Role of Tea and Its Components in Treatment of Neurodegenerative Diseases: A Review

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***Abstract*: Neurodegenerative diseases involve a heterogeneous group of disorders characterized by progressive impairment and degeneration of nerve structure and function, eventually leading towards the death of certain parts of the CNS and brain. The most common form of neurodegenerative diseases includes Alzheimer's disease (AD) leading towards progressive loss of memory, Parkinson's disease (PD) causing impairment in movements, Huntington's disease (HD) affecting the ability to walk, talk and think. The pathogenesis of these diseases mainly AD and PD are complex and there is no such cure for these diseases as the drugs that are currently in use shown to have an adverse effect on these diseases. However epidemiological studies have shown that consumption of tea has therapeutic effects in treating those neurodegenerative diseases especially the major tea components i.e. Catechins, Caffeine, Theanine, TFs in elderly persons. The major tea components are antioxidants which help to combat oxidative stress, the major reason behind all those neurodegenerative diseases, regulating signaling pathways as well as helps in metal chelation. The objective of this review is to summarize all the available information on different bioactive components of tea in the treatment of different neurodegenerative diseases.**

***Index Terms*: Tea, Bioactive components, Bioactivity, Alzheimer's, Parkinson's.**

INTRODUCTION

Neurodegenerative diseases are one of the rapidly rising diseases of the nervous system involving damage of the structure of the neurons as well as affecting their functions in the brain and spinal cord. These are mainly progressive and irreversible disorders featuring many debilitating, incurable diseases affecting mainly the elderly population causing a major threat to human health [***1***]. The two main characteristic features of neurodegenerative diseases are- impairment in movement which is known as ataxia and decline in memory which is known as dementia [***2***]. The most commonly occurring neurodegenerative diseases in aged people are Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) among which AD is an age-dependent, chronic neurodegenerative disease and the leading cause of dementia among the older people as well as the fourth most common cause of death in the western world [***3***]. AD is characterized by the gradual decline in memory of a person, affecting the ability to learn a lesson, make judgments, inability to communicate and carry out daily activities [***4***] whereas PD is characterized by impairment in movement resulting in tremor, rigidity, slowness of movement with difficulty in walking and gait eventually leading to thinking and behavioral problems along with dementia occurring in the advanced stages). HD appears to be multifactorial where the demise of neurons occurs due to a complex set of toxic reactions and is mainly characterized by involuntary jerking or writhing movements commonly known as chorea which affects muscle coordination leading to cognitive decline and psychiatric disorders [***3***]. Now the major reason behind all these neurodegenerative diseases is aging and oxidative stress along with mitochondrial DNA mutations plays a substantial role in aging. The brain and the CNS are more vulnerable to oxidative damage rather than any other organs as the comprising elements (i.e. lipid, protein, and nucleic acid) of these two major parts of the body are easily oxidizable [***4***]. Oxidative stress is a phenomenon results due to over-accumulation of ROS (Reactive Oxygen Species), which in normal and controlled condition regulates many physiological processes of the body thus help in maintaining homeostasis of the body but when there is an imbalance between generation and elimination of ROS it leads to severe deleterious effects to the cells, organ, and body causing oxidative stress. Oxidative stress can result from over-accumulation of ROS in many circumstances among which injury, inflammation, chronic disease, and aging are the major reasons [***3***].Oxidative stress causes oxidative damage to neuronal biomolecules leading to over-accumulation of iron in specific parts of the brain causing inflammation along with the proliferation of reactive microglia, the major pathological aspects behind the process of aging, and eventually the various neurodegenerative disorders including AD, PD, and HD[***5***].Apart from the above-mentioned processes, there are other additional complementary processes caused due to oxidative stress involve promoting amyloid β deposition, hyperphosphorylation of tau protein, increased level of acetylcholinesterase, the release of cytochrome c, reduced level of GSH(glutathione), increased α-synuclein aggregation, increased lipid peroxidation, increased expression of apoptotic proteins as well as a reduction in mitochondrial complex 1 activity and ubiquitin-proteasome system dysfunction [***6,7,8,910, 11, 12,13,14]***.All these mentioned physiological pieces of evidence indicate the various neurodegenerative diseases to be multifactorial and the treatment of these diseases appears to be difficult as most of these neurodegenerative disorders are of late-onset and remain asymptomatic for a long time until severity takes place. The therapeutic approaches towards these diseases are limited and need to start at the initial stage which may halt or slow down the progression of these diseases [***15***]. There are limited medications available in the market which has immense side effects so the goal in course of developing a potential drug against these diseases has recently shifted towards prevention of these diseases rather than treatment [***16***]. Since all these neurodegenerative disorders are mediated by one common factor i.e. over-accumulation of ROS, one potential strategy to control

these diseases has been focused on the application of antioxidants as a preventive as well as a therapeutic molecule. Antioxidants are substances that inhibit the oxidation of different biomolecules by scavenging free radicals produced due to over generation of ROS thus helps to combat oxidative damage to the cells and organs. The antioxidants are of two types- enzymatic and non-enzymatic where the enzymatic ones involve SOD(superoxide dismutase), catalase(CAT), glutathione peroxidase(GPx), thioredoxin reductase (TR), and the non-enzymatic ones include ascorbic acid, α-tocopherol, glutathione, and various secondary metabolites including the major one i.e. flavonoids **[*3*]**. Epidemiological evidence has shown that the various non-enzymatic antioxidants have an immense effect on the prevention of these neurodegenerative disorders.

