Chapter 19

Green Tea: Just a Drink or Nutraceutical

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Additional information is available at the end of the chapter

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1. Introduction

Brewed tea has been the most widely consumed beverage throughout history. Attractively, this is attributed to its present taste, aromatic odor and healthful effects to the human body. Tea (*Camellia sinensis*) is used for the production of green tea, oolong tea and black tea, depending on the fermentation process. Without fermentation, green tea can be made from fresh tea shoots at a high temperature, thereby inactivating the oxidizing enzymes such as polyphenol oxidase (PPO) and leaving the intact polyphenols. Many ingredients persisting in green tea products are flavonols, flavanols, chlorogenic acid, coumarylquinic acid, theogallin (3-galloylquinic acid), vitamin P (flavonoids), alkaloids, caffeine, theophylline, theobromine, theanine, volatile compounds, fluoride, minerals (e.g. aluminium and magnesium), trace elements and other unidentified compounds. During fermentation, these polyphenolic compounds undergo PPO-catalyzed oxidative polymerization giving rise to the formation of theaflavins and thearubigins which are the major antioxidants in black tea [1]. Besides being a world-wide, well-known beverage, green tea has many benefits for health, including anti-oxidative, free radical scavenging, iron-chelating, anti-hyperglycemic and anti-diabetic, weight-lowering, anti-aging, neuro-protective and rescue, thrombosis-inhibitory, anti-inflammatory, exercise-endurating, hepatoprotective, hepatic phase II enzyme activity-inducing, cardioprotective, neoangioprotective, anti-mutagenic, anti-carcinogenic and cancer-preventive, anti-microbial, as well as immunomodulatory activities. Tea products generally provide refreshment and diuretic benefits, as well as contributing to feelings of alertness; however; green tea extraordinarily exhibits such biological and pharmacological properties depending on several specific active phytochemical constituents; particularly catechins. Nowadays, crude extracts, purified catechin fractions and synthetic catechin derivatives of green tea are applicable in alternative and complementary medicines for the prevention, treatment and co-treatment of many diseases and disorders.

2. Sources and compositions of green tea

Tea has traditionally been cultivated across four continents in the manufacturing of a refreshing drink. The tea products that are available are directly related to the process used at the origin, and can be classified as black tea, green tea, yellow tea, red tea, green pressed tea, as well as instant tea and tea dyes [1]. Green tea is manufactured by using conventional and modified methods. One of these methods involves a 2-3-day process of to drying fresh tea leaves and then rolling the dry leaves with a commercial machine. Alternatively, another method involves the very rapid process of baking the tea leaves in a house-hold microwave oven (800 watt, 3 minutes) at a working temperature of 115 °C. This process will shock the persisting PPO enzyme and result in higher catechins content [2]. A typical green tea beverage is normally prepared at a proportion of 1 g dry weight of tea leaves in 100 ml of hot water in a 3-minute brew (an approximate temperature of 80 °C). This brew usually contains 250 – 350 mg tea solids, 30 – 42% catechins (74 mg) and 3–6% caffeine [3]. HPLC analysis shows the green tea extract (GTE) is comprised of at least six major catechins, including (-)-epicatechin (EC), (-)-epicatechin 3-gallate (ECG), (-)-epigallocatechin (EGC), (-)-epigallocatechin 3-gallate (EGCG), (+)-catechin (C) and (-)-gallocatechin (GC), of which EGCG is the major isomer followed by ECG, EGC and EC (Figure 1) [4]. Gallic acid (GA) is derivatized to one of the hydroxyl groups of the catechins, which has been directly attributed to the biological activities of the catechin species.

