Tea Polyphenols in Parkinson's Disease

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Mario Caruana and Neville Vassallo

Abstract

Parkinson's disease (PD) is a common motor neurodegenerative disorder with multifactorial etiology that is an increasing burden on our aging society. PD is characterized by nigrostriatal degeneration which might involve oxidative stress, α-synuclein (αS) aggregation, dysregulation of redox metal homeostasis and neurotoxicity. Although the exact cause remains unknown, both genetic and environmental factors have been implicated. Among the various environmental factors tea consumption has attracted increasing interest, as besides being one of the most consumed beverages in the world, tea contains specific polyphenols which can play an important role in delaying the onset or halting the progression of PD. Green and black teas are rich sources of polyphenols, the most abundant being epigallocatechin-3-gallate (EGCG) and theaflavins. There is now consistent mechanistic data on the neuroprotective and neuroregenerative effects of tea polyphenols, indicating that they do not just possess anti-oxidant or anti-chelating properties but may directly interfere with aggregation of the αS protein and modulate intracellular signalling pathways, both *in vitro* and in animal models. EGCG in green tea has been by far the most studied compound and therefore future investigations should address more the effects of other polyphenols, especially theaflavins in black tea. Nevertheless, despite significant data on their potential neuroprotective effects, clinical studies are still very limited and to date only EGCG has

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N. Vassallo (ed.), *Natural Compounds as Therapeutic Agents for Amyloidogenic Diseases*,
Advances in Experimental Medicine and Biology 863, DOI 10.1007/978-3-319-18365-7_6

reached phase II trials. This review collates the current knowledge of tea polyphenols and puts into perspective their potential to be considered as nutraceuticals that target various pathologies in PD.

Keywords
Parkinson's disease • Alpha-synuclein • Tea • Epigallocatechin-gallate • Theaflavins • Neuroprotection

6.1 Introduction

Parkinson's disease (PD) is the most common movement disorder and after Alzheimer's Disease (AD), the second most frequent progressive neurodegenerative disease (Toda 2007). The prevalence of PD worldwide ranges from 0.5 to 4 % among people aged 65 years or older. This figure is expected to rise significantly with the accelerated aging of human society (de Lau and Breteler 2006). In fact, it was predicted that by 2030, the number of PD sufferers will reach 9.3 million (Dorsey et al. 2007). PD is a debilitating disorder with varying patterns of degeneration in the dopaminergic and nondopaminergic neuronal systems (Braak et al. 2004). The major symptoms of PD include muscular rigidity, uncontrollable resting tremor, bradykinesia or akinesia, and impaired postural reflexes (Jankovic 2008). PD is distinguished from other forms of parkinsonism by the presence of Lewy bodies (LBs) and Lewy neurites (LNs), which are juxtanuclear and neuritic ubiquitinated protein aggregates composed predominantly of the presynaptic protein α-synuclein (αS) (Shults 2006). The etiology of PD in most patients remains unknown. It is assumed that both genetic and environmental factors with complex interactions are responsible for the development and progression of the disease (Fig. 6.1; Logroscino 2005).

The pathogenesis and relative selectivity of death of dopaminergic neurons in the substantia nigra (SN) *pars compacta* remains to be clarified (Kazantsev and Kolchinsky 2008). Various pathogenic mechanisms have been proposed through which dopamine-releasing neurons may be damaged in PD. These include deficiency in mitochondrial respiratory chain function (Fukae et al. 2007), apoptosis (Hartmann and Hirsch 2001), transition metal accumulation (Barnham and Bush 2008), oxidative stress (Friedman and Galazka-Friedman 2001), deficiency in the xenobiotic mechanism (Ramsden et al. 2001), inflammation (McGeer et al. 2001), and abnormal protein handling, aggregation and misfolding (Skovronsky et al. 2006). The most favoured ones are oxidative stress due to an increased production of reactive oxygen species (ROS), and cell toxic effects of αS protein aggregation and deposition, both finally leading to neuronal cell death by apoptosis (Soto 2003). Regardless of the cause of neuronal death, the plasticity of the *pars compacta* is very robust; symptoms do not appear until 50–80 % of SN dopaminergic neurons have died. Therefore, it is not surprising that diagnosis in the early course of disease is more than rare (Jankovic 2008).

The results of studies on twins suggested that genetic factors are important in early-onset PD cases while environmental factors play a predominant etiologic role in late-onset PD patients, thus implying the importance of non-genetic factors (Tanner et al. 1999; Wirdefeldt et al. 2004). Environmental factors such as coffee drinking and smoking have been demonstrated to lower the risk of PD (Hernan et al. 2002; Costa et al. 2010; Wirdefeldt et al. 2011). The effects of tea consumption on PD risk are currently the subject of considerable scientific debate as tea components, such as polyphenols, caffeine, and theanine, have been demonstrated to be neuroprotective in PD (Tan et al. 2008; Quintana et al. 2009). The benefits of tea drinking are of relevance to PD as tea is one of the main contributors of dietary polyphenols in Western countries due to its regular consumption (Erdman et al. 2007).

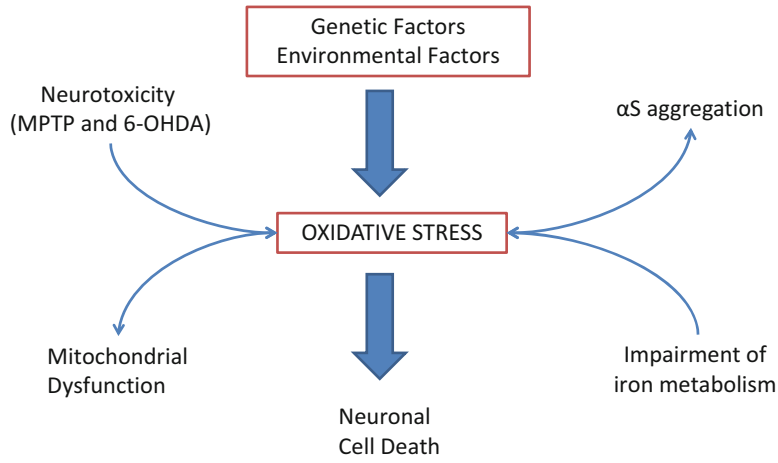

Fig. 6.1 Factors that contribute to oxidative stress and ultimately neuronal cell death in PD (*MPTP* N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, *6-OHDA* 6-hydroxydopamine, *αS* alpha-synuclein)

Thus, any evidence of the neuroprotective effects of polyphenols on PD could have a significant impact on public health. The purpose of this chapter is to provide a concise review of the most recent scientific evidence from epidemiological, experimental and clinical studies on the crucial role green and black tea polyphenols may have in the prevention and treatment of PD.