Tea brewed from the plant *Camellia sinensis* is one of the most popular aromatic beverages consumed worldwide and is well known for its aroma along with the signature astringency flavor due to the presence of large-scale secondary metabolites as well as various volatile components. Depending on the processing techniques and the extent of fermentation there are mainly three kinds of tea – green tea (GT), oolong tea, and black tea (BT) where green tea represents the conventional non-fermented one with no oxidation usually enriched with catechins, oolong tea represents the semi-fermented one and black tea represents the fully fermented ones with a good degree of oxidation where catechins get converted into theaflavins and thearubigins giving the black tea its characteristic color and aroma [***17***]. Over the years tea has become a hot topic of research due to its nutritional and therapeutic properties as tea contains a diverse group of bioactive compounds which are not only bio-stable but are direct-acting than any other component of other medicinal plants thus they hold the potentiality of being a therapeutic drug in the future scenario. Coming to the bioactive components of tea, fresh tea leaves are enriched in polyphenolic compounds comprising 36% of the total weight next to them come carbohydrate (25%), proteins (15%), amino acids (4%), and various inorganic elements[***18***]. The major and characteristic polyphenols of tea involve flavanols of which catechins are pre-dominant of which (-)-epicatechin (EC), (-)-epicatechin gallate (ECG), (-)- epigallocatechin (EGC), (-)-epigallocatechin gallate (EGCG), (+)-catechin (C), and (+)-gallocatechin (GC) are the important ones [***19,20***]. The catechins are shown to have radical scavenging effects as well as prevention of lipid peroxidation and the green tea EGCG has protective effects against hippocampal neuronal damage thus conferring neuroprotective effect [***21***]. In the processing of black tea, oxidation takes place which leads to the formation of catechin and gallic acid complexes i.e. theaflavins,thearubigins, and proanthocyanidin polymers [***22***]. The theaflavins (TFs) and thearubigin (TR) are the major nonvolatile pigments of black tea and are solely responsible for the characteristic color and astringency of black tea [***17***]. Both TFs and TR of BT have shown neuroprotective effect by inhibition of AChE (acetylcholinesterase), which plays a crucial role in the progression of Alzheimer's disease, in a dose-dependent manner [***23***]. Apart from these polyphenolic compounds, the major and important amino acid accounting 50% of the amino acid content which is unique to tea i.e. Theanine (γ-glutamylethylamine) plays a vital role in the treatment of various neuronal disorders as well as have cognition-enhancing properties assisting in the maturation of central nervous system thus helping in the function of the brain [***24***]. So the present study focuses on the effectiveness of tea and its bioactive components on the various neurodegenerative diseases particularly AD and PD induced via oxidative stress.

BIOACTIVE COMPONENTS OF TEA

Depending on the variation in the processing technique for the production of commercial tea the metabolites of different tea varies. The oxidation process plays a crucial role in the variation of metabolites as fresh tea leaves contains a significant amount of polyphenolic compounds (simple and complex polyphenols), 25% carbohydrates (pectins, glucose, fructose, cellulose), 15% proteins, 6.5% lignin, 5% minerals, and trace elements (magnesium, chromium, iron, copper, zinc, sodium, cobalt, potassium, etc.), 4% amino acids (such as theanine [5-N-ethyl-glutamine], glutamic acid, tryptophan, aspartic acid), 2% lipids, 1.5% organic acids, 0.5% chlorophyll as well as carotenoids[***18***] whereas a typical tea beverage containing 2.5 g of processed tea leaves brewed for 3 minutes in 250 ml hot water, usually contains 620–880 mg of different water-extractable solids [***25***]. The major constituents of tea biomolecules belong to the polyphenol group which mainly include six groups of compounds that remains the same for green tea black tea and oolong tea, such as phenolic acids (PA), flavones, flavonols, anthocyanins, flavanols, and hydroxyl-4 flavanols among which the most important tea polyphenols are the flavanols of which the flavon-3-ols commonly known as catechins are the predominant one [***26***]. The major catechins that are found both in green tea (GT) and black tea (BT) are - (-)-epicatechin (EC), (-)-epicatechin gallate (ECG), (-)epigallocatechin (EGC), (-)-epigallocatechin gallate (EGCG), (+)-catechin (C), and (+)-gallocatechin (GC) [***19,20***].These major catechins are mainly colorless water-soluble components contributing to the bitterness, astringency, and sweet aftertaste of tea [***27***]. Apart from these major six catechins the gallocatechin gallate (GCG), gallocatechin (GC), catechin gallate, epigallocatechin digallate, 3-O-methyl EC, 3-O-methyl EGC, and some other minor catechins are present in smaller fractions [***25***]. The amount of catechins varies considerably in different tea varieties with a concentration of 58.0-183.9mg/g,74.8-105.7 mg/g, 11.7-55.3 mg/g in green tea, oolong tea, and black tea respectively. The most abundant catechin found in all the varieties is EGCG which accounts for more than 40% of total catechin in green tea [***15***]. Depending on the oxidation process the number of total catechins varies where black has shown to contain fewer amounts of catechin than green and oolong tea. Apart from these flavanols tea has also been reported to contain flavonols and flavones along with their glycosides [***25***]. There are more than 20 flavonol glycosides (FOGs) are reported in tea and are mainly present in the form of mono-, di-, and triglycosides. The major three flavonol aglycones are kaempferol, myricetin, and quercetin[***28***]. Aglycones are compounds where the glycosyl group of the glycoside chain gets replaced by a hydrogen atom and these aglycones of tea make up to 0.5–2.5% wt/wt extract in tea infusions. The only flavone identified in tea is apigenin along with its glycosides which are present in small fractions. In recent studies with the use of different chromatographic and spectrometric methods like liquid chromatography with diode array and electrospray ionization mass spectrometric detection (LC-DADESI/MS) 19 O-glycosylated flavonols, 7 C-glycosylated flavones, 28 acylated glycosylated flavonols, and 3 flavonols are also identified from green teas and fermented teas [***25***]. In all the types of tea where complex polyphenols are represented mainly by catechins, some simple polyphenols are also present in significant amounts mainly represented by gallic acid and its quinic acid ester, theogallin.

In comparison to the other two types of teas black tea contains a higher amount of gallic acid and less amount of theogallin as during fermentation condensation of EC and theogallin takes place which gives rise to a theaflavin like compound, theagallinin [***25*].** The oxidation or so-called fermentation procedure plays a crucial role in the formation of the major black tea nonvolatile pigments. The oxidation process commonly known as fermentation is very much different from the actual anaerobic breakdown of energy-rich compounds such as carbohydrates to alcohol or organic acids using microorganisms but is mainly the oxidative polymerization and condensation of the Flavon-3-ols catalyzed by the endogenous polyphenol oxidases **[*17*].**The process allows the tea leaves to undergo enzymatic oxidation where the internal polyphenol oxidase causes the polymerization of the flavan-3-ols to catechin oligomers resulting in the formation of bisflavanols and the major two pigments of black tea i.e. theaflavins (TFs) & thearubigins (TRs) accounting for 3-6% and 12-18% of the dry weight of black tea. As a result, the percentage of catechins decreases in black tea and the rest are transformed into TFs & TRs, contributing to the sweet aroma of malt sugar and the dark brown hue of black tea [***18***]. The group of TFs is mainly comprised of four major TFs and some minor TFs with its related compounds of which the major ones are - Theaflavin(TF), Theaflavin 3-monogallate(TF3G), Theaflavin 3'-monogallate(TF3'G), and Theaflavin3,3'-digallate (TF3,3'DG) and the minor ones are isotheaflavin, neotheaflavin,theaflavic acids and theaflavates [***28***].

