Chapter

Remedial Effects of Tea and Its Phytoconstituents on Central Nervous System

Manisha Singh, Vandana Tyagi and Shriya Agarwal

Abstract

Tea in all its forms is one of the commonly consumed beverages globally, after water. Apart from just being a beverage, it also has extensive therapeutic values. The phytoconstituents of tea either in their pure form or as an extract are essential part of traditional as well as modern day medicines. Tea has shown its medicinal benefits in treating, improving and preventing many of the ailments ranging from being potential antimicrobial, antioxidant agent to being central nervous system (CNS) stimulants. This chapter focuses specifically on physiological impacts that each of its constituents have over our nervous system like role of L-theanine to enhance dopamine and serotonin levels, theobromine, and theophylline for stimulating CNS, caffeine to inhibit adenosine receptors, hence, causing increase in brain activity etc. along with many more neuroprotective properties of tea constituents.

Keywords: central nervous system (CNS), epigallocatechin-3-gallate (EGCG), epigallocatechin (EGC), epicatechin-3-gallate (ECG), and epicatechin (EC), theaflavin (TF-1), Laminin receptor (67LR)

1. Introduction

Tea is known as a part of many traditional medicinal practices (Ayurvedic, Chinese etc.) and as a health supplement of daily usage from ancient era. Tea (*Camellia sinensis*) belongs to Theaceae family and is known as a perennial shrub/tree which reaches up to the height of 30 feet, however it is pruned cropped at a lesser height of around 2–5 feet for cultivation. It is of various types such as black, white, green, oolong varieties. Rooibos or "Red" and Pu-erh tea are produced from tea plant leaves, which are oval and dark green in color, with notched boundaries, and its flowers are usually white, fragrant bunched, together or separately. The tea plant, *C. sinensis*, initially was an indigenous species that belonged to China but later spread to other parts of the world like—Indian subcontinent, Japan, Russia and then to Europe in the late seventeenth century. The various forms of tea (Green, oolong, and black tea) originated from the same plant (*C. sinensis*) but got differentiated, depending on their color display, organoleptic taste, distinctive flavor and their phytochemical content which was eventually a result of different fermentation processes adopted for their production [1].

There are two main varieties of the tea plant, named as *Camellia sinensis* and *Camellia sinensis var. assamica*. The Chinese variant, *Camellia sinensis*, has smaller leaves and is more tolerant to cold weather. It is observed as a perennial plant going up to the height of 3 m in case of *C. var sinensis*, whereas it was up to 10–15 m tall with less branching in *C. var assamica* [2, 3]. But since in tea cultivation practices the plants are usually pruned and are kept at lower height (1–2 m) hence, promoting them to spread their branches horizontally. In the ancient scriptures of China, tea processing and consumption from these two varieties are reported to be practiced from last 4000 years. The second variety, *Camellia sinensis var. assamica*, is a native to the Assam region in India and thrives well in tropical and low elevation areas in the Indian subcontinent. This variety of tea plantation is commonly cultivated in the tropical and subtropical regions of India and apart from its use as a beverage it has been reported for many utilities like—it has high medicinal value, used for extraction of oil (Tea Tree oil). As per the recent global studies conducting in 2016, it was found that Turkey was listed as one of the highest tea devouring country with consumption of approximately 6.96 pounds per year per capita. On the contrary, China was observed with little less annual consumption of around 1.25 pounds per year per person but, it has shown highest tea production globally, followed by India and Kenya at second and third positions respectively.

Also, on global platform it was estimated that, almost 3.8 billion gallons of tea, in which black tea has 80%, green tea 16% and remaining 4% was oolong, white and dark tea share was consumed in United States in the same year (2016) [4]. These data exhibit the ever-growing popularity of tea consumption among the masses irrespective of their region of cultivation.