6.2 Polyphenolic Components of Tea

Tea has been consumed as a beverage for well over 2,000 years, and its worldwide consumption is perhaps second only to water. The term 'tea' refers to the dried leaves of the plant *Camellia sinensis*, an evergreen shrub of the *Theaceae* family. The three principal varieties of tea are generally categorized by the process used in their manufacture: (i) fermented (oxidized) black tea (78 %, mainly consumed in Western Europe, the United States of America, Australia, and some Asian countries); (ii) unfermented (non-oxidized) green tea (20 %, mainly consumed in China, Japan, and India); and (iii) semi-fermented (semi-oxidized) oolong tea (2 %, consumed in south-eastern China and Taiwan) (Fig. 6.2; Graham 1992; Balentine et al. 1997). Another commonly used tea is the so-called 'herbal tea'. Herbal tea is made from any of a number of a variety of plants and herbs, and therefore, cannot technically be considered a true type of tea.

While tea consists of over 2,000 different chemical substances such as methylxanthine, caffeine, lipids, amino acids, mineral substances and volatile compounds, polyphenols are the most abundant (Wheeler and Wheeler 2004). Polyphenols are a diverse class of plant secondary metabolites and more than 8,000 polyphenolic compounds have currently been identified (Porat et al. 2006; Stevenson and Hurst 2007). Polyphenols are classified into different groups depending on the number of phenol rings and the chemical groups attached to the rings. They are characterised by a polyphenol structure, which generally consists of two aromatic rings (2-phenyl-1,4-benzopyrone) each containing at least one hydroxyl group, which are connected via a three-carbon bridge and become part of a six-member heterocyclic ring (Fig. 6.3; Beecher 2003; Porat et al. 2004; D'Archivio et al. 2007). Polyphenols can be divided into two main groups, the flavonoids and the non-flavonoids, with the flavonoids making up the largest and most important single group of polyphenols present in tea (Vassallo 2008). Black and green teas both contain similar amount of flavonoids, however they differ in their chemical structure. Green teas contain more of the simple flavonoids called flavanols (known also as catechins or flavan-3-ols). The principal four flavanols found in green tea are epicatechin (EC), epicatechin 3-gallate (ECG), epigallocatechin (EGC) and epigallocatechin-3-gallate (EGCG), where the latter is the most abundant (Rietveld

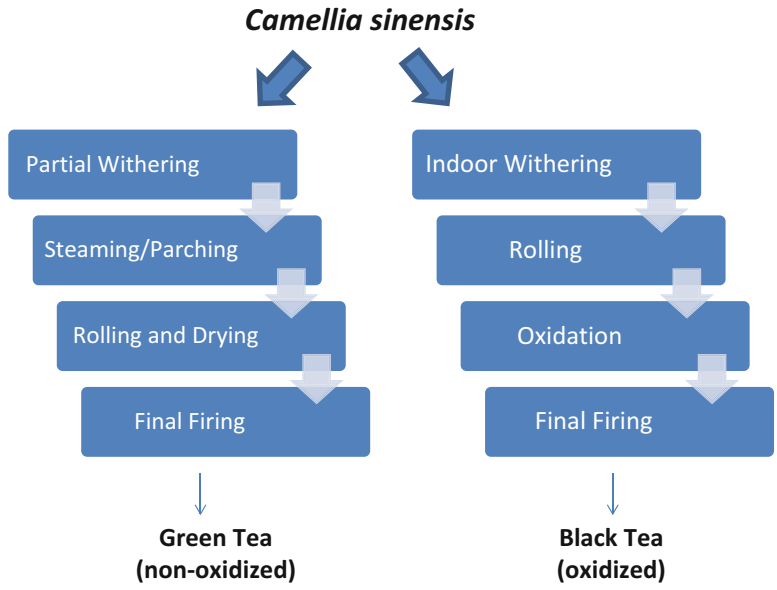

Fig. 6.2 Green and black tea processing. Tea is produced when freshly picked leaves are steamed, rolled and dried. Tea leaves contain polyphenol oxidase enzymes in separate layers of the leaf. When tea leaves are rolled or broken during industry manufacture, polyphenols known as flavanols (catechins) come in contact with polyphenol oxidase, resulting in their oxidation and the formation of flavanol dimers and polymers known as theaflavins and thearubigins. Tea leaves destined to become black tea are rolled and allowed to ferment (oxidize), resulting in relatively high concentrations of theaflavins and thearubigins and relatively low concentrations of flavanols. Green tea is withered and then steamed to inactivate polyphenol oxidase. Consequently, green tea contains relatively high concentrations of flavanols and low concentrations of theaflavins and thearubigins (Graham 1992; Balentine et al. 1997)

and Wiseman 2003). The oxidisation that the leaves undergo to make black tea converts these simple flavonoids to the more complex varieties called theaflavins and thearubigins (Khokhar and Magnusdottir 2002). The chemical composition of tea (Table 6.1) varies with the variety of plant and age of the leaf, the conditions under which it is grown, climate, season, and local agricultural practices (Aherne and O'Brien 2002).

Research interest in the benefits of tea drinking stems primarily from the presence of polyphenols which are believed to be the major component that provide health benefits (McKay and Blumberg 2002; Erdman et al. 2007). One cup of tea (2 g of tea leaves infused in hot water for 1–3 min) will provide 0.15–0.2 g of flavonoids. As little as 2–3 cups/day of tea will therefore supply a significant contribution to the total flavonoid intake in most individuals, which is estimated to average 1 g per day (Frei and Higdon 2003). In fact, it was estimated that black tea contributes 60–84 % of dietary flavonoids in Western populations (Hertog et al. 1993; Chun et al. 2007) and it has been reported that flavonoid intakes in tea consumers are twenty times greater than in non-tea consumers (Song and Chun 2008). This intake is higher than all other known dietary anti-oxidants, estimated to be around ten times higher than the daily intake of Vitamin C, and 100 times higher than that of Vitamin E and carotenoids (Scalbert and Williamson 2000). As the total polyphenol content of green and black teas is similar, it can be assumed that the impact on plasma levels post-consumption remains fairly the same (Rietveld and Wiseman 2003).