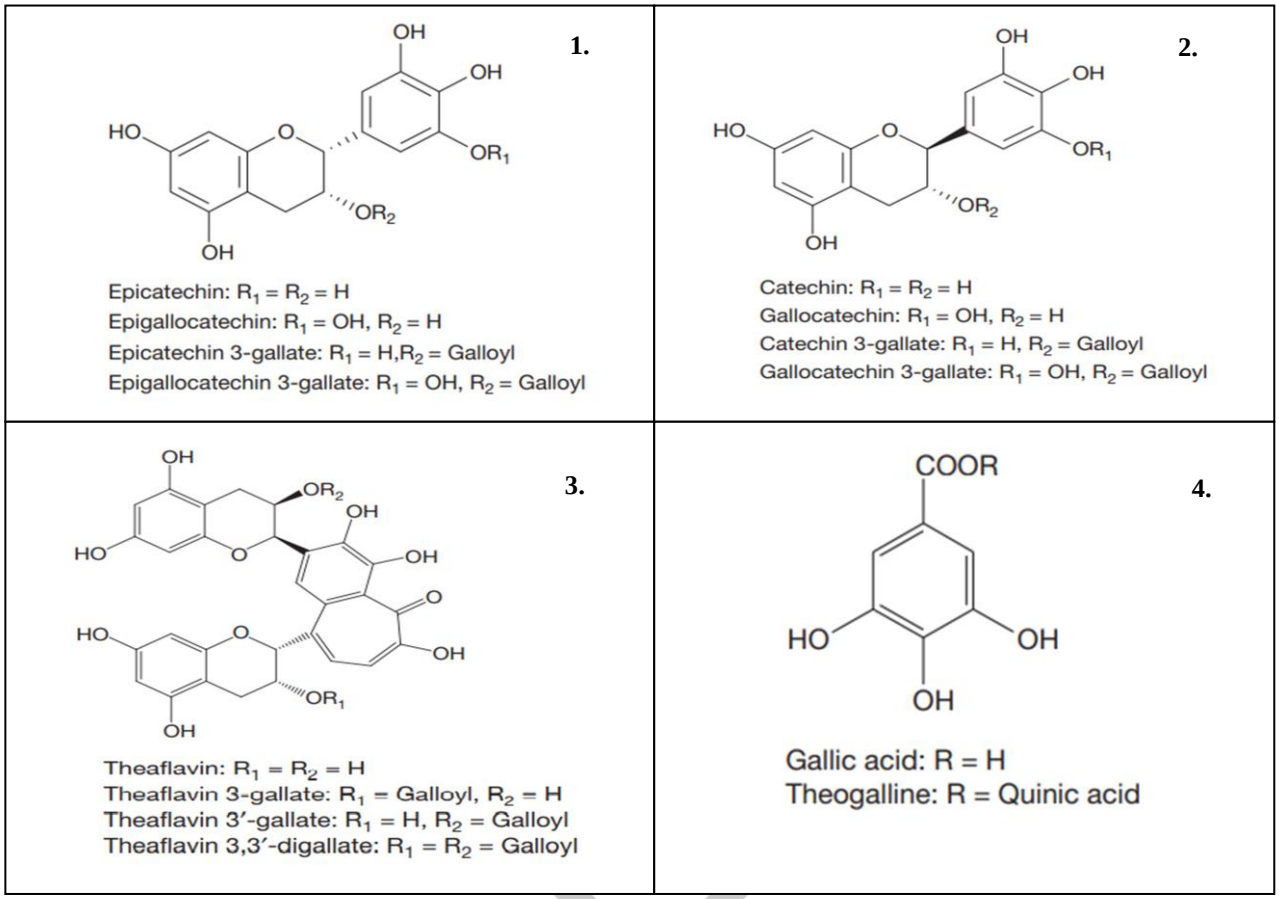

Fig 1, 2, 3, 4: structures of different bioactive components of tea - Catechins, TFs, Gallic acid and its quinic ester (*source: S sang et al., 2016*).

Thearubigins are brown pigments of black tea which are known to be heterogeneous polymers of flavan-3- ols and flavan-3-ol gallates and having bonds present at C-4, C-6, C-8, C-2′, C-5′, and C-6′ in the flavan-3-ol unit having a molecular weight not more than 2100 Da **[*29*]**. Apart from the polyphenols and flavonols, another reason for the great popularity of tea is mainly accounted for the presence of alkaloids especially caffeine, theobromine, and theophylline which are together known as methylxanthines as they are methylated derivatives of purine [***30***]. It has been found that the caffeine content in green tea and black tea remains more or less the same accounting for 2-5% of water-extractable tea solids as it remains very stable during the fermentation procedure [***25*].** Fresh tea leaves contain up to 30% protein among which processed tea contains 15–23% of proteins of which less than 2% being water-soluble. Among the 19 amino acids, theanine (N-ethylglutamic acid) is unique as it occurs exclusively in tea and accounts for as much as 50% of the free amino acids. It is found in both green and black tea but the amount is higher in green tea as most of it gets reduced during the fermentation process of black tea [***30,25***]. Theanine naturally occurs in tea as L-theanine and the biosynthesis of it occurs in young rootstocks of tea via condensation of glutamic acid and ethylamine catalyzed by L-theanine synthase [***30*].** Theanine is mainly responsible for the brothy taste of tea and the degradation of it is the main reason behind the biogenesis of tea aroma [***22***].