2. Potential health benefits of tea constituents

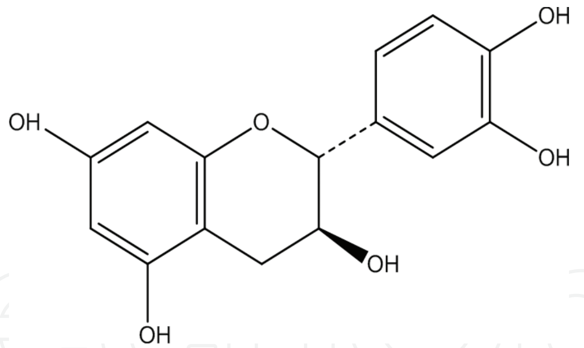
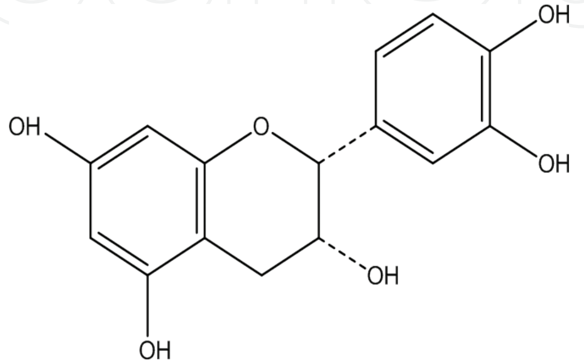
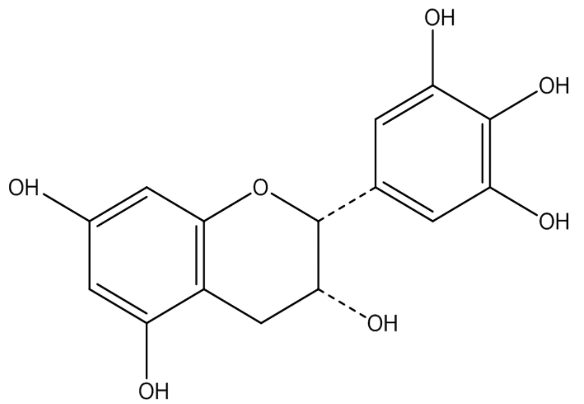
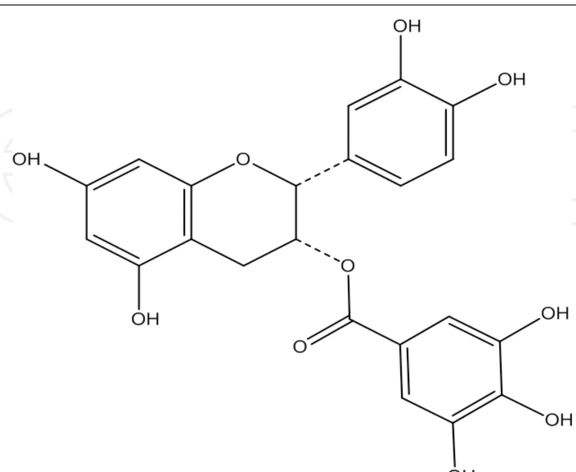
The commonly found and highest content of chemical constituents found in leaves of tea are polyphenols (catechins and flavonoids), inorganic elements (e.g., fluorine, aluminum, and manganese), alkaloids (caffeine, theobromine, theophylline, etc.), amino acids, volatile oils, lipids, polysaccharide, and vitamins. However, the polyphenolic content which is present in the highest concentration, is primarily responsible for its most of the therapeutic benefits. Consequently, flavonoid contents impart its antimicrobial, antioxidant, anti-allergic and anti-inflammatory effects. The phenolic content variants are further elaborated and sub-classified as catechin, gallocatechin, epigallocatechin, epicatechin gallate, epicatechin, and epigallocatechin-gallate (EGCG), the latter being the most active component [2, 5]. Further, the molecular structure of green tea polyphenols exhibits active hydroxyl hydrogen which effectively scavenge free radicals hence, slowing down the detrimental changes in most of the physiological processes existing in human body. Reportedly, tea polyphenols strongly exhibits the movement of glutathione peroxidase and superoxide dismutase causing higher scavenging rate. The phytoconstituents of tea reflects multiple therapeutic benefits on our various diverse physiological systems through various biochemical and pharmacological processes like—antioxidant activities, inhibition of cell proliferation, induction of apoptosis, cell cycle arrest and modulation of carcinogen metabolism [6, 7]. Similarly, in CNS, another constituent in green tea, L-theanine increases the dopamine and serotonin levels resulting in mood elevation and stress reduction. Also, caffeine content in same sources aids in increasing the focus, vigilance, concentration and reasoning ability [8]. Theobromine and theophylline are known as potential CNS stimulants. Numerous studies have shown that most of the tea polyphenols have reactive oxygen and nitrogen species (ROS) scavenging activity along with an ability to chelate down redox-active transition metal ions. Currently, apart from all the listed health benefits exhibited by the tea and its polyphenols, the focus is towards exploring its chemo preventive, hypolipidemic and anti-obesity effects in all sorts of possible *in vitro* and *in vivo* model systems [9].