6.3 Epidemiological Studies on Tea Consumption and PD

In the 1980s, PD prevalence was found to be low in Asian countries when compared to Europe and North America, which had significantly higher

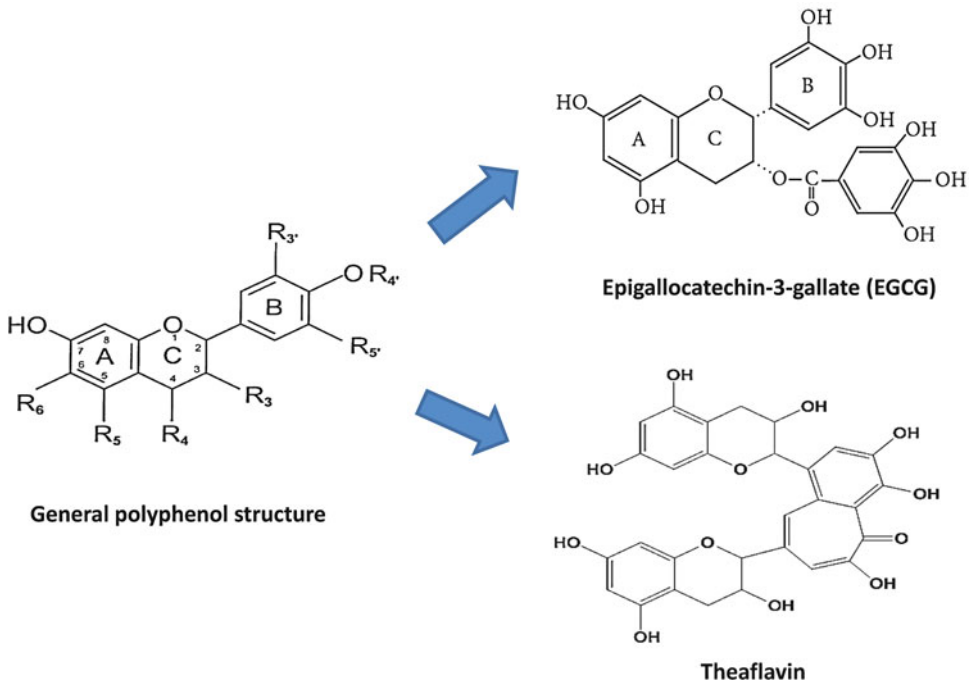

Fig. 6.3 General structure and numbering pattern for polyphenols. This figure shows the general structure and numbering pattern for common polyphenols. Every flavonoid subclass has its own unique linkages, unsaturation positions and functional groups. For most food flavonoids, R4′ = H, R5 = OH and R6 = H. Individual flavonoids within each subclass are characterised by unique functional groups at R3, R3′, and R5′. Chemical structures of epigallocatechin-3-gallate (EGCG) and theaflavin in green and black tea are shown. EGCG contains three heterocyclic rings (*A*, *B*, *C*) and the free radical scavenging property of EGCG is attributed to the presence of a trihydroxyl group on the B-ring and the gallate moiety at the 3′ position in the C-ring. Theaflavin is the polymeric form of EGCG

rates (Li et al. 1985; Zhang and Román 1993). Apart from genetic factors, dietary habits like green tea consumption, which is more consumed by the Chinese population when compared to Caucasian, could explain this attribute (Pan et al. 2003; Gao et al. 2012). Due to this possible link, in recent years, there were more studies devoted to exploring the effects of tea consumption on PD risk. Three case–control studies (in the US, Hong Kong and Singapore) and a cohort study of male health professionals in the US have all reported an inverse association between tea drinking and PD risk (Chan et al. 1998; Checkoway et al. 2002; Tan et al. 2003). One study found such an effect for men but not for women (Ascherio et al. 2001). On the other hand, a hospital based case-control study in France reported tea consumption to be a paradoxically risk factor for PD (Preux et al. 2000).

The authors attributing the protective effect of tea suggested caffeine as the main contributor. Similarly, a biologic effect of caffeine was suggested for a positive association of tea drinking and PD in a prospective study of over 29,000 Finnish adults for 13 years (Hu et al. 2007). In another prospective study of 63,000 Chinese adults, black tea showed an inverse association with PD risk, although this time the link was not confounded by total caffeine intake or tobacco smoking (Tan et al. 2008). Surprisingly in this study, green tea consumption after adjustment for cigarette smoking and total caffeine consumption was unrelated to PD risk. The authors speculated that the protective effect of black tea may be mediated via an estrogen-related pathway. This was based on what they had reported earlier that among the women in their study cohort, levels of circulating estrogens were highest in

Table 6.1 Average values for the different constituents present in green and black tea

	Black tea	Green tea
Catechins	3–10	30–42
Theaflavins	3–6	Negligible
Thearubigins	12–18	Negligible
Flavonols	6–8	5–10
Theogallin	Negligible	2–3
Phenolic acids (caffeic acid)	10–12	1–2
Theanine	Negligible	4–6
Other amino acids	13–15	4–6
Methylxanthines	8–11	7–9
Carbohydrates	15	10–15
Protein	1	Negligible
Minerals	10	6–8
Volatiles	<0.1	0.02

The values will differ dependent on the variety of leaf, growing environment, manufacturing, particle size of ground tea leaves and infusion preparation (Graham 1992; Harbowy and Ballentine 1997; Wang and Helliwell 2001; Astill et al. 2001)
Values reflect % weight of extract solids

regular black tea drinkers, intermediate in non-tea drinkers, and lowest in regular green tea drinkers; these differences were dose-dependent and significant (Wu et al. 2005).