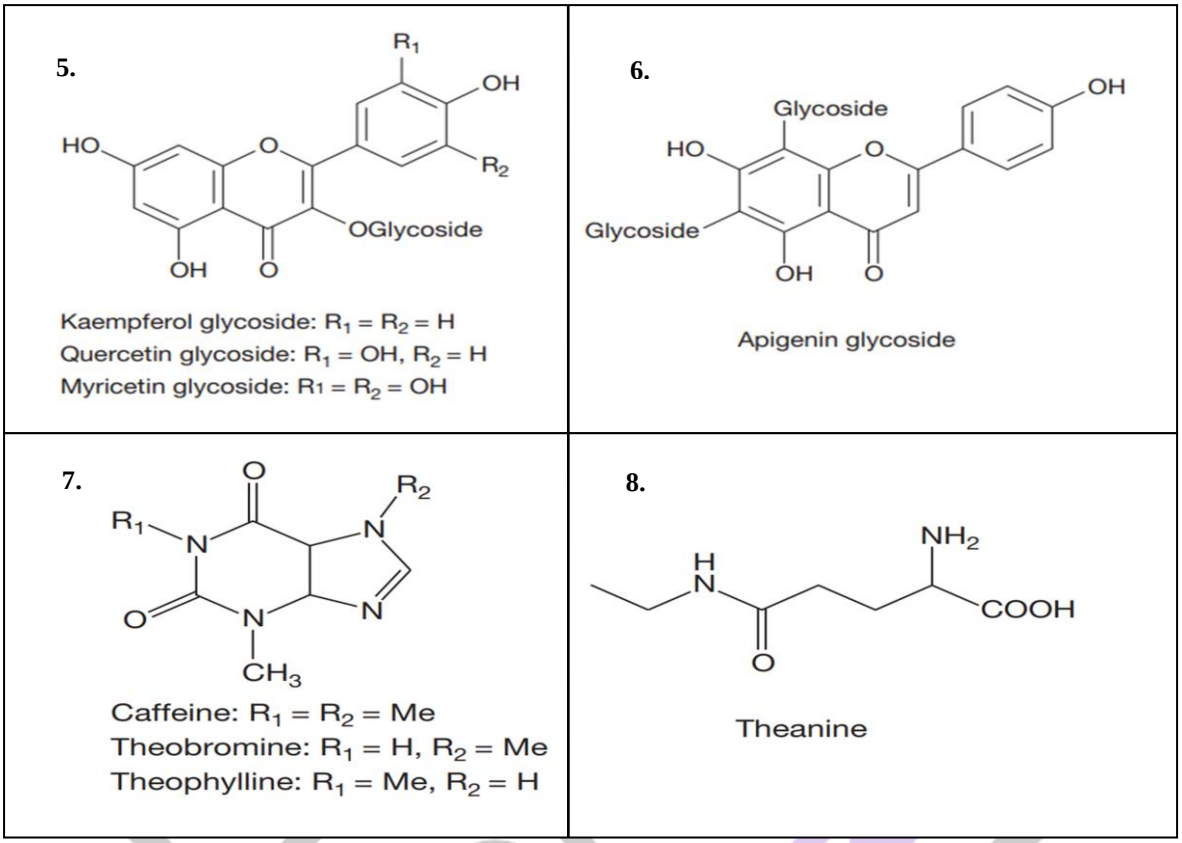

Fig 5, 6, 7, 8: Structures of different bioactive components of tea – Flavanols, Apigenin, Methylxanthines, and Theanine (*source: S sang et al., 2016*).

Form	Tea constituents	Green tea	Black tea	Oolong tea
Flavonol (Monomer)	Catechin,Epicatechin, Epicatechingallate, Epigallocatechin and Epigallocatechin gallate	Present	Present	Present
Flavanol (Dimer)	Theaflavin,Theaflavin3gallate, Theafl avin 3 O-gallate, Theafl avin 3,3'-digallate	---	Present	Present
Flavonol (Oligomer)	Thearubigin	---	Present	Present
Flavonol aglycones	Quercetin, Kaempferol, Myricetin	Present	Present	Present
Amino acid	Theanine	Present	Present	Present
Methyl xanthine	caffeine, theobromine, theophylline	Present	Present	Present
Polysaccharides	Galactose, Arabinose, Rhamnose, Xylose, Galacturonic acid, Mannose, Ribose and Glucuronic acid	Present	Present	Present
Trace minerals	Copper, Manganese, Iron and Zinc	Present	Present	Present

Table 1: Major bioactive components of tea.

Apart from theanine, the other amino acids which are found in Green tea, oolong tea, and Black tea involve glutamine and arginine which are essential under stress conditions. Coming to the minor but important constituents of tea involves carbohydrates which account for 5-7% of the dry weight usually contains pectins, glucose, fructose, cellulose, and sucrose. It also contains some major minerals and trace elements constituting 5% of the dry weight notably potassium, manganese, and fluoride ions. Tea also contains trace levels of lipids including the essential fatty acids (linoleic and α-linolenic acids), stigmasterol, and vitamins mainly vitamin B, C, and E [***31***]. This brief overview of the different complex constituents of tea helps to understand the various mechanisms associated with the consumption of tea in promoting health.

NEUROPROTECTIVE EFFECTS OF TEA

The health-promoting benefits ascribed to the consumption of tea are directly related to the presence of diverse bioactive components among which the bioactivity of green tea has been thoroughly studied whereas in recent studies the focus has been shifted towards the beneficial effects of black tea. The phenolic compounds, especially the complex polyphenols including the major polyphenolic group i.e. The flavonoids, are responsible for most of the health-promoting activities whereas the health effects of theanine in recent researches have become an emerging issue [***28***]. The most important medicinal value ascribed to the consumption of tea is its anticarcinogenic and antimutagenic effects. Apart from the anticarcinogenic and antimutagenic effects tea prevents cardiovascular diseases, diabetes, hypertension as well as it has anti-oxidative, anti-viral,anti-peridontitis,anti-metabolic activities[***32***]. The tea polyphenols are great antioxidants that inhibit the generation of ROS (reactive oxygen species) as well as chelation of transition metal ions (Fe & Cu) catalyzing those reactions [***29 ,33***]. Reactive oxygen species (ROS) are produced as a natural byproduct of cellular metabolism of the living system though excessive production of ROS due to various natural stresses can cause progressive oxidative damage to the cell which can be to DNA, Protein, and other biological macromolecules, thereby causing pathological changes to the cell eventually leading to various chronic diseases [***34***]. To combat those oxidative damage antioxidants play a pivotal role in preventing or slowing down the progression of the formation of ROS. Different antioxidative assays mainly including Ferric Ion Reducing Antioxidant Power – FRAP, Oxygen Radical Absorbance Capacity – ORAC, and Trolox Equivalent Antioxidant Capacity–TEAC has shown that consumption of catechins of tea in its monomeric or epimerized form results in a transient increase in total antioxidant capacity of plasma [***35,36***]. The growing interest in consumption of tea due to its health benefits is directly connected to the antioxidant activity of the tea polyphenols which fights the harmful effects on environmentally generated free radicals which mainly involves ROS like superoxide, hydroxyl, and peroxyl radicals which in normal conditions generates as a by-product of different essential metabolic processes. However different exogenous sources cause an imbalance in the generation and elimination of these free-radical which leads to harmful effects in different body parts causing oxidative damage [***37***]. The tea polyphenols and other bioactive components possess free radical scavenging properties as they scavenge superoxide and hydroxyl radicals, as well as the 1, 1-diphenyl-3- picrylhydrazyl radical (DPPH), peroxyl radicals, nitric oxide ion, carbon-center free radicals, singlet oxygen, and lipid-free radicals by prevention of the nitration of tyrosine residue [***38, 39, 40***].