3. Types of tea variants

Tea leaves are either classified on the basis of their consumption and texture it has or on the processing method adopted for their leaves. Hence, the classification, studied commonly for tea is based on its varied fermentation degree process and is comprised of basically three types: non-fermented (green), semi-fermented (oolong) and entirely fermented (black) [10]. The tea processing starts firstly, from picking up the appropriate and selected tea leaves from shrub or tea tree which undergoes fractional withering. Then roasting the same leaves to inactivate oxidative enzymes, followed by rolling up, drying and sorting the same leaves. The color of the final tea product is usually green tasting slightly constringent. So many countries like China, the taste of green tea is improvised by supplementing aromatic fruits (orange) or flowers (jasmine). Further, the tea processing steps in case of black tea is more complex, as after withering process the tea leaves are subjected for two steps fermentation processes, in the last step of fermentation they have been rolled up and then fermented. Lastly, they are roasted till they become dark-brown or brown black in color imparting a roasting aroma so as to block the activity of enzymes (polyphenol oxidase and glycosidase) along with further, fermentation of the same [5]. Another variant, oolong tea which is partially fermented type usually has shorter fermentation time in comparison to the black one.

3.1 Green tea

Green tea is a non-fermented tea which is largely consumed by the population of china and japan. After cultivation, tea leaves are first withered for the inactivation of enzyme (polyphenol) which is liable for oxidation of tea catechins into their oligomeric forms (thearubigins and theaflavins). To avoid the oxidation and polymerization of tea leaves, they are steamed up and dried at high temperatures [6, 9, 11]. The Chinese traditional dietary system do have another packed form of green tea called "black powder", named after type of leaves processing method. Where these leaves individually are stirred and wrapped into a round pellet looking like explosives. It prevents it from any kind of physical damage and maintains its fragrance and flavor. Polyphenols present in green tea are flavonols (quercetin, kaempferol, and rutin), caffeine, phenolic acids, theanine, flavor, and leucoanthocyanins, which show 40% of dry weight of leaves [12, 13]. The highly water-soluble parts of tea comprises of biochemical components like (−) epigallocatechin-3-gallate (EGCG), epigallocatechin (EGC), epicatechin-3-gallate (ECG), and epicatechin (EC) (As listed in **Table 1**) [9, 14]. Further, it's also been reported that 1 kg of green tea has around 191 g of the above listed catechins, 36 g of caffeine, and 5.2 g of flavonols [15]. In green tea there are 10–15% of polyphenols present whereas it's lesser in black tea, i.e. around 5%. Dry weight of green tea constitutes about 42% polyphenols which is composed of 26.7% of catechin-gallate components such as ECG (2.25%), EGC (10.32%), Catechins (0.53%), EGCG (11.16%) and Epicatechin (2.45%) [16]. It's been estimated that in one cup of green tea the expected concentration of EGCG is between 2.1–2.4 mg/mL and after testing the effects of both Green tea and EGCG (equivalent of 4–8 cups per day) on human subjects there was no appreciable side effects observed [17, 18]. Epidemiological

S. No	Polyphenols present	Structure of the polyphenols	Therapeutic benefit
1.	(+)-Catechin		Increases cellular lipid antioxidant activity, act as brain permeable iron chelator
2.	Epicatechin		It inhibits lipid peroxidation in cell membrane and generation of hydrogen peroxide ions in keratinomyocytes. Also, can induce ATF3 (tumor suppressor proteins) through EGR-1activation.
3.	(−) Epigallocatechin		Act as prophylactic agents against *Bordetella pertussis* infection.
4.	(−)-Catechin gallate (GC)		Antioxidant