It was suggested that the average 1.2 l of green tea consumed daily by many people in Asia offers sufficient anti-oxidants of the polyphenolic EGCG, and in turn reduces or cures diseases with an inflammatory component, together with improving neurologic and psychological health (Sumpio et al. 2006). In terms of a dose-response relationship, only few studies have stratified their results according to the number of cups of tea consumed daily. One study showed a dose-dependent protective effect of PD in tea consumers with an odds ratio (OR) of 0.48 for daily consumption of a cup of tea versus OR of 0.27 for daily consumption of two or more cups of tea (Fall et al. 1999), whilst another study showed a similar effect in coffee and tea consumers (Tan et al. 2003). In the latter study it was concluded that one unit of coffee or tea (three cups per day for 10 years) would lead to a 22 and 28 % risk reduction of PD, respectively. On the contrary, another study could not demonstrate such dose-dependent protective effect in their hospital based case-control study (Paganini-Hill 2001). More evidence was provided by an Israeli study of 278 PD patients whose motor symptoms appeared to be delayed by 7.7 years ($p < 0.01$) when they drank more than three cups of tea per day (Kandinov et al. 2009). Two recent systematic reviews showed that tea drinking can lower the risk of PD, but no apparent dose-response relationship was found as would be expected (Quintana et al. 2009; Li et al. 2012). The latter may arise from the fact that black tea and green tea differ markedly in the nature of their polyphenols and only few studies reported stratified results according to the types of tea. It is also important to note that the contents of the bioactive compounds in tea may fluctuate because of differences in producing areas, materials, and manufacturing (Crozier et al. 2009). While the addition of milk to tea does not seem to interfere with flavonoid absorption or activity (Hollman et al. 2001), it is not obvious if other factors do – such as the frequency and timing of tea intake in relation to meals, the addition of sucrose or lemon, and variations in gut microflora. Therefore, although a positive association has turned up repeatedly in epidemiological studies between tea and PD, a clear biologic basis for this phenomenon has yet to be identified.

When reviewing the literature, the strongest and most consistent environmental associations were those between cigarette smoking, coffee/tea drinking, and a reduced risk of PD as noted in several US and European populations (Tanner et al. 2002; Hernan et al. 2002; Ritz et al. 2007; Hancock et al. 2007; Saaksjarvi et al. 2008). However, the strength of the evidence for the described inverse associations seems to be weaker for tea than for smoking or coffee drinking. The precise reasons for this are not known, although tea has not been investigated in relation to PD risk as extensively or explicitly as coffee has – perhaps because consumption of coffee is far more prevalent in North America and Europe, where most research on PD has been undertaken.

Moreover, the selection of patients and the type of control groups, for example the inclusion of patients with preclinical stage of PD, may result in conflicting results (Schrag et al. 2002). It is unclear from epidemiological studies whether the active ingredient/s mediating this neuroprotective effect in tea is actually caffeine or the polyphenols in tea. In most cases, this work can only be conducted in experimental designs not least because practical and ethical constraints limit such research in humans.

6.4 Neuroprotective Actions of Tea Polyphenols in PD

6.4.1 Tea Polyphenols and *In Vitro* Studies

Numerous *in vitro* studies have clearly demonstrated that specific tea polyphenols might contribute to prevent PD pathology and act towards neuroprotective capacities (Levites et al. 2002a; Bastianetto 2002; Bastianetto and Quirion 2004). Cell culture studies have demonstrated that flavanols reduced damage produced by hydrogen peroxide (H_2O_2), 4-hydroxynonenal, rotenone, and 6-hydroxydopamine (6-OHDA) in primary rat mesencephalic cultures, as shown by increases in cellular viability and [^{3}H] dopamine uptake (Mercer et al. 2005; Vauzour et al. 2008). Other *in vitro* studies demonstrated that EGCG is able to rescue and reduce viability of neuroblastoma SH-SY5Y cells when administered up to 3 days after long-term serum starvation, a model of apoptotic damage (Reznichenko et al. 2005). As reviewed elsewhere, polyphenolic compounds provide neuroprotective effects through a variety of biological actions such as anti-oxidant, anti-chelating, anti-aggregating, anti-inflammatory, anti-carcinogenic, anti-viral, anti-microbial and anti-clotting activities (Scalbert et al. 2005; Ramassamy 2006; Rahman et al. 2007; Moon and Shibamoto 2009; Obrenovich et al. 2010; Albani et al. 2010; Choi et al. 2012). With regards to specific tea polyphenols, the most important plausible mechanisms cited that may be exhibiting neuroprotective effects in PD are: (i) anti-oxidant and anti-chelating activities; (ii) inhibition of αS aggregation; and (iii) modulation of cell signalling pathways (Pan et al. 2003; Higdon and Frei 2003; Amit et al. 2008), which will be reviewed in the next sections.

6.4.1.1 Anti-oxidant and Iron-Chelating Activity

Substantial evidence of the potent anti-oxidant effects of the main tea polyphenols (flavanols and theaflavins) comes from *in vitro* studies, where they were shown to: (i) directly scavenge reactive oxygen (ROS) and nitrogen oxygen (NOS) species; (ii) inhibit 'pro-oxidant' enzymes, such as nitric oxide synthase, xanthine oxidase, cyclooxygenases and lipoxygenases; (iii) inhibit redox-sensitive transcription factors such as nuclear factor-κB and activator protein-1; (iv) induce phase II and anti-oxidant enzymes such as glutathione S-transferases and superoxide dismutases; and (v) bind and chelate excess of divalent metals such as iron (Fe^{2+}) and copper (Haenen et al. 1997; Nakagawa and Yokozawa 2002; Higdon and Frei 2003; Stevenson and Hurst 2007; Aron and Kennedy 2008; Mandel et al. 2008; Perron and Brumaghim 2009; López-Lázaro 2009). The oxygen radical absorbance capacity (ORAC) assay has demonstrated that both green and black tea have much higher capacity against free radicals than vegetables, for instance garlic and spinach (Cao et al. 1996).

The capacity of polyphenols to act as anti-oxidants is dependent upon their molecular structure, the position of hydroxyl groups, and other substitutions in their chemical structure (Tsao 2010). Although the oxidisation process modifies the type of flavonoids present, the total level and their overall anti-oxidant activity, is similar in both teas (Leung et al. 2001; Luczaj and Skrzydlewska 2005). EGCG has an important anti-oxidant and iron-chelating function and this could be attributed to the 3′,4′-dihydroxyl group in the B-ring, as well as the gallate group which may neutralise Fe^{2+} to form redox-inactive iron, thereby protecting cells against oxidative damage (Fig. 6.3; Kumamoto et al. 2001). In addition, the feature of tea polyphenols as potent chelators

of transitional metals, such as iron and copper, is owed to the OH at position 3′ of the C-ring, the OH at positions 3′ and 4′ of the B-ring, or the three OH groups present in the gallol moiety of some polyphenols, such as EGCG and ECG (Nanjo et al. 1996). In a recent study examining the differential potency of a series of polyphenols to prevent DNA damage caused by Fe^{2+} and H_2O_2, it was found that among the 12 phenolic compounds tested, EGCG was the most potent, inhibiting over 90 % of the iron-mediated DNA break (Perron et al. 2008). By correlating the pK_a and IC_{50} values of phenolic compounds for inhibition of Fe^{2+}/H_2O_2-induced neurotoxicity, it was suggested that the binding of the polyphenols to iron was essential for their anti-oxidant activity (Perron et al. 2010). In one experiment performed on rat brain tissue, it was shown that lipid peroxidation was enhanced by iron ascorbate but inhibited in brain mitochondria by both black and green tea extracts (Jeong et al. 2004).