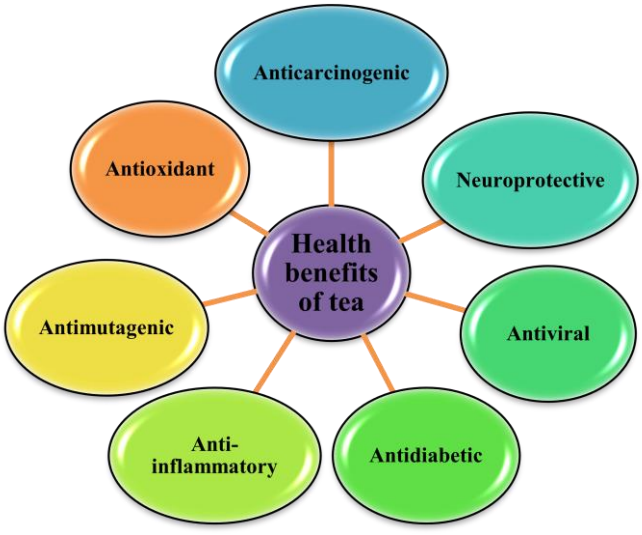

Fig 9: Various health benefits of tea

Now coming to different neurodegenerative diseases, some pieces of evidence indicates overproduction of ROS and oxidative stress are one of the main reasons behind the progression of different neurodegenerative diseases like AD and PD. Different In vitro work techniques such as cell culture and enhanced chemiluminescence demonstrated that tea extracts of green, white, and black tea have considerable antioxidant activities due to the presence of catechins, theaflavins, thearubigins, and theanine [***41***].

Role of Catechins: Catechins have been reported to be one of the main antioxidants to support the nervous system against free radicals. The main factor involved in the neuroinflammation of almost all kinds of neurodegenerative diseases especially AD &

PD is the activation of microglia thus one of the effective methods for the survival of the neuronal cells is microglial inactivation [***15***]. Neuronal injury leads to the secretion of pro-inflammatory elements like cytokines, cytotoxic elements which trigger neuronal death [***42***]. Lee et al., in a study using lipopolysaccharide-injected mice (250 µg/kg/day for 1 week), demonstrated that pre-administration of EGCG (1.5 and 3 mg/kg for 3 weeks) prevented memory impairment in lipopolysaccharide-induced mice and suppressed the levels of cytokines and inflammatory proteins seen in non-treated controls [***43***]. Another in vitro study of BV-2 microglia showed that EGCG successfully inhibits the reactions related to lipopolysaccharide-induced inflammation which mainly involves the production of nitric oxide, expression of cyclooxygenase-2, and inducible nitric oxide synthase expression [***44***]. Catechins have shown to attenuate 6-hydroxydopamine (6-OHDA)-induced oxidative stress in rats and SH-SY5Y cells which in turn increases glutathione and tyrosine hydroxylase levels, reducing the content of free radicals as well as regulating ROS-(nitric oxide) NO pathways [***45, 46 47***]. 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a neurotoxin that causes symptoms similar to PD by destroying the neurons which produce dopamine in the substantia nigra. EGCG has been shown to reduce MPTP-induced oxidative damage to PD mice and the possible mechanism associated might be the inhibition of expression level of inducible nitric oxide synthase (iNOS) [***48***]. The two main pathological characters associated with AD involve the accumulation of Aβ and tau protein, however, aggregated α-synuclein within the pars compacta of the substantia nigra is the main characteristic feature of PD. In recent years, increasing shreds of evidence suggest that metal ions are the major reason behind the deposition of Aβ and hyperphosphorylation of tau, leading to the formation of neurofibrillary tangles and amyloid plaques in the development of AD [***49***]whereas in PD patients the level of iron increases in the substantia nigra pars compacta (SNpc) [***50***]. Epidemiological evidence demonstrated that EGCG can effectively chelate metals, as EGCG possesses 3',4'-dihydroxyl, and gallate groups in the B and C rings, respectively. Thus, ferric metal may be neutralized to an inactive form and may inhibit metal-induced oxidative stress that then protects the neuronal cells against damage [***51, 52***]. It has also been reported that to reduce the toxic levels of Aβ EGCG in presence of an iron-responsive element regulates amyloid precursor protein (APP) [***52***]. Hung et al, using electrochemical measurements found that EGCG along with other flavonoids can chelate copper and can be a potent metal chelator in the treatment of AD & PD [***53***]. Okadaic acid (OA) is a toxin that mainly causes neurotoxicity and green tea catechins have been reported to reduce OA-induced primary hippocampal neuron damage [***54***]. In "Swedish" mutant Aβ precursor protein (APP) overexpressing mice, it was found that intraperitoneal injection (20 mg/kg) of green tea EGCG decreases the levels of Aβ and formation of plaques by promoting the non-amyloidogenic α-secretase proteolytic pathway[***55***]. Proapoptotic (p53 and Bax), Bcl-XL, and cyclooxygenase (COX) proteins have been implicated in Aβ-induced neuronal death. The protective effects of EGCG are considered to be independent of the regulation of p53, Bax, Bcl-XL, and COX proteins. This suggests that EGCG has protective effects against Aβ-induced neuronal apoptosis by scavenging ROS, which is beneficial for the prevention and slowing of AD [***56***]. An important Aβ-degrading enzyme is Neprilysin (NEP) found in the brain which indicates that defective enzyme expression may facilitate deposition of Aβ in sporadic late-onset AD patients. Cultured rat astrocytes treated with EGCG have shown a significant reduction in the expression of NEP in a concentration- and time-dependent manner. The expression of NEP in cultured astrocytes was suppressed due to activation of extracellular signal-regulated kinase (ERK) and PI3K. Reduced NEP expression was accompanied by an increase in NEP release into the extracellular medium. The culture medium from EGCG-treated astrocytes facilitated the degradation of exogenous Aβ, suggesting that EGCG may have a beneficial effect on persons with AD by activating ERK- and PI3K-mediated pathways in astrocytes, thereby increasing astrocyte secretion of NEP and facilitating degradation of Aβ [***57***]. An array of protective effects initiated by green tea catechins involves attenuation of 6-OHDA-induced early apoptosis, prevention of the decrease in mitochondrial membrane potential, suppression of intracellular free Ca2+ accumulation, and scavenging of free radicals (reactive oxygen species, ROS) in a dose- and time-dependent manner towards successful treatment of Parkinson's disease[***47***].