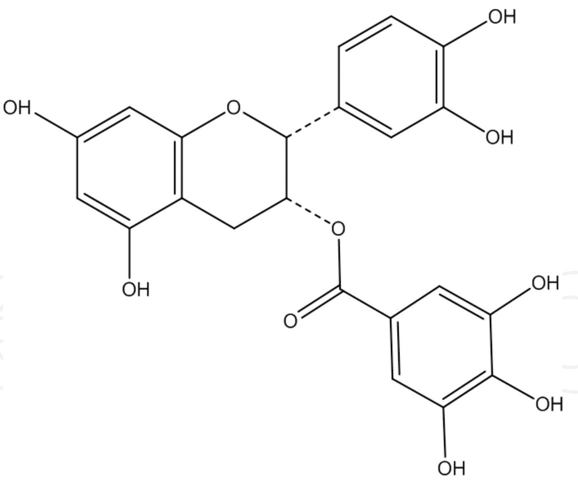
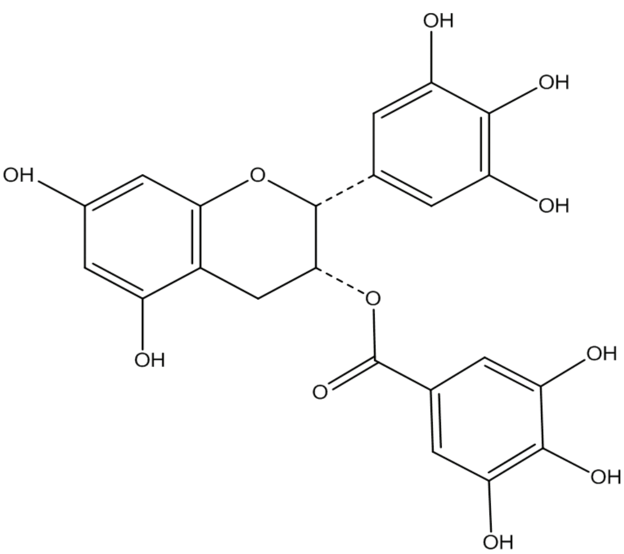
S. No	Polyphenols present	Structure of the polyphenols	Therapeutic benefit
5.	(+)-Epicatechin gallate (ECG)		Radical scavengers and Protective effect on lipid peroxidation in phospholipid Bilayers, Antioxidants
6.	(−)-Epigallocatechin gallate (EGCG)		Has strong antioxidant and anti-inflammatory activities, induces cell apoptosis by hindering cellular cycles in pancreatic cancer, and decreases autoimmune reactions.

Table 1.
Representing the types and structure of phytocompounds present in the green tea with their therapeutic benefits.

studies too, have suggested protective and suppressive effects against many types of human cancer (including that of skin, lung, liver, esophagus, and stomach) after tea consumption [19–21].

3.2 Black tea

This variety of tea is very famous in North America, Europe, and India. Black tea is extracted from the new, soft, firstly appeared leaves of *Camellia sinensis* and is one of the most broadly devoured non-mixed drinks. The flavor, quality and taste of these drinks tends to change with variation in their topographical and climatic conditions [22, 23]. This variety of tea offers, its simple quality parameters, specifically, theaflavins, thearubigins, and caffeine. Theaflavins adds to the abstinence (liveliness) and splendor, while thearubigins adds to the shading and body (mouth feel); and caffeine is responsible for stimulatory impact of dark tea. In Black tea, the compound is permitted to act in a way that the leaves are completely aged to give the trademark fragrance and shade of dark tea [24, 25]. Arranged by squashing tea leaves and permitting enzyme mediated oxidation, which leads to the formation of oligomeric flavanols by tea catechins, including theaflavins, thearubigins, and different oligomers [26–28]. Further, the associated compounds like Theaflavins includes, combination of theaflavin (TF-1), theaflavin-3-gallate (TF-2a), theaflavin-3′-gallate9TF-2b), and theaflavin-3, 3′-digallate (TF-3), having lower tea catechin content (3–10% [w/w]), with theaflavins and thearubigins showing around 2–6% (w/w) and 10–20% (w/w) dry weight. Theaflavins, are orange or orange-red colored benzotropolone structure formed due to co-oxidation and oxidative dimerization of catechins (**Table 2**) [29, 30].