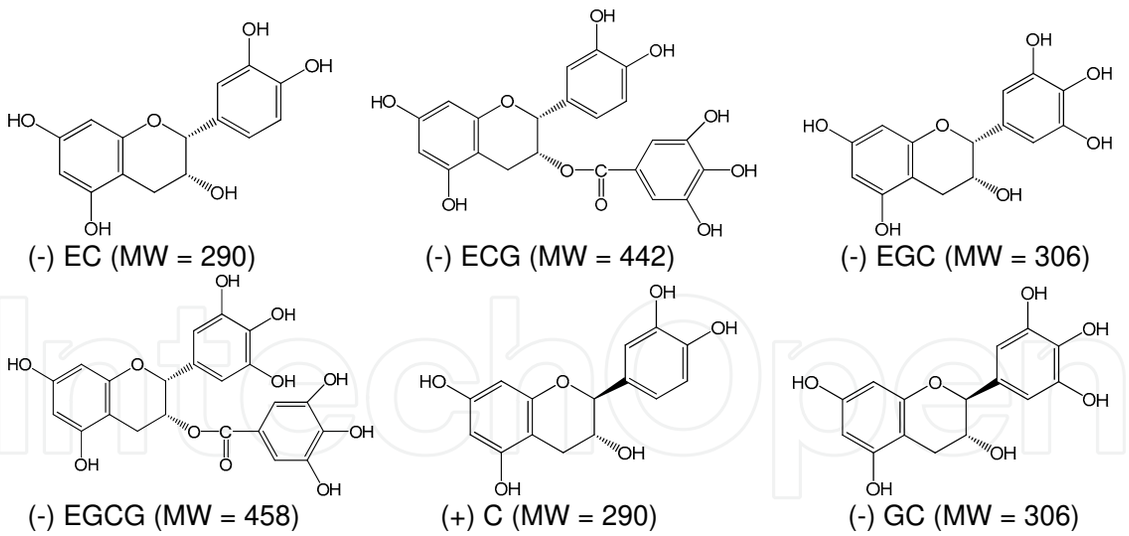

Figure 1. Chemical structures of catechins in green tea (Redrawn from [4])

Moreover, tea products have different amounts and compositions of catechins, which is possibly due to biodiversity, different processing methods, different planting areas and different varieties of tea strains. For instance, Khokhar and colleagues reported that 1 g dry weight of tea product contained 48.4 mg total catechins (9.1 mg EGC, 7.9 mg EC, 22.9 mg EGCG, and 8.5 mg ECG) for Ceylon (NL) black tea; 5.6 mg total catechins (<0.5 mg EGC, 3.1 mg EC,

1.8 mg EGCG, and 0.8 mg ECG) for Yule (India) black tea; 7.5 mg total catechins (<0.5 mg EGC, 4.0 mg EC, 2.6 mg EGCG, and 1.0 mg ECG) for PG tips (UK) black tea;5.15 mg total catechins (16.3 mg EGC, 4.7 mg EC, 26.3 mg EGCG, and 4.4 mg ECG) for Chinese green tea; 84.9 mg total catechins (28.7 mg EGC, 9.4 mg EC, 40.8 mg EGCG, and 5.9 mg ECG) for Japanese green tea; and 21.1 mg total catechins (7.7 mg EGC, 1.7 mg EC, 11.5 mg EGCG, and 0.5 mg ECG) for Chinese oolong tea [5]. EGCG has so far received the most attention because it represents approximately 59% catechin content, EGC at approximately 19%, ECG at approximately 13.6%, and EC at approximately 6.4% of the total catechin content [6]. Green tea also contains other phenolic acids, such as chlorogenic acid and caffeic acid, as well as other flavonols, such as kaempferol, myricetin and quercetin [7].

Green tea catechins have proven to be quite stable in water that is room temperature; however, they can be destroyed at a rate of 20% under brewing at 98 °C for 7 hours and epimerized to other derivatives (e.g. EGCG → GCG) under autoclaving at 120 °C for 20 minutes [8]. Fresh tea leaves are unusually rich in polyphenolic catechins that may constitute up to 30% of the dry leaf weight [9]. As a result of the immediate inactivation of PPO enzyme, the compositions of catechins in green tea are very similar to those of the fresh tea leaves. Various quinines, which are subsequently produced by the enzymatic oxidations, undergo condensation reactions to produce *bis*-flavanols, theaflavins, epitheaflavic acids and thearubigens. These compounds impart the characteristic taste and color properties of black and oolong tea [10].

In our Thai green tea, EGCG was found to be the most abundant catechin (at about 60% of the total catechin content), followed by EGG, ECG, and EC, respectively and the assay yield of the total green tea catechin content was found to be 26-29 g/100 g dry tea leaves (Table 1) [2]. In comparison, Taiwan green tea (1 g dry weight) contained 93.3 mg total catechin content, followed by 43.2 mg EGCG, 33.6 mg ECG, 0.7 mg C, 3.3 mg EC and 2.7 mg ECG [11].

Amounts	EGCG	EGC	ECG	EC	Total catechins
mg/g dry weight	169.4±7.2	60.1±6.2	19.3±2.6	16.3±5.6	279.8±15.2
% (*w*/*w*)	60.6±2.2	21.5±1.4	6.9±1.0	5.9±2.1	100

Table 1. HPLC analysis of catechin compositions in six green tea extract solutions (2 g%, *w*/*v*).