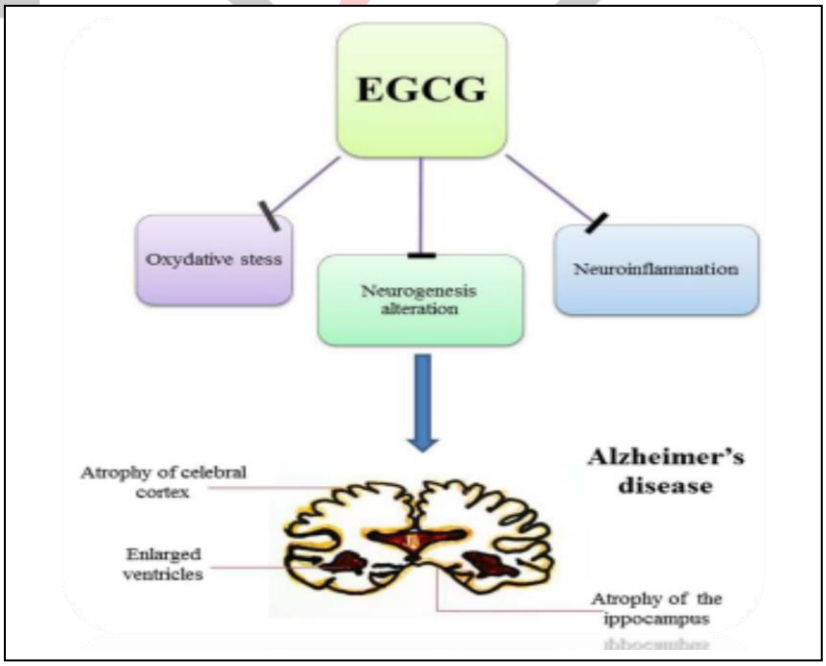

Fig 10: The potential effects of EGCG in Alzheimer's pathogenesis (*source: Cascella et al, 2017)*.

Role of Theanine: L-Theanine (-glutamyl ethyl amide), an amino acid predominantly present as well as unique to tea, has recently received attention due to its neuroprotective properties. The chemical structure of L-theanine resembles that of glutamate which is an essential component in protein biosynthesis as well as an excitatory neurotransmitter, playing an important role in memory and learning by producing synaptic plasticity, known as long term potentiation (LTP) [***58***]. The glutamic acid is released by neuronal cells as a transmission of impulse which contributes to signal transduction via stimulation of the glutamate receptors as well as the opening of ion channels [***59***]. The glutamic acid is then taken into glial cells by glutamate receptors and there the glutamic acid gets transformed into glutamine by glutamine transporters which again get transferred to neurons where this glutamine again gets transformed to glutamic acid. However, when the intracellular energy source ATP is depleted due to injury like ischemia, depolarization of the neuronal membrane occurs which leads to the release of excessive glutamic acid and lack of ability to reabsorb this glutamic acid by the glutamate transporter, results in an excessive concentration of glutamic acid in the extracellular space. This excessive glutamic acid binds to N-methyl-D-aspartate (NMDA) and non-NMDA receptors in the postsynaptic membrane leading towards increased cell permeability to Ca2+. A high concentration of free Ca2+ is thought to cause neuronal death by abnormal activation of various enzymes in the cell or by increasing the number of superoxide radicals [***60, 61, 62***]. Theanine is a natural glutamate antagonist which protects as well as prevents neuronal death when the cells were exposed to theanine [***63***]. The death of hippocampal CA1 (Cornus ammonis) pyramidal neurons by transient forebrain ischemia and the death of the hippocampal CA3 region by kainate was prevented by the administration of Theanine[***64***]. Being structurally similar to glutamate and glutamine, L-theanine exerts its neuroprotection by inhibition of substrate-binding in AMPA (IC50= 24.6 ± 0.9 μM), kainate (IC50= 41.5 ± 7.6 μM) and NMDA-glycine (IC50= 0.011 ± 0.002 μM) receptors thus causing favorable downregulation of glutamate exotoxicity[***65***]. L-theanine is capable of regulating overall glutamate synthesis and inhibits the transportation of glutamine in neurons and glial cells as it also binds and influences group I metabotropic receptors (mGluRs) having a direct effect in the glutamatergic pool [***66,67***]. Most importantly, L-theanine can inhibit neuronal death by glutamate excitotoxicity and promote dopaminergic neuronal survival thus aids towards a potent therapeutic agent in the treatment of PD. L-DOPA (L-3,4-dihydroxyphenylalanine) the amino-acid precursor of the neurotransmitter dopamine is currently one of the most effective drugs available for symptomatic treatment of patients with PD though it has adverse side effects which become evident after a particular duration of treatment [***68,69***]. The most common side effect observed in Parkinsonian patients treated with L-DOPA is Dyskinesia. The underlying mechanism behind L-DOPA-induced dyskinesia (LID) is still not clear, but recent epidemiological evidence disclosed that one of the pathophysiological changes involved in the development of dyskinesia is excessive release of striatal glutamate [***70***]. Experimental observation in dyskinetic MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) primates showed that Long-term administration of L-DOPA alters striatal NR2B subunit of NMDA receptors via up-regulation of it [***71***]. In another experiment 6-hydroxydopamine, lesioned rats exhibited symptoms resembling PD, where studies on the binding of the receptor demonstrated a significant increase in the expression of NR2B subunit after a regular administration of L-DOPA [***72***]. These kinds of experimental outcomes indicated a positive beneficial treatment strategy against LID as L-theanine shows an antagonistic effect on glutamate receptors. Kim et al. in an *in-vitro* experiment observed the effects of L-theanine on rotenone and dieldrin-induced neurotoxicity. These are environmental toxins that are responsible for the etiology of Parkinson's disease. L-theanine was found to attenuate the toxin-induced DNA fragmentation as well as apoptosis, and up-regulation of haem oxygenase. Pretreatment with the amino acid has been shown to block the toxin-induced down-regulation of ERK1/2 and BDNF in SH-SY5Y cells [***73***]. Theanine has also shown to exert its neuroprotective effect in case of Alzheimer's disease as Di et al. in his in-vitro experiment showed that administration of Theanine attenuates glutamate-induced amyloid β neurotoxicity, as well as apoptosis in human APP transgenic SH-SY5Y cells as well as it, suppressed the activation of c Jun N-terminal kinase, caspase-3[***74***].

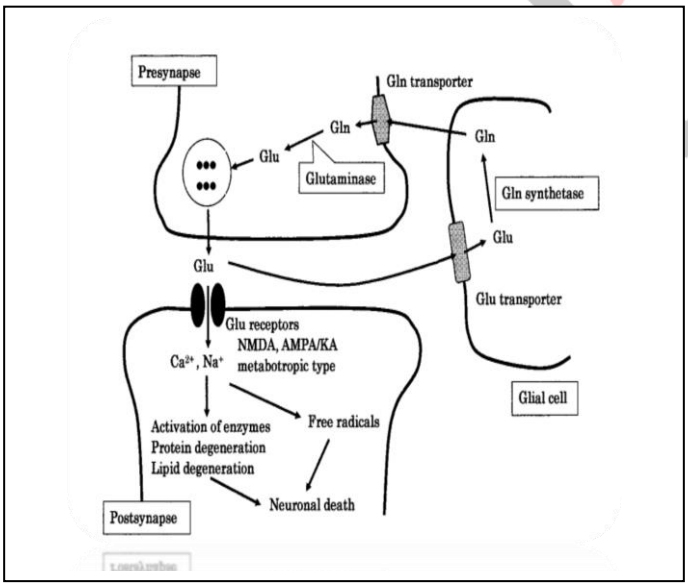

Fig 11: A Schematic Depiction of the Glutamate Receptor, Glutamine/Glutamate Cycle, and Neuronal Death (*source: Kakuda et al., 2002*).