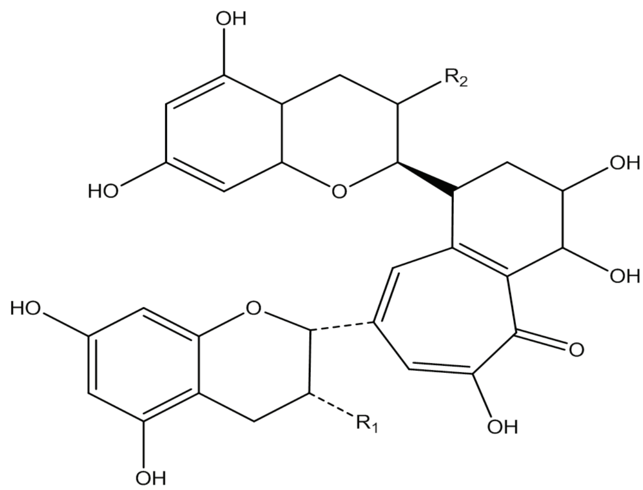
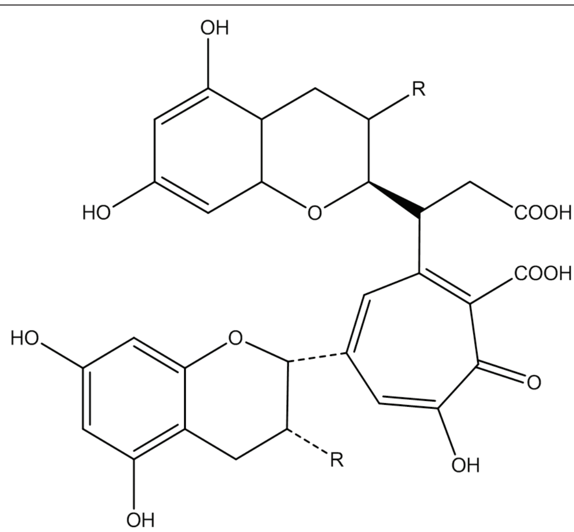
S. No	Polyphenols present	Structure of the polyphenols	Therapeutic benefit
1.	Thearubigins		Shows antioxidative properties, prevent activity of enzymes participating in enzymatic lipid peroxidation
2.	Theaflavins		shows inhibitory effect against phytopathogenic bacteria, induce apoptosis, strong antioxidants, prevent free radical generation, show metal chelating abilities

Table 2.
Representing the types and structure of phytocompounds present in the black tea with their therapeutic benefits.

3.3 Oolong tea

Oolong tea is a conventional Chinese tea with a different, unique production method and one of the most popular beverages in china with its Chinese name meaning as "Black dragon tea". It is a semi fermented tea with restricted time of oxidation as compared to black tea and contains phytocompounds of both black and

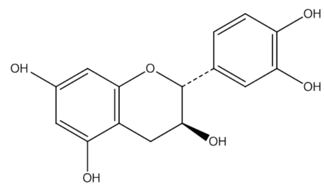
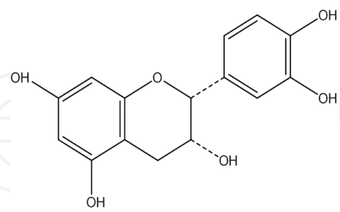
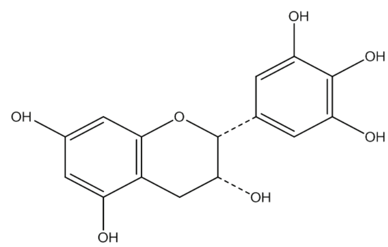
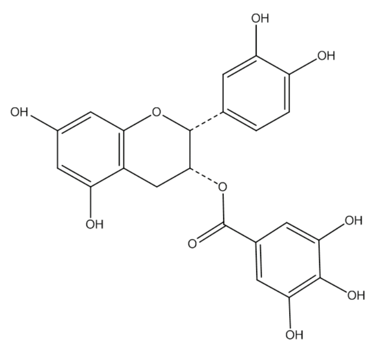
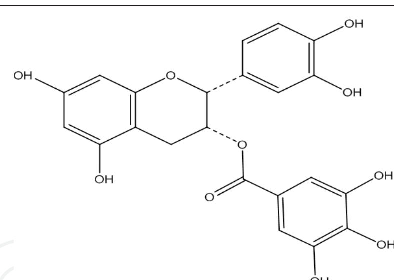
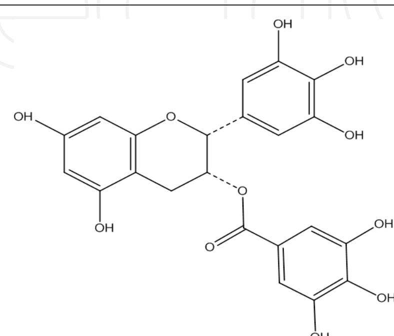
S. No	Polyphenols present	Structure of the polyphenols	Therapeutic benefit
1.	(+)-Catechin		Increases cellular lipid antioxidant activity, act as brain permeable iron chelator
2.	Epicatechin		It inhibits lipid peroxidation of cell membrane and induces tumor suppressor proteins
3.	(−) Epigallocatechin (EGC)		It acts as prophylactic agents against *Bordetella pertussis* infection.
4.	(−)-Catechin gallate (GC)		Antioxidant
5.	(+)-Epicatechin gallate (ECG)		Radical scavengers and Protective effect on lipid peroxidation in phospholipid Bilayers, Antioxidants
6.	(−)-Epigallocatechin gallate (EGCG)		Has strong antioxidant and anti-inflammatory activities, induces cell apoptosis by hindering cellular cycles in pancreatic cancer, and decreases autoimmune reactions.