The anti-oxidant and metal-complexing properties of tea polyphenols may be of significance in the treatment of PD, since oxidative stress and accumulation of Fe^{2+} at brain areas associated with neurodegeneration have been clearly demonstrated (Zecca et al. 2004). The anti-oxidant activity could protect the dopaminergic system against free radicals, anion superoxide, lipid free radicals and hydroxyl radicals, together with neurotoxic apoptosis induced by hydroxydopamine in the cell (Weinreb et al. 2004). Also, at the central nervous system (CNS) level it may inhibit the peroxidation and lipid accumulation of Fe^{2+} compounds, and this could be the main mechanism for neuroprotection (Soto-Otero et al. 2000; Pan et al. 2004; Levites et al. 2002b). Nevertheless, it is currently more accepted that neuroprotective effects of tea polyphenols are only partly attributed to the free radical scavenging or metal chelating properties and that other properties such as targeting of specific signalling pathways and interaction with specific proteins, including αS, contribute to neuroprotection (Kaur et al. 2003; Masuda et al. 2006; Ramassamy 2006; Vafeiadou et al. 2007; Weinreb et al. 2010).

6.4.1.2 Inhibitory Activity on α-Synuclein Aggregation

Ample evidence suggests that disturbance of neuronal membranes by the soluble oligomers of the protein αS is a likely first step in the pathophysiological cascades of PD, where partial aggregated and oligomerized intracellular αS was shown to be cytotoxic and synaptotoxic (Periquet et al. 2007; Selkoe 2008). A considerable amount of scientific data shows that a possible neuroprotective characteristic of polyphenolic compounds is exerted through anti-aggregating properties (Caruana and Vassallo 2011). In relation to PD, such properties were initially tested *in vitro* on the inhibition of the assembly of αS into filaments/fibrils (Conway et al. 2001). For example, tea polyphenols such as EGCG and black tea extract, inhibited wild-type (WT) αS filament assembly and were also found to disaggregate preformed fibrils (Zhu et al. 2004; Porat et al. 2006; Masuda et al. 2006; Ono and Yamada 2006; Meng et al. 2010; Grelle et al. 2011). Recently, EGCG efficiently inhibited fibril formation of αS (Ehrnhoefer et al. 2008; Bae et al. 2010) and also transformed large αS fibrils into smaller non-toxic, amorphous protein aggregates (Hudson et al. 2009; Bieschke et al. 2010). Biophysically, EGCG was postulated to directly bind to unfolded polypeptide chains via hydrogen bonds and hydrophobic peptide backbone interactions, and inhibit beta sheet formation which is the early event in the amyloid formation cascade (Wang et al. 2010). Interestingly, this effect was evident only with flavanols carrying a gallate moiety with a high affinity for metals, such as ECG and EGCG. In this regard, another study showed that only gallate forms of flavanols were able to protect hippocampal cells against amyloid-induced toxicity (Bastianetto et al. 2006). Thus, it is possible that the anti-fibrillogenesis action of polyphenols would also result from an iron-complexing radical scavenging-mediated action.

Since it is hypothesised that small αS oligomers, rather than fibrils, may be the primary toxic species, it was also shown that polyphenolic compounds inhibit and destabilise early stage aggregates (Caruana et al. 2011). Interestingly *in vitro* studies have shown that

the anti-oxidant activities of such polyphenols are not likely to be directly involved in the inhibition progress (Zhu et al. 2004; Johnston and Brotchie 2004; Caruana et al. 2011). Specific structural features, rather than broad biochemical characteristics, determine the anti-aggregation effects of polyphenols. In fact, flavonoids with three vicinal hydroxyl groups exhibited enhanced inhibitory effects on αS aggregation (Meng et al. 2009; Berhanu and Masunov 2010; Caruana et al. 2011). Essentially, a polyphenolic inhibitor, with its polyaromatic nature is able to use aromatic recognition elements to bind the monomer/oligomer, whilst utilizing the vicinyl hydroxyl groups to electrostatically block the progress of the self-assembly process (Gazit 2002; Porat et al. 2006).

The lipophilicity of biologically active compounds is usually one of their most important pharmacological features, and interactions with membranes play an essential role in their biological activity (Hendrich 2006). It is well established that small αS oligomers can interact with and perturb membranes, thereby leading to cell death (Lashuel et al. 2002; Quist et al. 2005; Winner et al. 2011). Similarly, polyphenolic compounds, including tea polyphenols, interact with and alter lipid membranes (Blazovics et al. 2000; Oku et al. 2003; Chen et al. 2011; Duchnowicz et al. 2012; Sharma et al. 2012). Indeed, it was revealed that EGCG inhibits amyloid formation less efficiently at phospholipid interfaces than in bulk solution (Engel et al. 2012). Hence, it is relevant to know how polyphenolic compounds directly effect lipid membranes and how efficiently they can inhibit αS aggregation specifically at the phospholipid membrane interface. Furthermore, it has been established that tea flavanols can adsorb to membranes through associations with the polar headgroups of phospholipids and could protect the integrity of lipid bilayer from disrupting agents (Verstraeten et al. 2003; Sirk et al. 2008, 2011). Such polyphenol-lipid interactions may provide a level of protection for the bilayer from the αS oligomers (or/and monomer aggregation at the membrane surface), contributing to preserve the structure and function of biological membranes. Not many studies have to date examined the interaction of polyphenols with neuronal membranes and their protective effect on αS-induced membrane dysfunction. For example, black tea extract (80 % theaflavin) was found to strongly protect against membrane perturbation induced by aggregated WT and mutant αS (Caruana et al. 2012). Moreover, black tea extract inhibited permeation of mitochondrial membranes by αS oligomers (Camilleri et al. 2013). The importance of mitochondria in the pathogenisis of PD and the cytoxicity of oligomeric αS is extensively reviewed elsewhere, and tea polyphenols have been capable of protecting such insults (Büeler 2009; Camilleri and Vassallo 2014; Caruana and Vassallo 2014). Therefore, it is important that the intracellular effects of polyphenols at the membrane level are known, enhancing our understanding of the pharmacological and therapeutic activities of such bioactive compounds.

