

Review Article

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Therapeutic Potential of Green Tea Catechins - A Magical Herb

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ABSTRACT

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There is an increasing interest in health benefits of foods and facing a large health problems due to rise in the occurrence of lifestyle disorders such as cancer, heart diseases, diabetes and obesity. Therefore, a lot of interest is generated on the dietary substances, especially, the natural ones that enhance the health of the population. Green tea is a 'non-fermented' tea, which is the most popularly consumed beverage in the world. It contains more catechins, than black tea or oolong tea. The health-beneficial effects of green tea are primarily attributed to its polyphenols; around 60–80% of polyphenols in green tea are catechins, which belong to flavan-3-ols, commonly known as catechins, particularly (-)-epigallocatechin-3-gallate. This review depicts the recent findings on the medicinal properties of green tea, focusing on the biological properties of the green tea catechins such as antioxidative, anti-hypertensive, antiobesity, anticarcinogenic, cardioprotective, antibacterial activities and anti-inflammatory. Recommendations are also made to increase the bioavailability of the catechins through nanotechnological delivery mechanisms.

Introduction

Today, tea is the most regularly consumed beverage in worldwide. There are mainly four types of tea derived from the leaves of *Camellia sinensis* plant with different processing methods such as green, white, oolong and black tea. The minimal processing, drying is required to produce green and white tea. White tea (non-oxidized) is manufactured from very young leaves and buds, Green tea (non-oxidized) from mature

leaves, Oolong tea (partially oxidized) from partially fermented mature leaves, whereas black tea (oxidized) from fully fermented mature leaves (Wanda, 2017). Nearly 2.5 million tons of tea leaves are produced annually all over the world, among that 20% is green tea (Jayakeerthana, 2016). Green tea has attracted the interest of consumers due to its health benefits against a variety of disorders, ranging from weight loss to cancer. Several reports showed that these non-nutrient bioactive compounds have antioxidant,

anticancer, antiobesity and other pharmacological and biological functions, thus making them an excellent source for nutraceutical applications. The health-benefits of green tea are mainly due to their polyphenol content; around 60–80% of polyphenols are flavan-3-ols, commonly known as catechins. Catechins are the major components of tea; which constitute about 30% of the dry weight of green tea, and 9% of black tea (Pradeep, 2017).

Nutritive value of green tea

Green tea contains complex proteins (15-20%), free amino acids (1-4%) such as glutamic acid, tryptophan, arginine, lysine, glycine, serine, aspartic acid; tyrosine, valine, leucine, threonine and theanine are also present based on dry weight basis. Carbohydrates (5-7%) in green tea constitute cellulose, fructose, pectins, glucose and sucrose. Minerals and trace elements (5%) such as calcium, magnesium, iron, copper, zinc, molybdenum, chromium, manganese selenium, sodium, phosphorus, nickel, potassium, fluorine, cobalt, strontium and aluminum are present in green tea on dry weight. Traces of lipids mainly rich in essential fatty acids such as linoleic and α -linolenic acids and sterols mainly stigmasterol, vitamins such as B, C and E, xanthic bases (caffeine, theophylline), volatile compounds (aldehydes, alcohols, esters, lactones, hydrocarbons) and pigments (chlorophyll, carotenoids) are also present. Many studies have been conducted on tea leaves and its infusions due to its nutraceutical importance. The composition of green tea and green tea infusion is depicted in Table 1. Fresh leaves contain on an average about 3-4% alkaloids known as methylxanthines, such as caffeine, theobromine, and theophylline (Chaco *et al.*, 2010, Jayakeerthana, 2016). The medicinal properties of green tea are mainly due to the

flavonoids. The flavonols (quercetin, kaempferol and rutin), phenolic acids, caffeine, theanine and leucoanthocyanins, account up to 40% of the dry weight of green tea leaves. Polyphenols are powerful antioxidants and free radical scavengers (Wanda, 2017).

About 80-90% of the major flavonoids of green tea are various catechins, the four major catechins are mainly (-)-epicatechin (EC), (-)-epigallocatechin (EGC), (-)-epicatechin-3-gallate (ECG) and (-)-epigallocatechin-3-gallate (EGCG). Among these, the most abundant is EGCG (~ 59%) followed by EGC (~ 19%), ECG (~14%) and EC (~ 6%) (Anandh and Liu, 2008; Jigisha *et al.*, 2012). Green tea has far higher levels of catechins than black tea. A cup of green tea contains 100–200 mg of EGCG, whereas gallic acid and catechin are present in trace amounts.