Table 3.
Representing the types and structure of phytocompounds present in the oolong tea with their therapeutic benefits.

green tea. It has approximately half of the EGCG from green tea, while double quantity of polymerized polyphenols and theaflavins of black tea. The procyanidins produced in oolong tea are formed due to its unique fermentation process. The

Polyphenols	Chemical structure	Oolong tea phytocompound concentration (mg/g)	Green tea phytocompound concentration (mg/g)
Caffeine	$C_8H_{10}N_4O_2$	64	53
Flavanol with galloyl moiety			
Catechin	$C_{15}H_{14}O_6$	30	43
Epicatechin	$C_{15}H_{14}O_6$	6	25
Gallocatechin	$C_{15}H_{14}O_7$	10	5
Epigallocatechin	$C_{15}H_{14}O_7$	2	8
Flavanol without galloyl moiety			
Epigallocatechin gallate	$C_{22}H_{18}O_{11}$	14	29
Gallocatechin gallate	$C_{22}H_{18}O_{11}$	16	19
Epicatechin gallate	$C_{22}H_{18}O_{11}$	3	6
Catechin gallate	$C_{22}H_{18}O_{10}$	7	5
Oolong tea polymerized polyphenols (OTPP)		114	–

Table 4.
Comparing the polyphenolic contents of oolong and green tea.

leaves are first withered, sun dried and then allowed for oxidation before rolling and twisting. *Camellia sinensis* is used for the production of Oolong tea and tastes very different from green and black tea. The tea processing method differs which makes them significantly different from each other, even if they are produced from the same plant [31].

As all tea leaves are green when they are plucked. Green tea undergoes, heating process in order to inhibit the oxidation of tea leaves. They are rolled up to break the cell structure. While, oolong tea is plucked and kept in optimized condition and allowed for oxidation. Due to difference in its processing method oolong tea tastes different from its sub varieties. It shows a sweet and fruity flavor with striking honey odors to woody and dense with roasted aromas, or even green and fresh with flowery aromas. They are processed by different methods as some are wrapped-curled into small beads and others are rolled into curly leaves. In china, oolong tea is added with flavors like jasmine flowers (**Tables 3** and **4**) [32].

4. Therapeutic benefits of tea in CNS health

As discussed earlier, the health-promoting properties of the tea plants are often credited to their active ingredients including polyphenols. Tea flavanols are a group of natural polyphenols (epicatechins) found in most of the varieties of tea. Their therapeutic benefits although are immense, but they do have contributed exclusively in neural health of living beings. Likewise, the polyphenols of green tea are reported extensively in preventing neuronal degradation by inhibiting neurotoxin formation in cells [33, 34]. Also, in one of the recent study done, with transitional metal (iron and copper) chelating property or EGCG, suggested its possible effective role in treating certain forms of neurodegenerative diseases. Similarly, the antioxidative property of EGCG exhibits protection against advanced glycation end products (AGEs) induced neuronal cells injury along with inhibit AGEs—AGE receptor (RAGE) interaction intervened pathways, suggesting a possible therapeutic role of tea catechins for neurodegenerative diseases. Hence, both black and green tea varieties are reported to contribute immensely for the protection against neurodegenerative diseases [34–36]. Also, oxidative variations of cellular components such as nucleic acids, lipids, and proteins are prevented by bidirectional antioxidative property [37]. The oxidation of these components in aqueous phase is responsible for initiation of membrane lipid peroxidation [35].