6.4.1.3 Modulation of Intracellular Signaling Pathways

While there has been a historical spotlight on the anti-oxidant properties of tea polyphenols, there is a general consensus that such flavonoids and their corresponding *in vivo* metabolites may also exert modulatory actions intracellularly through direct action on various signalling pathways in a concentration-dependent manner (Mandel et al. 2004; Williams et al. 2004; Ramassamy 2006; Campos-Esparza and Torres-Ramos 2010). Various inhibitory or stimulatory actions of tea polyphenols on these pathways have been studied, including phosphoinositide 3-kinase (PI3K), protein kinase B (Akt/PKB), protein kinase C (PKC), and mitogen-activated protein kinase (MAPK) (Levites et al. 2002b; Vauzour et al. 2007). The effects of tea polyphenols on signaling pathways in relation to PD will be reviewed briefly.

Most studies related to modulation of cell signalling pathways have been carried out on flavanols found in green tea, but not theaflavins. Table 6.2 summarizes cell signalling pathways targeted by different tea polyphenols. Protein kinase C (PKC) is the target of many flavonoids for providing survival signalling. For example, EGCG at a dose of 2 mg/kg body weight markedly in-

Table 6.2 Cell signalling pathways targeted by different tea polyphenols in neuronal cell lines

Tea polyphenol	Activation (+) Deactivation (−)	Signalling pathways	Neuroprotection	References
EGCG; ECG	–	MAPK	Prevent apoptosis, oxidative stress and endothelial barrier dysfunction, improve mitochondrial functions	Huang et al. (2007), Hwang and Yen (2009), Yang et al. (2010)
EGCG; ECG	–	JNK	Prevent oxidative stress and apoptosis	Choi et al. (2005), Huang et al. (2007)
EGCG; ECG; EC	+	ERK1/2	Prevent oxidative stress and apoptosis	Schroeter et al. (2007)
EGCG, EC	+	PKB	Anti-oxidant defence, prevent oxidative stress-induced apoptosis, stimulate eNOS activity, regulate mitochondrial function	Schroeter et al. (2007), Vauzour et al. (2007), Na et al. (2008), Hwang and Yen (2009), Yang et al. (2010)
EGCG	+	PKC	Neuroprotective	Levites et al. (2002b)
EGCG	+	PI3K	Prevents oxidative stress-induced apoptosis, protects oxidative damage, stimulate eNOS activity	Levites et al. (2002b), Yang et al. (2010), Xi et al. (2012)

The activation of ERK, Akt/PKB, PI3K, and PKC is important to improve cell survival, and the down-regulation of P38 and JNK in preventing apoptosis. The activation of signalling pathways is shown as (+) while down-regulation of signalling pathways by tea polyphenols is shown as (−)
MAPK p38 mitogen-activated protein kinase, *PKB* protein kinase B, *ERK* extracellular signal-regulated protein kinase, *JNK* c-Jun N-terminal kinase, *PI3K* phosphatidylinositol-3 kinase, *PKC* protein kinase C, *eNOS* endothelial nitric oxide synthase, *EC* (−)epicatechin, *ECG* (−) epicatechingallate, *EGCG* (−)-epigallocatechingallate

creased PKC in the membrane and cytosolic fractions of mice hippocampus. EGCG restored the reduced PKC and extracellular signal-regulated kinase (ERK1/2) activities caused by 6-OHDA toxicity, and protected against neuronal apoptosis (Levites et al. 2002a). EGCG is also involved in rapid PKC-mediated degradation of the Bcl-2-associated death promoter (Bad) by the ubiquitin proteosome system, thus neutralizing their pro-apoptotic function (Calixto et al. 2004).

Tea polyphenols have been shown to interact with ERK, c-Jun N-terminal kinase (JNK) and p38 pathways of the mitogen-activated protein kinases (MAPKs). EC was shown to modulate protein kinase signalling pathways, depending on the concentration of the compound administered (Schroeter et al. 2007). EC stimulated ERK1/2 and phosphoinositide-3-kinase (PI3K)-dependent cAMP response element-binding protein (CREB) phosphorylation at lower concentrations of 100–300 nM but this effect was no longer apparent at the higher concentration of 30 μM. These dose-dependent effects may be important to explain the anti- versus pro-oxidant actions of the tea polyphenols. EC also stimulated ERK and Akt phosphorylation. A 15-min exposure of EC increased the mRNA levels of the glutamate receptor subunit (GluR2) by 60 %, and resulting in increased GluR2 protein. This suggests that EC has the potential to increase CREB-regulated gene expression and increase GluR2 levels and thus modulate neurotransmission, plasticity, and synaptogenesis (Schroeter et al. 2007). EGCG inhibited H_2O_2-induced phosphorylation of JNK and p38 MAPK pathway after a 60-min exposure. EGCG also inhibited H_2O_2-induced caspase-3 activation at concentrations between 1 and 50 μM (Choi et al. 2005). Thus, MAPK-related signalling may regulate expression of apoptotic genes, preventing apoptosis, and promoting cell survival. Another observation demonstrates that EGCG at concentrations between 5 and 25 μM

inhibits angiotensin II-induced endothelial stress fibre formation and increased permeability via inactivation of p38/heat shock protein 27 (HSP27) pathway and suggests that EGCG may protect against endothelial barrier dysfunction and injury (Yang et al. 2010). EGCG treatment also increased the nuclear accumulation, anti-oxidant response element (ARE) binding, and transcriptional activity of nuclear factor erythroid 2-related factor 2 (Nrf2). Furthermore, EGCG activated Akt and ERK1/2. These findings suggest that Nrf2 mediates EGCG-induced expression of some representative anti-oxidant enzymes, possibly via Akt/PKB and ERK1/2 signalling, which may provide the cells with acquired anti-oxidant defence capacity to survive the oxidative stress (Na et al. 2008). In addition to MAPKs pathway, flavonoids and their metabolites have been also shown to modulate cell survival signalling due to their interaction with the PI3K/Akt pathway (Kyoung et al. 2010). The PI3K/Akt pathway is one of the strongest intracellular pro-survival signalling systems. EGCG activated Akt and ERK1/2 signalling cascade in MCF10A cells (Na et al. 2008). This effect was mediated partially via the activation of the downstream pAkt and pBad pathways.