3. Nutritional value of green tea

In general, an antioxidant refers to any substance capable of preventing the oxidation catalyzed by reactive oxygen species (ROS)/reactive nitrogen species (RNS). Thus, an antioxidant that protects against iron toxicity is a substance that can: i) chelate iron and prevent the reaction with oxygen or peroxides; ii) chelate iron and maintain it in a redox state that makes iron unable to reduce molecular oxygen; iii) trap already formed radicals, which is a putative action of any substance that can scavenge free radicals in biological systems, regardless of whether they have originated from iron-dependent reactions or not. Not only can natural products chelate

iron, but also synthetic compounds are capable of chelating iron *in vivo*, thereby limiting its participation in free radical reactions. Thus, iron chelators also serve as antioxidants by suppressing iron-mediated oxidation in biological systems. Surprisingly, thiol compounds (e.g. glutathione) that are synthesised by mammals can afford significant antioxidant protection. This protection is related to the ability of glutathione to trap radicals, reduce peroxides, as well asits ability to work to maintain the redox state of the cells [12].

The potential of green tea to prevent or ameliorate chronic diseases is currently the subject of considerable scientific investigations. Although a number of mechanisms have been proposed for their beneficial effects, the radical scavenging and antioxidant properties of green tea catechins are frequently cited as important contributors. Emerging evidence has also shown that catechins and their metabolites possessmany additional mechanisms of action [13] by affecting numerous sites, potentiating endogenous antioxidants and eliciting dual actions during oxidative stress. Much of the evidence supporting an antioxidant function for green tea catechins is derived from assays of their antioxidant activity *in vitro*. However, the evidence that green tea catechins are acting either directly or indirectly as antioxidants *in vivo* is limited [14]

4. Anti-oxidative and iron-chelating properties

Green tea catechins stoichiometrically bind ferric ion to form a redox-inactive iron-phenolic complex [15, 16] and potentially protect vital biomolecules from oxidative damage. Incredibly, the catechins could be capable of chelating excessive redox iron in iron overloaded diseases, such as thalassemia, and play important preventive or/and protective roles in this unpleasant condition [2, 17-19]. The phytochemical compounds therefore play a double role in reducing the rate of oxidation because they can participate in: i) iron chelation [19], and ii) trapping radicals [2, 20]. Catechins can protect culture cells from iron-mediated damage [21, 22], ameliorate iron accumulation [17] and inhibit hepatic iron-induced lipid oxidation [23], and also play a dual effect in decreasing labile plasma iron (LPI) in iron-loaded rats [18]. Animal studies offer a unique opportunity to assess the contribution of green tea administration to the physiological effects on different models of oxidative-related diseases. In a combination of free-radical scavenging activity with iron-chelating properties, green tea may have a capacity of chelating excess iron in iron-overloaded conditions and play important preventive and/or protective roles in this unpleasant condition.

Like the deferiprone (DFP) treatment, oral administrations of GTE and EGCG significantly lowered levels of plasma non-transferrin bound iron (NTBI) and LPI in wild-type (WT), heterozygous β-globin gene knockout (BKO) thalassemic and double heterozygous β-globin gene knockout carrying human β^E gene (DH) mice (strain C57BL/6J) with iron overload, when compared to the DW group (Table 2) (Sakaewan Ounjaijean and Somdet Srichairatanakool, unpublished data). Elimination of these two toxic irons by green tea extract and EGCG fraction would relieve redox iron-induced oxidative stress and tissue damage in the body. GTE treatment efficiently depleted plasma malondialdehyde (MDA) concentrations in the iron-

loaded mice (approximately 50% in WT, 30% in BKO and 40% in DH mice), whereas EGCG treatment caused significantly lower plasma MDA levels (approximately 30% in all the mice), suggesting that GTE and EGCG are strong antioxidants and exert potent anti-plasma lipid peroxidation. Consistently, the GTE and EGCG increased levels of reduced glutathione (GSH) in the plasma of all the mice despite under iron overload. Thus, it can be said that green tea catechins, particularly EGCG, chelate the redox irons and consequently inhibit the iron-catalyzed lipid peroxidation reactions in plasma lipids, as well as membrane phospholipids, resulting in an improvement of a powerful antioxidants as reduced glutathione is reduced in the plasma compartment.