Health benefits of green tea catechins

The components in green tea undergo metabolic processing such as glucuronidation, methylation and sulfation in the body, which produces some active metabolites. The catechins and their metabolites may be identified in blood plasma, urine, and several tissues (Lambert *et al.*, 2007). However, the bioavailability of catechins is very poor due to various reasons such as poor stability to heat, light, alkaline pH. Recently, the health benefits of green tea and its constituents such as prevention of cancer and cardiovascular diseases and the antioxidative, anti-inflammatory, antiarthritic, antibacterial, antiangiogenic, antiviral, neuroprotective and cholesterol-lowering are under investigation.

Molecular mechanisms of green tea catechins

The health benefits of green tea are mainly associated with antioxidant properties and the

ability of its polyphenolic catechins to scavenge reactive oxygen species (Yang *et al.*, 2004). The difference in the properties are due to their structure, which consists of the phenolic hydroxyl (OH) groups such as ungalloylated catechins on B-ring (EC and EGC) and galloylated catechins (ECG and EGCG) in the B- and D-rings (Figure 1). The presence of 3, 4, 5-trihydroxy B-ring position has been shown important for antioxidant and radical scavenging activity. Rice-Evans *et al.*, (1995) postulated that the green tea catechins were more effective as antioxidants than vitamins C and E, and the effectiveness of radical scavenger order is shown to be EGCG > EGC > EC > catechin. However, the metal-chelating properties of green tea catechins are also responsible to their antioxidative property (Hider *et al.*, 2001; Kumamoto *et al.*, 2001).

Antioxidant effect

Nowadays, green tea is one of the most commonly used nutraceuticals due to its antioxidant property. Antioxidant is a substance that inhibits the cellular damage of reactive oxygen species mainly as, singlet oxygen, superoxide, hydroxyl radicals, peroxy radicals, and peroxy nitrite. The disturbance in the balance among antioxidants and ROS results in oxidative stress, which leads to damaging of cells (Chaco *et al.*, 2010). Catechins show the antioxidant activity through various mechanisms as shown in Figure 2: (1) direct mechanism such as scavenging the reactive oxygen species (ROS) and chelating metal ions (2) indirect mechanisms such as inhibiting pro-oxidant enzymes, inducing antioxidant enzymes, and redox sensitive transcription factors (Cabrera *et al.*, 2006). Catechins can stabilize ROS and directly prevents oxidative injury by free radical scavenger (Heim *et al.*, 2002; Nijveldt *et al.*, 2001). The mechanisms of green tea catechins for free radical scavenging activity

may involve the electron delocalization, intra- and intermolecular hydrogen bonds formation, molecular rearrangement and chelation of metal ions that may be involved in oxidation.

EGCG is considered as one of the most active compound and well known for its strong antioxidant properties, suggesting that the presence of O-trihydroxyl group and 3-gallate esters plays an important role in antioxidant activity, radical scavenging effect and preventing oxidative destruction of many biological compounds (Liao *et al.*, 2001). Consumption of green tea in average limit (1–6 cups / day) enhanced the plasma and blood antioxidant potential, hence leads to a reduced oxidative damage in macromolecules such as DNA and lipids (Henning *et al.*, 2003).

Anticarcinogenic property

Currently, cancer is a major source of morbidity and mortality worldwide. Many researchers studied the effect of green tea on cancer therapy (Zaveri, 2006). Mainly EGCG has been extensively used in cancer research. There are several anticarcinogenic mechanisms was attributed to EGCG that may include inhibition of angiogenesis, DNA hypermethylation, NF-kB, telomerase activity, proliferation and metastasis of tumor cells; initiation of tumor suppressor genes and promotion of tumor cell apoptosis as depicted in Figure 3 (Subramani and Natesh, 2013; Butt *et al.*, 2015; Granja *et al.*, 2016).

Epidemiologic studies conducted in Japan reported that cancer onset in, who had consumed 10 cups of green tea every day, was 8.7 years later among women and 3 years later among men, when compared to individuals who had consumed less than 3 cups per day. Cooper *et al.*, (2005) also proposed a possible correlation between high consumption of green tea and low prevalence

of prostate and breast cancer in Asian countries. However, because of the many variables in lifestyle innate, a definitive relationship between green tea and its cancer prevention effects could not be concluded. Nevertheless, from the above studies, consumption of green tea is beneficial.