Moreover, these water soluble tea polyphenols, particularly catechins have effective potential to scavenge free radicals and reduce the versatility of free radicals in the lipid structures too. Polyphenols enters the phospholipids bilayer, coating it with film and, balancing out the impact, by adjusting the lipid pressing ability [38]. They also contain higher amount of chemically dynamic metal particles (iron and copper) creating *in-situ* oxygen radicals by Fenton's response [39, 40].

Due to the existence of hydroxyl ions on polyphenol ring metal chelation effects can be observed. Metal Chelating effects by Green and Black Tea additionally, restricts lipid per oxidation and secures the essential lipid structures present in cerebrum leading to reduce oxidative stress [10, 27, 41]. Furthermore, it's been observed in research studies that the phytocompounds of tea (Green/Black) also prevents, the division of mitochondrial layer against iron induced lipid per oxidation and enhanced the survival rate in many *in vivo* models [42, 43]. Hence, it can be concluded from the recent research updates, that the high metal chelating quality of its constituents may provide a unique essential neuroprotection against many neurological disorders [44].

One of the essential pathological cause in Alzheimer's disease (AD) is irregular contact of free chelatable iron which is responsible for the deposition of neocortical amyloid peptide and deposition of metals, phosphorylation of tau and formation of tangles due to production of tau protein from microtubules [45, 46]. Also, the activation of amyloid cascades, which produces amyloid by β-amyloid precursor protein (APP), accumulates in the presence of divalent metal ions into amyloid fibrils leading to a major cause of AD [47, 48].

Recent studies have reported that the delay in onset or slowdown of the neurodegenerative process along with minimal neural deterioration was observed in the population consuming tea infusions on regular basis [49]. There scientific correlation suggests that the reduction in amyloid beta (Aβ) fibril production in the presence of EC and EGCG is suspected to regulate the amyloid protein precursor (APP) enzyme activity [50]. Additionally, it been also suggested that the regular consumption of tea (green and black) may lead to the acetyl cholinesterase (AChE) activity inhibition, further causing halt in acetylcholine production [51, 52]. Besides this, it was found that there was inhibition of butyrylcholinesterase (BuChE) enzyme deposits in the brain of AD subjects after consuming green tea or black tea for certain time [53]. These research findings advices that active phytocompounds present in tea can be used to obstruct the development of AD [54].

5. Mechanism of tea polyphenols

5.1 Mechanism of action of EGCG to improve cardiovascular function and anticancer activity

Tachibana et al. [55] studied the effect of tea polyphenols, and suggested that EGCG directly binds to the Laminin receptor (67LR), located on the peptide LR161-170. This receptor shows a high expression only in cancerous cells. This suggests that EGCG specifically binds to the cancer cells and binding of EGCG with 67LR receptor activate the enzyme protein kinase B which further activate ENOS pathway leading to vasodilation that contributes to the improvement of cardiovascular function of cell [16, 55]. It also elevates the activity of CGMP that activate the PKC/Acidic sphingomyelinases that induces the apoptosis in cancerous cells.

5.2 Antagonistic actions of theanine on glutamate receptors

Nozawa et al. [56] discovered the death of 50% of neurons at higher concentration of glutamate but when pre-treated with theanine, the possibility of death was significantly decreased. Many more recent updates suggested that increased glutamate level in cell may lead to massive influx of Ca^+ ions and increases the formation of ROS which leads to the death of neuronal cells. In order to avoid the toxicity of glutamate, the glutamate receptors binds with theanine. Theanine has same structure as glutamate so in presence of theanine it shows a competitive inhibition and inhibit the binding of glutamate to its receptor. Furthermore, Kakuda et al. [57] studies the inhibiting effect of glutamate receptors by theanine that suggests the neuroprotective role of theanine. It shows the specific binding of theanine to NMDA receptor to inhibit the glutamate binding affinity. Theanine has an antagonistic effect to glutamate receptors. Glutamine, derived from glutamate, is synthesized by glutamine synthetase. Theanine can inhibit the transport of glutamine and regulate the glutamate-glutamine cycle in the neurons and, thus, shows the neuroprotective effect of tea (**Figure 1**) [58].