Mice	N diet	Fe diet (0.2% ferrocene, w/w)			
	+DW	+DW	+GTE (90 mg/kg/day)	+EGCG (50 mg/kg/day)	+DFP (50 mg/kg/day)
	Plasma NTBI concentrations (μM)				
WT (n = 24)	-0.27±0.23	11.17±0.26*	6.83±1.49†	6.80±1.75†	6.81±2.23†
BKO (n = 16)	0.34±0.26	19.78±1.36*	10.20±1.92†	10.66±1.60†	11.75±1.21†
DH (n = 10)	-0.07±0.11	13.41±1.84*	7.74±1.38†	7.81±0.71†	7.83±1.41†
	LPI concentrations (μM)				
WT (n = 24)	-2.49±1.00	1.19±0.42*	-2.26±1.98†	-2.47±1.25†	-2.01±2.76†
BKO (n = 16)	0.87±0.22	2.30±1.08*	0.30±2.57†	-0.21±1.37†	0.35±1.05†
DH (n = 10)	-0.15±0.52	0.81±0.26*	0.26±0.61†	0.47±0.63	0.34±0.70
	Plasma MDA concentrations (μM)				
WT (n = 24)	13.39±5.10	39.97±8.67*	23.26±8.30†	28.39±6.66†	32.58±8.73†
BKO (n = 16)	26.80±3.59	54.34±9.88*	37.62±9.23†	41.85±11.8†	52.29±7.51†
DH (n = 10)	18.79±2.31	46.89±4.56*	26.62±5.14†	32.72±2.46†	38.13±5.09†
	Plasma GSH concentrations (μM)				
WT (n = 24)	11.53±2.50	7.73±4.70*	15.15±7.72†	16.04±6.61†	15.89±8.43†
BKO (n = 16)	7.73±4.25	6.24±3.89	15.12±9.76*,†	15.63±7.74*,†	16.50±8.75*,†
DH (n = 10)	10.97±5.00	5.81±1.44*	14.78±5.16†	17.03±7.27†	14.19±4.89†

*p <0.05 compared to N diet; †p <0.05 compared to DW.

Table 2. NTBI, LPI, MDA and GSH concentrations (mean+SD) in the WT, BKO and DH mice fed with a normal (N) diet (iron content 180 mg/kg) and an iron (Fe) diet (iron content 780 mg/kg) and treated with deionized water (DW), 90 mg/kg/day GTE, 50 mg/kg EGCG and 50 mg/kg DFP for 6 months.

5. Fate of green tea catechins in the body

5.1. Gastrointestinal absorption

Among these polyphenolic compounds, the hierarchy of antioxidant activity is ECG > EGCG > EGC > GA > EC ≈ C [24]. With the chelating activity of such prooxidant metals as iron (Fe^{2+}),

green tea is able to reduce dietary nonheme iron absorption [25]. The ratio of EGC, EGCG, ECG or EC to the iron was 3:2, 2:1, 2:1 and 3:1, respectively [26]. Unlike most flavonoids, tea catechins existing as aglycone are found in the blood following oral ingestion and subsequently metabolized in the liver by methylation, sulfation and glucoronidation reactions [27]. Structure-activity studies have shown that the presence of the galloyl ring in the 3-position and trihydroxyphenyl B ring are of significant importance in terms of the antioxidant properties of the catechins [26].

After green tea (25 mg/kg) and pure EGCG fractions (10 mg/kg) were intravenously administered into rats, a study of the pharmacokinetic (concentration-time curves) properties of the catechins in the plasma was conducted. Beta-elimination half-lives ($T_{1/2}\beta$) were found to be 212, 45, and 41 minutes; clearances were 2.0, 7.0, and 13.9 ml•minute/kg; and apparent distribution volumes (V_d) were 1.5, 2.1, and 3.6 dl/kg for EGCG, EGC, and EC, respectively. In comparison, EGCG had a shorter $T_{1/2}\beta$ (135 minute), a larger clearance (72.5 ml•minute/kg), and a larger volume (V_d) (22.5 dl/kg) than the other two. When the green tea was intragastrically given (200 mg/kg), around 0.1, 13.7 and 31.2% of EGCG, EGC and EC were detected in the plasma compartment. The EGCG level was found to be the highest in the intestine samples and declined with a $T_{1/2}$ of 173 minute. EGC and EC levels were found to be the highest in the kidneys and declined rapidly with $T_{1/2}$ of 29 and 28 minute, respectively. EGCG, EGC, and EC levels in the liver and lungs were lower than those recorded in the intestine and the kidney [28]. This implies that EGCG is mainly excreted through bile, while EGC and EC are excreted through urine and bile. Inter-individual variations in the bioavailability of green tea catechins can be substantial and may be due, in part, to differences in colonic microflora and genetic polymorphisms among the enzymes involved in polyphenol metabolism [29]. The effect of green tea drinking may also differ by genotype [30].