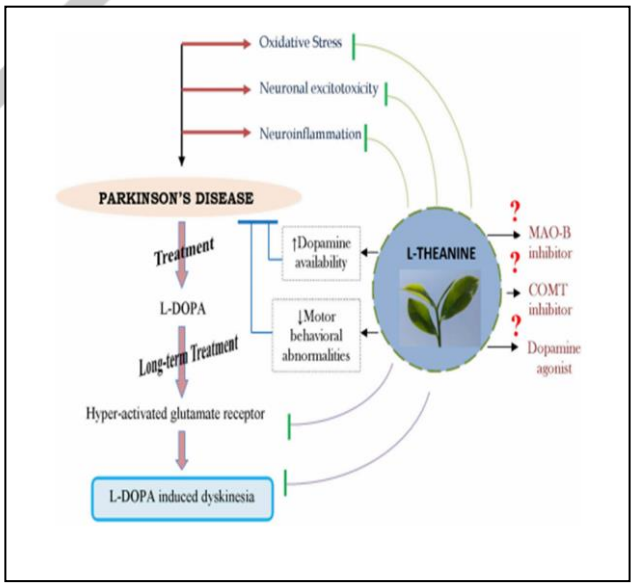

Fig 12: Probable mechanism of action of L-Theanine with relevance to Parkinson's disease pathology (Source: *S. Deb et al., 2019*).

Role of Caffeine: Caffeine (1,3,7-trimethylxanthine) is the major pre-dominant purine-based alkaloid present in tea among all the other alkaloids and is much known for its psychostimulant activities.it has been proven that caffeine is a good antioxidant as it scavenges free radicals(ROS) as well as inhibits lipid peroxidation[***75***]. The chronic administration of caffeine has been shown to ameliorate oxidative stress along with improved mitochondrial functioning in various neurotoxic situations [***76***]. Ullah et al. in an experiment using a rat model demonstrated that caffeine can reverse oxidative stress as well as to attenuate inflammation induced by D-galactose which causes aging of rat brains [***77***]. Caffeine is a structural antagonist of adenosine as both of them possess purine backbones which allow caffeine to bind with the adenosine receptors (ARs) as a competitive antagonist [***78***]. The adenosine receptors (A1R, A2AR, A2BR, and A3R) are mainly G-protein coupled receptors that are expressed in a variety of cells including the microglia, the striatum, and spinal cord of the central nervous system [***79, 80***]. Now the receptors of A2AR, A2BR are coupled to stimulate with Gs proteins whereas the receptors of A1R and A3R are coupled to inhibit Gi proteins respectively. The simultaneous activation and inhibition process of these proteins leads to activation and inhibition of neuronal excitability [***81, 82***]. In an experimental model of ischemia-reperfusion (IR), the A2AR antagonist i.e. caffeine significantly reduced the levels of glutamate protein as well as inhibited activation of pERK thus lowering the downstream hippocampal inflammatory response [***83***]. Along with it caffeine also reduced the levels of pro-inflammatory biomarkers like nuclear factor (NF)-κB, TNF-α, interleukin (IL)-6, and prostaglandin E2 as well as increased the anti-inflammatory biomarker IL-10 [***84***]. Furthermore, the inhibition of A2AR promotes neurotransmission of dopamine by enhancing the affinity of dopamine D2 ligands to D2 receptors [***85***]. In another study, caffeine has been shown to induce an increase in specific cellular endopeptidase (NEP) activity in neuroblastoma cell line SK-N-SH, and activity of it was stronger than the other two alkaloids of i.e. theophylline and theobromine and the amino acid Theanine[***86***]. The beneficial effects of Caffeine in the treatment of AD are associated with its interaction with β- and γ-secretase. In a study conducted by Arendash et al, it was found that APPsw mice treated 1.5 mg/d of caffeine showed a reduction in the deposition of Aβ in the hippocampus by 40% and in the entorhinal cortex by 46%. With caffeine, the levels of Aβ1-40 and Aβ1-42 were reduced in the cortex by25% and 51%, respectively, and in the hippocampus by 37% and 59%, respectively [***87***]. Caffeine consumption in humans at a dose equivalent to 500 mg causes a reduction in activation of NF-κB pathway, c-Raf-1, and production of BACE-1 in APPsw mice. Furthermore, GSK-3 is known to regulate Aβ production. It is also involved in the activity of presenilin (PS)-1 and γ-secretase as well as tau hyperphosphorylation. The concentration of Caffeine at 10-20 μmol/L decreases the GSK-3α and GSK-3β which in turn decreases Aβ levels [***87***]. 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is a neurotoxin that when converted to MPP+ can effectively cross the blood-brain barrier where it specifically binds with dopaminergic receptors[***88***]. There it causes severe energy crisis by inhibiting the complex I of the electron transport chain thus leading towards cell death and hence causing insufficiency of dopamine in the striatum. The neurotoxicity caused by MPTP also leads to microglial proliferation and severe neuroinflammation thus MPTP is an excellent model for neurodegeneration in PD [***89***]. In male PD mice Caffeine intake for 8 days at 0.9 mg/d, 30 minutes prior to MPTP administration attenuated neuron damage and improved motor function by 60.6% expressed by improvement in grip strength [***89***]. Another study found that pretreatment with caffeine attenuated MPTP-induced dopamine loss by 38%as compared to the control dopamine levels without caffeine in a dose-dependent manner in young male mice [***90***].

In an experimental AD mouse model, activation in upregulation of A2AR causes the abolishment of long-term synaptic potentiation (LTP) in CA3 pyramidal cells whereas the A2AR antagonists i.e. caffeine reverts the inhibition of LTP which provides theoretical support for treatment of AD patients at the onset of the disease [***91***].Furthermore deletion of A2AR or A2AR caused by treatment with their antagonist significantly improved memory in the THY-Tau22 mouse model [***92***]. Pretreatment with caffeine exerts protection against Aβ and AlCl3 induced damage to SH-SY5Y cells via inhibition of A1R and A2AR [***93***]. More interestingly, caffeine has proven to increase neuronal viability as it is a positive modulator of NMNAT2 i.e. nicotinamide mononucleotide adenylyltransferase 2 which is mainly required for the growth and survival of axons, and in AD patients the level of NMNAT2 decreases. Caffeine in both in vitro and in vivo has been shown to restore the expression of NMNAT2 to normal levels thus it exerts protection against neuronal damage [***94,95***].