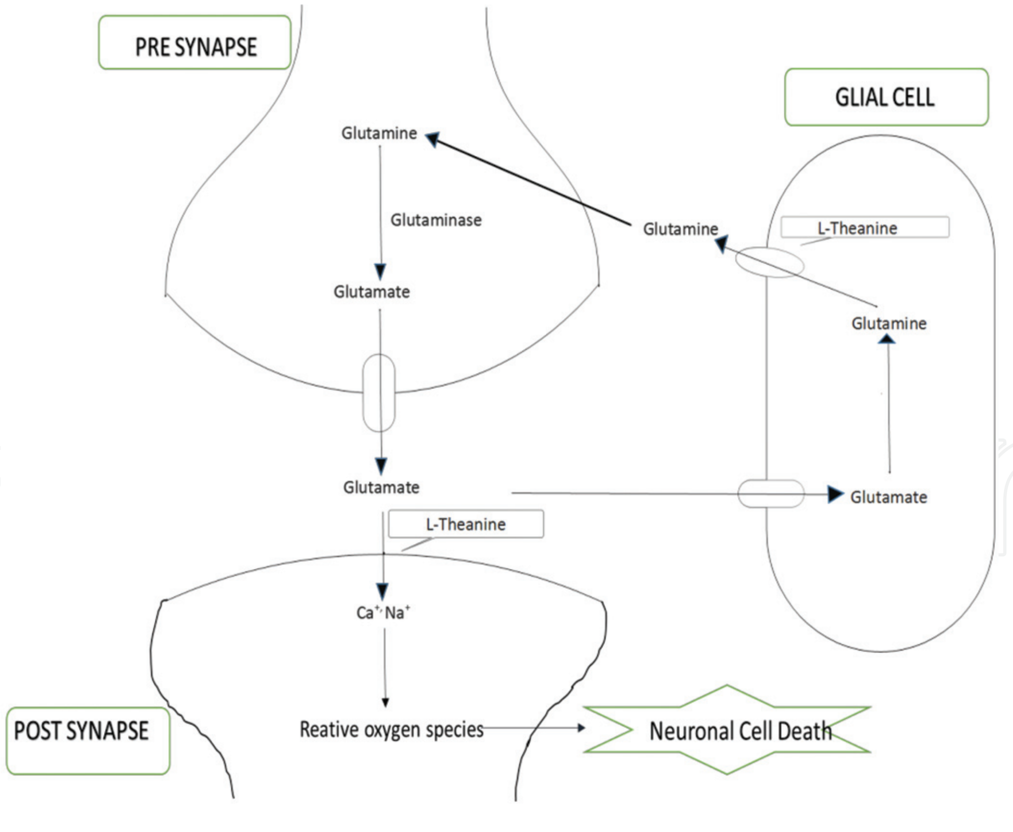


Figure 1.
Schematic representation. Inhibition effect of theanine on glutamate receptor.

5.3 Therapeutic limitations of tea compounds

Although being therapeutically crucial compound tea phytocompounds do have certain harmful side effects, if over consumed or overdosed like—higher Caffeine content, Aluminum presence and the effects of tea polyphenols on iron bioavailability [59, 60]. In the study done by Lin et al. [31], it was been reported that the caffeine content in tea is available in following order: black tea > oolong tea > green tea > fresh tea leaf. Similarly, Cabrera et al. also studied the caffeine content and its after effects in 45 samples of tea and determined that black tea has the high concentration of caffeine (41.5–67.4 mg/g), whereas oolong and green tea samples have less amount of caffeine content of 32.5 and 29.2 mg/g, respectively [61]. The harmful effects of caffeine content in tea are listed as—vomiting, sleep disorder, nervousness, tachycardia, and epigastric pain etc. [62]. Hence, tea intake is strictly restricted in patients suffering from cardiovascular problems. Breastfeeding and pregnant women should avoid over-consumption of green tea because it do causes tachycardia in them giving rise to higher health risks to fetus [63, 64]. The presence of aluminum in black and green teas also suggested increased accumulation of the same inside the body affecting the neural well-being and causing neurological disorders [65].

6. Conclusion

It can be concluded in the review that tea polyphenols with other constituents have a very high therapeutic potential including the potency to decrease the threat of diseases such as cancer, cardiovascular, diabetes and neurodegenerative diseases. It has proven to be a strong antioxidant agent that shows a therapeutic effect of tea. To evaluate the efficacy of tea many experiments are being conducted which shows a promising data from many trials and other ongoing trials are conducted to study the therapeutic effect of tea. Because less information is available about bioavailability of tea polyphenols after intake of tea, studies of bioavailability polyphenols of tea is needed on animals and humans to evaluate its protective role.

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