Studies in animal models have revealed that green tea and EGCG can inhibit carcinogenesis at all stages, viz. tumour initiation, promotion, malignant conversion and progression (Chung *et al.*, 2003). This multifacrious inhibition of the tumorigenic process is attributed to a combination of antioxidative, antiproliferative and pro-apoptotic effects. Green tea polyphenols mainly, EGCG have shown to hinder the process of angiogenesis, tumor metastasis and invasion in animal models (Fassina *et al.*, 2004).

Cardiovascular disease

Cardiovascular disease (CVD) is a class of disorder involving various factors such as inflammation, a disturbance in the balance between the production of ROS (free radicals) and antioxidant defenses, platelet adhesion, and metabolism of lipid. Green tea catechins can show both direct and indirect antioxidant effects on cardiovascular system (Stangl *et al.*, 2007). Hypercholesterolemic rats were treated with green tea and examined for the effect on HMG CoA reductase and other lipid enzymes. They revealed a lowering of serum total cholesterol and elevated HDL levels. The mechanism of action of cardiovascular function was also related to LDL-cholesterol oxidation. The oxidation of LDL cholesterol, associated with a risk for heart disease and atherosclerosis, was inhibited by green tea due to EC and EGCG antioxidant activity. Tea catechins were shown to lower or prevent the deposition of cholesterol accumulation in several tissues, including liver and heart in

rats with hypercholesterolemia (Miura *et al.*, 2001).

Antiinflammatory effect

Inflammation is a body response to foreign substances in the human body, leading to damage in the cell tissues. The defense mechanism of anti-inflammatory effect after consumption of green tea catechins showed improvement of production of IL-10 (anti-inflammatory cytokine), increase of IL-6 secretion and mediated signaling pathway; reduced production of destructive matrix enzymes such as metalloproteinases via TNF- α induced phosphorylation of MAPKs (mitogen-activated protein kinases) and decreased expression of the CCR₂ (chemokine receptor) and reduced levels of the proinflammatory cytokines IL-1 and TNF. EGCG is best known for its higher antioxidant activity and also has capacity to decrease the rheumatoid arthritis, inflammation response in the body. EGCG showed strong inhibition of IL-1 β inducible nitric oxide synthase (NOS), cyclooxygenase (COX-2) expression and activity in cartilage cell cultures. The overexpressions of NOS and COX-2 are mediated by NF-kB, which can also modulate in the presence of EGCG (Singh *et al.*, 2002).

Antimicrobial property

Green tea catechins affect the growth of a large number of microorganisms, which include Gram-positive and Gram-negative aerobic bacteria, anaerobic bacteria, viruses and fungi. The antimicrobial mechanisms of green tea catechins are mainly due to the destruction of the bacterial cell membrane, prevention of bacterial fatty acid synthesis and other enzymes such as protein tyrosine kinase, cysteine proteinases, DNA gyrase, ATP synthase and inhibition of efflux pump activity (Wanda, 2017). EGCG and ECG have

shown marked inhibition of microbial growth at doses more than 25-50 µg/mL. The complete inhibition was observed at 100 µg/mL with EGCG and inhibitory effect of EGCG was higher when compared to ECG (Umegaki *et al.*, 2016). EGCG is also useful in the inhibition of various viruses, such as enterovirus, adenovirus, influenza, hepatitis and herpes virus.

The molecular targets such as NF-κB (Nuclear factor kappa-light-chain-enhancer of activated B cells) and the MAP-kinases pathway are deregulated by the viral infection. EGCG is one of the essential immune response, which helps to combat with the viral infection. The antifungal activity of EGCG was also reported against pathogenic yeasts, such as *Candida albicans*. However, the mechanism of action was unclear (Mollashahi *et al.*, 2015).

Antiobesity property

Obesity is characterized as excessive accumulation of fat in the body that may have significant negative impact on overall health and may lead to the development of certain diseases, such as diabetes and arteriosclerosis. EGCG plays an important role, which directly interferes with the lipid digestion by inhibiting the enzyme known as phospholipase A₂ and thereby prevents the lipid / cholesterol emulsion interfere in the gut (Granja *et al.*, 2017). The mechanism of EGCG on reduction of obesity and diabetes may also associate with certain pathways, such as energy balance modulation, food intake, endocrine systems, redox status, lipid and carbohydrate metabolism (Chaco *et al.*, 2010). The EGCG is capable of elevating the lipid metabolism, leading to excess burning of calories and ensuing fat loss. It can also interfere with the digestion of starch by inhibiting α-amylase. In addition, EGCG ingestion is very useful during a weight loss