Role of Theaflavin: Theaflavins are the major black tea pigments resulting from oxidation of the catechins and are mainly comprised of four major TFs - Theaflavin(TF), Theaflavin 3-monogallate(TF3G), Theaflavin 3'-monogallate(TF3'G), and Theaflavin3,3'-digallate (TF3,3'DG). Research evidence showed that TFs are good antioxidants as they actively scavenge free radicals as well as are good metal chelators. Anandhan et al in their experiment, using MPTP/p lesioned animal models showed the protective effects of TFs against MPTP animals. In that experiment, the locomotor activities of the MPTP/p group involving peripheral, central movements, rearing, and grooming activities significantly decreased whereas the locomotion and rearing activities of the MPTP/p+TF (10 mg/kg) group significantly increased when compared to the MPTP/p group [***96***]. The Chronic treatment with MPTP/p shows a significant increase in the release of anti-inflammatory cytokines IL-1b, TNF-a, IL-6, IL-4, and IL-10 in the striatum. When treated with TF the release of cytokines decreases significantly. This indicates the protective effect of TF against MPTP-induced neurotoxicity by a reduction in the inflammatory response to MPTP [***96***].MPTP being a neurotoxin causes dopaminergic neurodegeneration, as well as activation of microglia in human brains thus MPTP, treated animals are widely used as animal models of PD, and treatment with TFs confers neuroprotection against neurotoxic effects of MPTP [***97,98***]. Thus TFs prove to be a potent therapeutic drug against neuroinflammation and apoptosis-associated progression of PD. TFs also prevent neurotoxicity induced by Aβ and α-synuclein as well as protect PC12 cells from H2O2induced oxidative stress. Furthermore, pretreatment with TFs in a dose-dependent manner causes prevention of apoptosis of SH-SY5Y cell induced by 6-OHDA, by inhibition of production of ROS and NO [***99,100,101***].

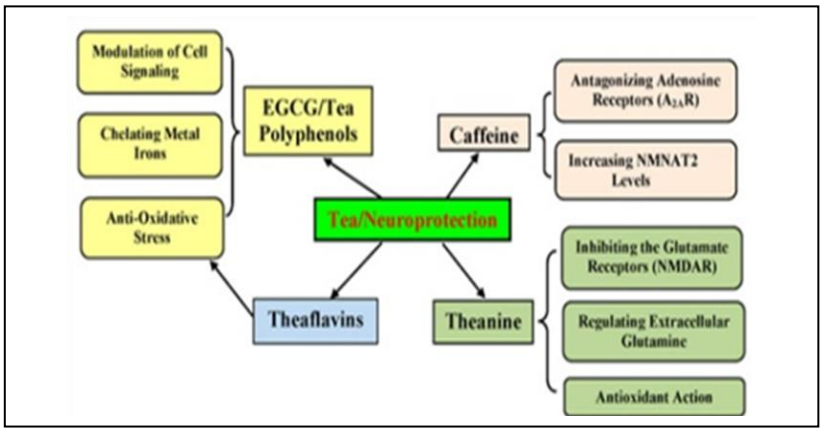

Fig 13: Neuroprotective mechanism of tea *(Source: Chen et al., 2018)*.

Role of other bioactive components of tea: Apart from the neuroprotective effects of the tea polyphenols, caffeine, theanine & theaflavins, the other bioactive components of tea like rutin, quercetin also plays a significant role in conferring protection against neuronal disorders. Rutin is a glycosylated flavonoid represented by a disaccharide that can inhibit mitochondrial damage by attenuating oxidative stress as well as decreases TNF-α and IL-1β generation in microglia thus modulates the production of proinflammatory cytokines [***102***]. Rutin exerts its neuroprotective effect by inhibiting lipopolysaccharide (LPS) or interferon-γ (IFNγ) induced microglial activation [***103***]. In a classic in vitro model of Parkinson disease rutin has been shown to inhibit neurotoxicity induced by 6-OHDA in PC-12 cells via an increase in the levels of antioxidant enzymes and modulation of multiple protective genes, especially by suppressing Park2, Park5, Park7, Casp3, and Casp7 [***104,105***]. Quercetin, another flavonoid of tea is also known to be a neuroprotective agent as it blocks the production of reactive oxygen species (ROS) as well as prevents lipid peroxidation thus inhibiting oxaliplatin-induced neurotoxicity [***106***]. The combined action of quercetin along with desferrioxamine reduces 6-HODA-induced oxidative stress and neuronal damage via an increase in the antioxidative defense system which mainly involves an increased level of glutathione (GSH) and the enzyme superoxide dismutase (SOD) as well as an increased level of dopamine in the striatum [***107***]. In the transgenic AD mice model (3 9 Tg-AD), quercetin showed a significant effect by decreasing extracellular β-amyloidosis, tauopathy, astrogliosis, and microgliosis in the hippocampal region. The results of this study were supported by reduced levels of paired helical filament (PHF), b-amyloid (bA) 1-40, and bA 1-42 and a decreased BACE1- mediated cleavage of APP [***108***]. Many of the researches are focused on the affectivity of a single component of tea but tea is composed of various bioactive components and when consumed the bioactive components act synergistically. So the affectivity of the synergistic action of the various bioactive components like the catechins, caffeine, Theanine, and others remains under the veil and needs to be elucidated.

CONCLUSION

As summarized in the article, all the available data (*in-vitro*,*in-vivo*) indicated the emerging and promising role of the different bioactive components of tea as potential therapeutic agents in combating different neurodegenerative disorders particularly AD and PD. Many of the experiments highlighted mechanisms by which the different bioactive components (EC, EGCG, Theanine, Caffeine, TFs, Aglycones) exerts protection against neurotoxicity. The bioactive components not only protect from neurotoxicity induced by oxidative stress but also modulate different signaling cascades, anti-apoptotic processes as well as showed anti-amyloid effects. The anti-amyloid activities are most important in treating Alzheimer's disease and the mechanisms by which these bioactive components exert their protection involves prevention of Aβ induced protein misfolding and membrane damage, inhibition of cleavage of APP by regulating the related enzymes, suppression of aggregation of Aβ oligomers, inhibition of hyperphosphorylation of TAU protein, etc. in case of the other neuronal disorders L-theanine has proven to combat glutamate toxicity whereas caffeine has shown to combat neuroinflammation induced by MPTP in PD. In conclusion, this review aimed to summerize the available information about the various neuroprotective properties ascribed to the various bioactive components of tea as well as to unlock the link between consumption of tea and prevention of different neurodegenerative disorders so that the elucidated mechanism of action of these compounds provide a new insight in the development of a potent neuroprotective drug.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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