EGCG and other flavanols found in green tea are by far the most intensely investigated, with no studies being reported on other black tea constituents. Thus, besides its free radical scavenging, iron chelating, and anti-aggregating properties, EGCG can exert its action on different sites of the apoptotic pathways, including altering the expression of anti- and pro-apoptotic genes. These studies further implicate that green tea extract may also exert protection through controlling calcium homeostasis, activation of MAPK, PKC, anti-oxidant enzymes and survival genes, thus potentially preventing progression of PD.

6.4.2 Tea Polyphenols and *In Vivo* Models of PD

A number of studies have reported on the protective effects of tea polyphenols against brain damage in various animal models of PD (Dajas et al. 2003; Mandel and Youdim 2004; Mandel et al. 2008). Studies have used either a single compound such as EGCG, or a complex mixture of extracts from tea (Mercer et al. 2005; Masuda et al. 2006; Weinreb et al. 2008; Chen et al. 2008). Green or black tea polyphenol extracts, as well as individual EGCG, attenuated striatal dopamine depletion and SN dopaminergic neurons loss when given chronically to mice, rats or monkeys treated with the parkinsonism-inducing neurotoxins, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) or 6-OHDA (Levites et al. 2001; Chaturvedi et al. 2006; Chen et al. 2014). One study concluded that EGCG does not protect against 6-OHDA-induced loss of nigrostriatal neurons in rats (Leaver et al. 2009). More recently, it was demonstrated that stand-alone polyphenols including EC, EGC, and EGCG protect, rescue and most importantly restore the impaired movement activity (climbing capability) induced by paraquat in *Drosophila* models of PD (Jimenez-Del-Rio et al. 2010). Significantly, these findings receive further support from a recent *in vivo* preclinical neurorescue/neurorestorative drug cocktail study, demonstrating that synergistically EGCG and rasagiline (whilst individually having no profound protective effect) almost completely restored nigrostriatal dopaminergic neuron degeneration caused by MPTP (Reznichenko et al. 2010). Therefore, in a combination therapy regime, EGCG may have the potential to complement the pharmacological activities of current drugs in PD (Chen et al. 2008). Table 6.3 summarizes the most relevant studies concerning the neuroprotective and neurorestorative activities of tea polyphenols in animal models concerning PD.

Understanding the *in vivo* effects of tea consumption is far from complete. Evidence that tea polyphenols are acting directly or indirectly as anti-oxidants *in vivo* exists, but is far more limited when compared to *in vitro* studies. Administration of green tea extract and, in one case, black tea extract, attenuated decreases in superoxide dismutase (SOD) activity caused by infection, ethanol or the carcinogen, 3-methylcolanthrene (Frei and Higdon 2003; Higdon and Frei 2003).

Table 6.3 Neuroprotective and neurorestorative activities of tea polyphenols in animal models of PD

PD model	Tea polyphenol and oral dose	Neuroprotection	References
6-OHDA rat	(i) Black tea extract (1.5 %) *ad libitum*	Improvement of spontaneous locomotion, striatal dopamine and anti-oxidant enzymes, prevention and rescue of SN dopaminergic neurons	Chaturvedi et al. (2006)
	(ii) Green tea (150 mg/kg/day)	Protected dopaminergic neurons and preserved the free radical scavenging capability of both the midbrain and the striatum.	Guo et al. (2007)
MPTP mice	(i) EGCG (2 and 10 mg/kg/day), or Green tea extract (0.5 and 1 mg/kg/day)	Prevented dopamine neuron loss and depletion in striatal dopamine and hydroxlase protein levels	Levites et al. (2001)
	(ii) EGCG (25 mg/kg/day), and green tea (5 ± 0.7 ml)	Prevented the loss of tyrosine hydroxylase (TH)-positive cells in the SN and of TH activity in the striatum, preserved striatal levels of dopamine and its metabolites	Choi et al. (2002)
	(iii) EGCG (5 mg/kg/day)	Rescue of striatal dopamine depletion and SN dopaminergic neurons loss-induced by MPTP	Reznichenko et al. (2010)
	(iv) Theaflavins (10 mg/kg/day)	Reduces oxidative stress, improves motor behaviour and expression of dopamine transporter and vesicular monoamine transporter 2 in striatum and SN	Anandhan et al. (2012a, b)
MPTP monkey	Green tea extract (40 mg/kg/day)	Alleviates motor impairments and dopaminergic neuronal injury in the SN, inhibition of MPTP-induced accumulation of neurotoxic αS oligomers in the striatum and other brain regions	Chen et al. (2014)

6-OHDA 6-hydroxydopamine, *MPTP* N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, *SN* substantia nigra

Another study showed that green tea consumption prevented decline in glutathione peroxidise, indicating a protection in age-related oxidative damage in the brain (Kishido et al. 2007). While green and black tea administration improved the resistance of lipoproteins to *ex vivo* oxidation in several animal models, the improvement was generally much less than that conferred by supplementation with other anti-oxidants. Such an observation raises the question of whether tea polyphenols are present in sufficient quantities *in vivo* to work through an anti-oxidant mechanism (Lotito and Frei 2006; Stevenson and Hurst 2007; Spencer et al. 2009). Some studies have shown that blood concentrations of polyphenols are not high enough to add significantly to the body's total anti-oxidant capacity (D'Archivio et al. 2007; Ghosh and Scheepens 2009). In fact, it was estimated that, after ingestion, up to 95 % of polyphenols undergo structural modification, that in turn may change the 'biological activities' of polyphenols as observed in the *in vitro* studies (Lotito and Frei 2006; Stevenson and Hurst 2007). In turn, there is evidence that polyphenols may be working through other mechanisms, for instance, by protecting endogenous anti-oxidant enzymes such as ascorbic acid in the human body against oxidation consequently improving the overall anti-oxidant level *in vivo* (Aron and Kennedy 2008). This indirect contribution to anti-oxidant effects requires polyphenols at concentrations much lower than would be essential for chemical anti-oxidant protection *in vitro* (Spencer et al. 2009). In other words, polyphenols may act beyond their anti-oxidant activity when not present at suitable concentrations to exert anti-oxidative effects (Saura-Calixto et al. 2007).