program because it is strongly related with improvement of circulation, activity of free radical scavenging, and enhancement of mood (Scholay *et al.*, 2012). *In vitro* studies revealed that green tea extracts containing 25% of catechins have the ability to inhibit the gastric lipase significantly, and to a lower extent of pancreatic lipase. It is shown that green tea catechins interfere with fat emulsification process, before enzymes acted, and was also essential for lipid intestinal absorption (Chantre and Lairon, 2002). EGCG also exhibited a fatty acid synthase inhibitor activity, reduction on the *de novo* lipogenesis and secretion of VLDL, having an influence on the increase of adiponectin production, which constitutes activation of AMPK by liver kinase B1 (LKB1) as shown in Figure 4. EGCG showed a potential therapy for the prevention of liver damage in high fat diet associated obesity (Santamarina *et al.*, 2015).

Antidiabetic property

Epidemiological studies showed that EGCG has a great effect on glucose tolerance and insulin sensitivity. It is associated with the prevention and inhibition of diabetes mellitus through a several effects, such as inhibition of insulin resistance, improvement of insulin secretion, regulation of glucose uptake, increases the glucose tolerance and its role in oxidative stress and inflammation (Chowdhury *et al.*, 2016).

The researchers have also reported that EGCG mimics insulin, which enhances the tyrosine phosphorylation of insulin receptor and its substrate thereby impede gene expression of the gluconeogenic enzyme PEPCK (phosphoenolpyruvate carboxykinase) enzyme. Currently, the green tea catechins were demonstrated to modify glucose metabolism in experimental models of type II diabetes mellitus.

Table.1 Approximate composition of green tea and its infusion

Components	Green Tea*	Green tea Infusion†
		(%)
Protein	14.5	Traces
Amino acids	3.98	3.43
Fiber	25.4	Nil
Carbohydrates	6.97	4.3
Lipids	6.89	Traces
Pigments	1.94	Traces
Minerals	5.2	4.45
Phenolic compounds[#]	29.43	4.5
Oxidized phenolic compounds[§]	Nil	4.5

