma can be implanted beyond the uterine cavity in endometriosis, a persistent condition. Vascular endothelial growth factor (VEGF) is one of the important causes in endometriosis and is the main catalyst for angiogenesis. Quantitative real-time PCR and terminal deoxynucleotidyltransferase-mediated dUTP nickendlabelling were used for evaluation. Endometriotic lesions were less prevalent with EGCG administration compared to the control and saline given groups (P 0.05) (Zhou et al., 2014).

8.21 Antidiabetic effect

Type 2 diabetes (T2DM) is described as a relatively high level of blood glucose. This disease leads to various risk factors like heart disease and kidney failure. Catechin is very commonly consumed in Japan, when evaluated for T2DM for a period of 12 weeks in a double-blind controlled study. Catechin beverages showed significant decrease in waist circumference as compared to control group, thus having antidiabetic effect in T2DM (Zhao et al., 2014).

9.Challenges & Opportunities Towards Optimum Bioavailability:

Catechins shows very low plasma levels ranging from micro level to nano level in rat model. Evaluation of green tea three catechins mainly (-)-epicatechin (EC), (-)-epicatechin gallate (ECG), and (-)-epigallocatechin gallate (EGCG), showed increased pre-systemic metabolism and lower second pass metabolism. Catechin and epicatechin was further evaluated in rat plasma and urine for their bioavailability through oral administration during 24hour time using HPLC-mass spectrometry, after treatment with b-lucuronidase and/or sulfatase. Non- methylated conjugate was present both for catechin and epicatechin in plasma. Excretion of metabolites in urine was lower for both the catechin and catechin mix groups, highlighting the lesser bioavailability of

catechin. Further the results suggest that in combination, catechin and epicatechin might be absorbed competitively in gastrointestinal tract of rats (Manach et al., 1999). The naturally occurring polyphenolic compounds such as quercetin and catechin when evaluated for pharmacokinetic studies showed incorporation of methyl groups for Quercetin more than catechin in plasma, evaluated in both the liver and plasma. Conjugation was mostly dominated in plasma level. Catechin and Quercetin metabolites were mainly formed by glucuronidated and glucurono-sulfo conjugates respectively. Comparatively the concentration of quercetin and catechin derivatives was lower than in plasma, without any accumulation. Liver by product showed methylation number about (90-95%), whereas plasma level also showed the presence of non-sugar moieties giving reflection about their bioavailability, emphasizing that their systemic metabolites are conjugated derivatives (Catterall, King, Clifford, & Ioannides, 2003).

Out of the four Catechins, (-)-epigallocatechin-3-gallate (EGCG) is scientifically proven for various ailments but its limited bioavailability has been a challenge for the scientist.(Baba et al., 2001) One of the reasons was the unstable nature of EGCG above pH 7.4 due to oxidative dimerization in authentic intestinal juice (pH 8.5) and mouse plasma (pH 7.8) with decreased in concentration mainly due to dehydrogenation and decarboxylation alkaline solutions (Vyas et al., 2007). In vitro studies showed that the effective concentrations of EGCG ranged from 1-100 µ mol/l. However, following oral administration in human subjects or animals, the peak plasma levels of tea Catechins were usually in the sub-or low-micro molar range (Yoshino, Suzuki, Sasaki, Miyase, & Sano, 1999). Temperature, pH and other ingredients play an important role in stability of compound, therefore evaluation of these parameters are very important. Green tea Catechin was found to stable in aqueous medium at temperature, but as the temperature increased, there was degradation in Catechins and further increase leads to epimerization of Epigallocatechin gallate to gallocatechin gallate. Epimerization was found very common and stable at low pH. Epigallocatechin gallate was found lesser stable in alkaline and neutral media. When Epigallocatechin gallate was protected for reactive hydroxyl group and evaluated with HPLC, it was found that its analogs were more stable with increased activity and bioavailability (Z. Chen, Zhu, Tsang, & Huang, 2001). Catechin is present as (+)-enantiomer in most of the sources but chocolate mainly contains (-)-Catechin, Comparative analysis of (-) and (+)-Catechin enantiomer in jejunum and ileum in the rat showed poor bioavailability both at intestinal absorption and plasma concentrations level with non-significant results., though the content present in the dietary products was good (Donovan et al., 2006; Kofink et al., 2007).

Novel drug delivery system/Formulations: To overcome the poor bioavailability problems associated with delivery of catechins, several novel drug delivery systems like transdermal patches, liposomes, elastic liposomes, nanoparticles, micelles and sustained release drug delivery has been approached (Table 3).

Table 3 : Novel Drug Delivery Systems (NDDS) for Catechins with Enhanced Bioavailability

NDDS (Category)	References
Transdermal Patches	Lambert, Kim, Zheng, & Yang, 2006
Catechin Liposome	Cheng et al., 2021;Batchelder, Calder, Thomas, & Heard, 2004; Fang, Lee, Shen, & Huang, 2006; G. Chen et al., 2014; Jaiswal et al., 2013
Elastic liposome:	Benson, 2010; Jaiswal et al., 2013
Catechin Nanoparticles	Bulboaca et al., 2020; Suner et al., 2021; Barras et al., 2009; Y. B. Huang et al., 2011; Y. C. Chen et al., 2010; Qian et al., 2020; Han, Lee, Jung, Park, & Hyon, 2009; Imam et al., 2021; Y.-J. Chen et al., 2020; Smith et al., 2010; Dube, Nicolazzo, & Larson, 2010; Gan et al., 2022; Veiko, Lapshina, & Zavodnik, 2021; Wong et al., 2013
Miscelles	X. Chen et al., 2008; Liang, Chung, Gao, Yongvongsoontorn, & Kurisawa, 2018; Haratifar, Meckling, & Corredig, 2014
Sustained release dosage forms	(Haratifar & Corredig, 2014; J. S. Lee, Chung, & Lee, 2008; J. S. Lee, Lim, Chung, & Lee, 2022).

10. Conclusion

Catechins have therapeutic potential against a variety of diseases, but their poor bioavailability has hampered the development of pharmaceuticals. Bioavailability has been enhanced by structural modifications and advanced delivery systems. Catechins modulate cellular signalling and exert antioxidant effects, according to in vitro and in vivo research. To fully transition catechins from foods to medicines, additional optimization of pharmacokinetics, safety, effectiveness, and synergistic combinations is required. Consuming catechin-rich foods and nutraceuticals may provide health benefits pending further research. In conclusion, addressing the bioavailability issues associated with these multifaceted phytochemicals will allow their full pharmaceutical, nutritional, and nutraceutical potential to be realized.

Authorship contribution statement

S. Chanda contributed in designing, writing, editing, revising and supervising the manuscript, RK Tiwari supervised and contributed in writing, editing and revising the manuscript, K. Singh and S. Sharma contributed in writing, editing and revising the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

No data was used for the research described in the article.

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