It is well known that tea polyphenols differ in their bioavailability and bioactivity. The rather poor bioavailability of EGCG needs to be considered when results obtained *in vitro* are extrapolated to situations *in vivo*. Most of the ingested EGCG is actually not absorbed in the blood, since absorption takes place in the small intestine and substantial quantities pass from the small to the large intestine where it undergoes further degradation by the action of local microbiota (Auger et al. 2008; Stalmach et al. 2009; Roowi et al. 2010). Bioavailability studies for EGCG indicate that peak plasma concentrations are reached after 1–2 h in healthy subjects with one oral dose (800 mg) in the morning after an overnight fasting period; these levels diminish gradually to undetectable levels within 24 h (Chow et al. 2005). The elimination half-life of EGCG is around 3.4 ± 0.3 h (Lee et al. 2002). It was argued that since green and black tea display similar anti-oxidant potential *in vivo*, despite containing different classes of polyphenols, it can be assumed that at least some of the thearubigins and theaflavins are absorbed (Leung et al. 2001; Rietveld and Wiseman 2003). However, the bioavailability of individual thearubigins and theaflavins has thus far not been directly evaluated in human studies. Nevertheless, although the bioavailability of tea flavonoids is low, repeated consumption of tea drinks resulted in a significant accumulation of flavanols in most body organs with relatively high peak plasma levels (Henning et al. 2008). The lack of a precise analytical method to estimate the presence of the more bioavailable flavanols in green tea compared to theaflavins and thearubigins in black tea *in vivo* may lead to an underestimation of the bioactivity of black tea when compared to green tea (Kumar and Pandey 2013). There has been extensive debate about whether the addition of milk to tea affects the bioavailability of flavonoids. Studies have clearly shown that plasma levels of polyphenols such as flavanols increased significantly after tea consumption and were unaffected by the addition of milk even when considering *in vivo* anti-oxidant potential (Kyle et al. 2007). Assuming that small micromolar quantities of tea polyphenols can exhibit bioactivity *in vivo*, current data suggests that long-term consumptions of tea can result in the absorption and retention of sufficient amounts of polyphenols to exert the required effects in plasma and tissues.

Despite the increasing amount of evidence favouring the bioavailability of polyphenols in the systemic circulation, less information is available regarding their ability to cross the blood-brain barrier (BBB) and reach the CNS (Williamson and Manach 2005; Crozier et al. 2009). Flavanols were shown to cross a cellular model of the BBB in a time-dependent and stereo-selective manner (Faria et al. 2011). Multiple animal models have demonstrated that EGCG and EC cross the BBB, reaching a concentration of 0.5 nmol/g in rat brain in the case of EGCG consumption (500 mg/kg) and to co-localise within the brain tissues independently of their route of administration (Nakagawa and Miyazawa 1997; Abd El Mohsen et al. 2002; Adachi et al. 2006). These findings suggest that tea polyphenols are potential biologically active nutrients for direct neuroprotective and neuromodulatory actions. Although the uptake and distribution of dietary polyphenols within the brain is somewhat documented, more uncertainty revolves around the dosage, absorption, metabolism, tissue distribution, and intracellular accumulation and excretion of such compounds. Thus future work is required to investigate this further (Schaffer and Halliwell 2012; Vauzour 2012).

6.5 Clinical Studies with Tea Polyphenols in PD

Despite numerous efforts in the search for disease-modifying therapies in PD, currently the only approved treatment, apart from rasagiline, are agents that target symptoms without modifying the actual pathophysiology of the disease (Olanow et al. 2009). A double-blind, randomized, placebo-control delayed clinical study to evaluate the safety, tolerability, and efficacy of green tea polyphenols in slowing disease progression in patients with early PD, was conducted by the Chinese Parkinson Study Group (CPSG); 410 untreated people with early

PD were enrolled at 32 Chinese Parkinson Study Group sites. Participants were randomized to 0.4, 0.8, or 1.2 g of green tea polyphenols daily or placebo in the first phase of the study, and at 6 months the placebo group switched to 1.2 g of green tea polyphenols daily for 6 more months. Although insomnia was slightly increased, it was found that green tea polyphenols were well tolerated and provided a mild symptomatic relief in early untreated PD (Chan et al. 2009). Data from Chow and colleagues also confirmed that a daily dose of 800 mg caffeine-free EGCG for 4 weeks is safe and well tolerated in healthy human subjects (Chow et al. 2003).

Nonetheless, to date clinical trials so far have failed to identify compounds such as tea polyphenols with compelling proof for disease-modifying properties. One important reason is the lack of a reliable biomarker that can be used to track disease progression (Gerlach et al. 2012). An urgent need for suitable biomarkers in PD together with well-designed controlled studies to assess a risk reduction of PD with tea polyphenols should be prioritized so as to support the evidence derived from *in vitro* and *in vivo* studies.

6.6 Conclusion

Tea is one of the most frequently consumed beverages in the world and its medicinal effects have a long, rich history. In this review we have shown that in the last decade there has been an extensive interest in tea polyphenols as a potential therapeutic agent in PD (Mandel and Youdim 2004; Spencer 2008). Indeed, there is convincing evidence to suggest that the consumption of green and black tea exerts a beneficial effect in reducing the risk of PD, due to its polyphenolic content which exhibits numerous biochemical activities. From the epidemiological data reviewed, it was determined that the dose for the daily intake of tea should be around 2–3 cups/day, in order to induce neuroprotection. The observed beneficial effect, mostly from case–control studies, of tea drinking should now be investigated further in large prospective cohort studies.

There seems to be a consensus that the efficacy of green tea is likely to be mediated by the effects of EGCG, whilst the main bioactive constituents of black tea are the theaflavins. It is clear that EGCG has been the polyphenolic compound of choice most extensively investigated both *in vivo* and *in vitro*, and therefore future studies should now address the effects of other important tea polyphenols, especially theaflavins. While many of the mechanisms underpinning their beneficial effects have been highlighted, it has become clear that apart from the classical anti-oxidant properties, tea polyphenols may in part incur neuroprotection in PD through specific cell signalling pathways and prevention of αS aggregation.

Finally, the extent of their contribution *in vivo*, and at physiological relevant concentrations remains to be ascertained. Conflicting epidemiological inferences and discrepancies between *in vitro* and *in vivo* studies may be due to erratic bioavailability of tea polyphenols. Although more urgent work needs to be done to prove whether tea polyphenols can be translated in PD patients and to clarify their absorption, metabolism, and potential toxicity in humans, their multiple biological activities, and especially in combination with other compounds that possess neuroprotective moieties, may offer a superior therapeutic effect in delaying the initiation and progression of PD.

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