* On dry weight basis

† Infusion time: 180 seconds

Especially flavonoids

§ Especially thearubigins and theaflavins

Fig.1 Structure of major catechins present in green tea

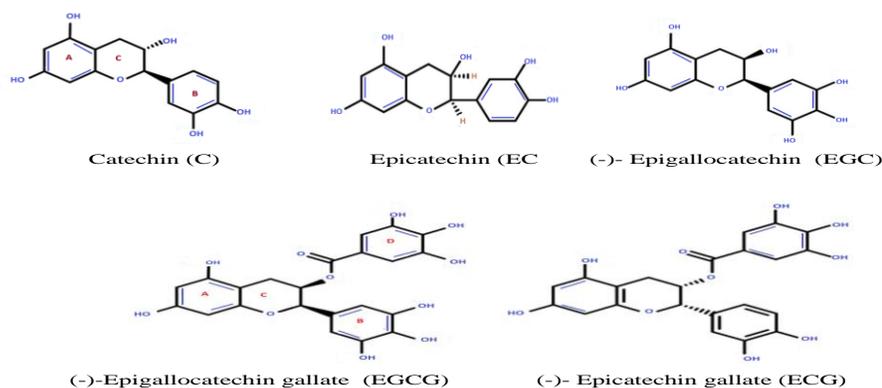


Fig.2 Antioxidant mechanism of catechins

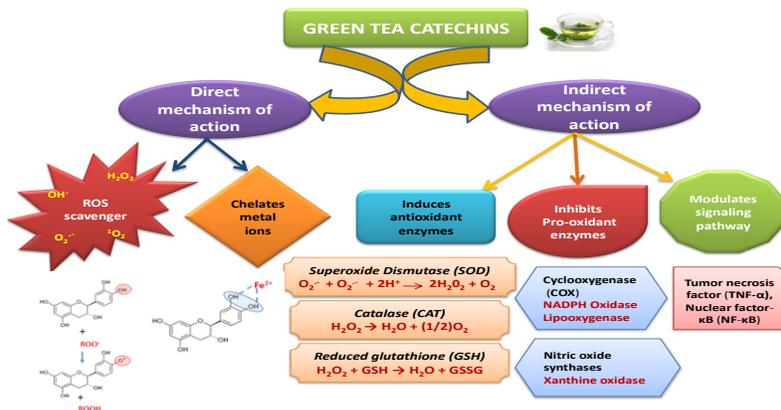


Fig.3 Mechanism of apoptotic cell death by EGCG

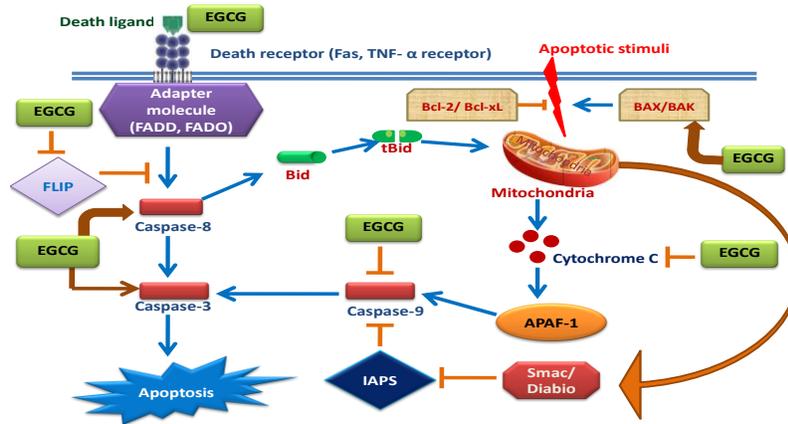
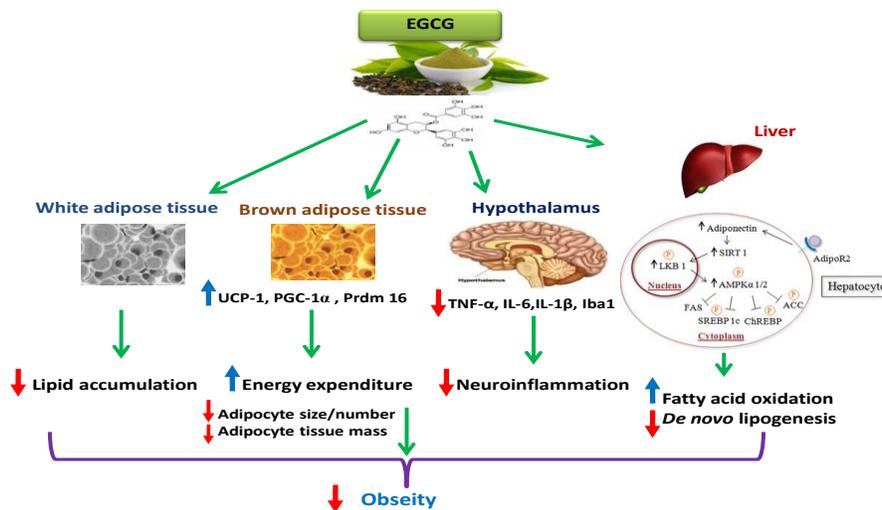


Fig.4 Antiobesity mechanism of EGCG



Antihypertensive property

The observational studies and trials on vasodilation on blood pressure (BP) of green tea and its extracts have been investigated in large quantities for decades. The mechanism associated to antihypertensive effect may be due to the angiotensin peptide hormone that causes vaso- constriction and a subsequent increase in BP, and it is a part of the renin-angiotensin system, which is a major target, that lowers the blood pressure. The effect of

green tea catechins on hypertension may be related to its inhibition of angiotensin converting enzyme (ACE). Yang *et al.*, (2004) observed that habitual consumption of green tea 120 ml/day for more than a year reduced the risk of high blood pressure significantly. The effect on the ACE activity and antihypertensive is mainly due to the presence of higher amount of O-methylated derivative i.e. (-)-epigallocatechin-3-O-(3-O-methyl) gallate of EGCG (Kurita *et al.*, 2010).

Other properties

Dental Caries

Dental plaque is the major pivotal agent for the initiation of gingivitis. Gingival disease can lead to periodontitis, which if left untreated may finally compromise the entire periodontium. Prevention of dental caries is mainly due to the EGCG, which will bind and inhibits salivary and bacterial amylases, especially α -amylase. It also stops the acid generation from carbohydrates by inhibiting the transcription and function of lactate dehydrogenase (LDH). Oral bacteria such as *Streptococcus mutans*, plays a major role in promoting the tooth decay, which forms a biofilm on the surface of teeth. EGCG may inhibit or remove the bacteria from teeth, thereby decreases the formation of biofilm and inhibits the bacteria to develop an acid environment. EGCG also hinders the hydrogen binding and hydrophobic interactions of collagenolytic bacteria. Green tea consumption regularly increases the oral peroxidase activity (Kato *et al.*, 2009, Hara *et al.*, 2012, Narotzki *et al.*, 2013).

Effect on skin

In vitro and *in vivo* animal and human studies demonstrated that green tea catechins are photoprotective in nature. The clinical trials in humans showed the inhibition of solar ultraviolet B light induced skin disorders such as photoaging, melanoma and non melanoma skin cancers (Katiyar, 2003).

Limitations of catechins

Although the catechins reported to have therapeutic effects, their applicability to humans is limited. Catechins are very sensitive and unstable to oxidising enzymes, heat, and high pH. They have limitations such as poor bioavailability and stability. Its

consumption is not preferred by many due to its odd taste.

Bioavailability of catechins

Catechins readily undergo a number of metabolic processes such as glucuronidation, methylation, and sulfation in the body, by intestinal microflora and enzymes, are poorly bioavailable (Pradeep *et al.*, 2017, Qiao *et al.*, 2014). The catechins and its metabolites may be identified in blood plasma, urine, and several tissues (Lambert *et al.*, 2007). In humans, the concentration of catechins in plasma primarily increased from 2 to 4 hours. However, the bioavailability of catechins is relatively lower; the plasma catechin (EGCG and EGC) concentration was only 0.2 to 2% when ingested in healthy people, which affects the biological activity within the target tissues (Cabrera *et al.*, 2006). Therefore, bioavailability of catechin represents a big challenge. Generally, catechins are easily metabolized by enzymes and microbes and this group of compounds have short plasma half-lives (2-3 h). The half-lives of green tea catechins are 2-4 h and their absorption and removal are rapid in humans. The peak times are in the range of 1 and 3 h with low peak plasma concentrations in the μ M range (Fu *et al.*, 2008). Another study emphasized that the bioavailability of the green tea catechins was shown to be low, resulting in systemic levels in humans 5 to 50 times less than concentrations showed biological activities in *in vitro* systems. Results from other researchers also confirmed the bioavailability of catechins was lower than 5% (Catterall *et al.*, 2003).

Stability of catechins

Catechins are sensitive to several environmental factors such as heat and light, and readily undergo degradation in oxidation with a consequent loss in activity. A number

of studies have shown the instability of catechins compounds. One study focusing on the pH stability of catechin isomers from green tea found that they were extremely unstable and degraded almost completely in a few minutes in the alkaline solution (pH > 8), whereas in the acidic solution (pH < 4) they were very stable at least for 18 h (Pradeep *et al.*, 2017). The stability of green tea catechins in sodium phosphate buffer with a pH ranging between 5.0 and 7.4 showed a pH-dependent trend. Among the various catechin isomers, EGCG was quite unstable shown almost complete degradation when incubated for 3 h at pH 7.4. Other researchers also reported that green tea catechins were more vulnerable to degradation caused by elevation of temperature, pH and chelating metal ions (Sang *et al.*, 2005). The instability is part of the reason for the poor bioavailability and also presents as an issue in the manufacture process.

Strategies to overcome limitations

Several novel and promising nanotechnological methods have been employed to improve bioavailability of catechins such as nanoemulsion, niosomes etc. Nanoencapsulation of catechins represents a viable and efficient approach to increase their physical stability under GI conditions, protecting them from interacting with other components of digestion and premature degradation in the body. It helps in increased bioactivity due to the nanosize. Bio-degradable nanoparticles of 100 nm size showed 15- to 250-fold higher uptake efficiency as compared to larger sized microparticles (>500 nm). Studies on nanoencapsulation revealed that EGCG stability was significantly increased, enhanced bioavailability and improved its sustained release in controlled manner, which may partially increased cellular uptake of EGCG. Therefore nanoencapsulation of catechin

helps to increase their bioavailability and can preferably be used as delivery mechanism for fortification in foods.

In conclusion nowadays, green tea extracts are considered as one of the most promising nutritional therapy for several diseases and consequently, it is being studied enormously worldwide. A number of epidemiological scientific studies have confirmed the well being of green tea catechins. In this review we covered physiological benefits of green tea catechins such as antioxidant, antimutagenic, antidiabetic, anti-inflammatory, antimicrobial and antiviral, and above all, cancer-preventive properties. Though all the evidence from research on green tea is very positive, future studies are necessary to understand its contributions and impact on human health, and advice its regular consumption in western diets, in which green tea consumption is limited. Nanoencapsulation of green tea catechins is a promising tool for increasing their bioavailability and effective delivery.

Conflicts of Interest

The authors and co- authors declare no conflicts of interest.

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