Following oral administration of green tea catechin solutions (0.6%, *w*/*v*) to the rats, plasma levels of the catechins measured at 6:00 AM., 9:00 AM., 0:00 PM and 6:00 PM on the same day were found to be 983.9±114.2, 372.89±56.7, 186.89±34.5 and 548.1±221.6 ng/ml EGC; 1,527.3±163.7, 449.2±82.7, 224.6±58.0 and 845.6±374.0 ng/ml ECG; and 105.0±12.6, 85.5±15.8, 95.7±18.3 and 114.8±45.6 ng/ml EGCG, respectively, for which the plasma EGCG concentrations were found to be even lower than those of EGC and EC. There wasa gradual increase in plasma concentrations of EGC, EC and EGCG during Days 1-4. Levels of EGC and EC in the plasma on Day 14 were approximately three times higher than those on Day 1. Plasma levels of these three catechins decreased after Day 14, and by Day 28, plasma levels of the EGC and EC returned to the levels recorded on Day 1. On Days 4, 14 and 28, the catechins were mostly present in glucuronic acid (MW=194)/sulfuric acid (MW=98) conjugated-EGC (91.4, 95.6 and 86.4 ng/ml, respectively) and-EC (92.4, 95.5 and 89.4 ng/ml, respectively), while a much lower proportion of EGCG was found in the conjugated form (21.2, 60.7 and 39.3 ng/ml, respectively). The highest EGC concentration was found in the bladder; the highest EGCG concentration was found in the large intestine; very high concentrations of EGC and EGCG were found in the kidneys, prostate gland and lungs; and low levels of these three catechins were present in the liver, spleen, heart, and thyroid glands [31].

5.2. Organ metabolism

EC was not glucuronidated by uridine diphosphate-glucuronosyltransferases (UGT) and sulfotransferases (SULT) in human liver and small intestinal microsomes. However, the compound was efficiently glucuronidated in rat liver microsomes with the formation of two different glucuronides, and was also sulfated in human liver cytosol, mainly through the SULT1A1 isoform, as well as in the intestine through the SULT1A1 and SULT1A3 isoforms. In comparison, the EC was much less sulfated in the rat liver than in the human liver [32]. EGCG and ECG constituents in green tea drinks (10%, *w*/*v*) almost completely, competitively inhibited the activities of the SULT1A1 and SULT1A3 enzymes that play an important role in the presystemic inactivation of β_2 agonists in the liver and intestine, respectively [33]. When EGCG was glucuronidated by the liver microsomal UGT enzymes; four EGCG-glucuronides were identified as EGCG-3-glucuronide, EGCG-3'-glucuronide, EGCG-4'-glucuronide and EGCG-7-glucuronide. Under the same conditions, EGC was metabolized into two EGC-glucuronides as EGC-7-glucuronide and EGC-3'-glucuronide [34]. Since rate of the glucuronidation of EGCG and ECG in liver microsomes is rather low (12.2±0.2 and 7.5±0.2%, respectively for 3 hours) due to the galloyl ring, the two potent catechins are therefore recognized to be circulating in the plasma in unconjugated forms [35]. One study claimed that catechins were toxic to rat liver cells in the order of EGCG (LD_{50} 200±19 μM) > ECG (LD_{50} 2,000±214 μM) > GA (LD_{50} 3,000±298 μM), EGC (LD_{50} 3,000±304 μM) > EC (LD_{50} >10,000 μM), and this was likely due to the mitochondrial membrane potential ($\Delta\psi_m$) collapse, and the depletion of GSH and ROS formation. The EGCG and GA dose dependently affected GSH conjugation, methylation, metabolism by NAD(P)H:quinoneoxidoreductase 1 (NQO1) in the hepatic detoxification step (Figure 2), as monitored by a significant increase of plasma alanine aminotransferase (ALT) activity in mice [36].

5.3. Excretion

Most polyphenolic catechins in green tea may not be absorbed in the small intestine. The nonabsorbed catechins will be converted by large bow bacterial flora into simpler phenolic compounds, such as hippuric acid, then absorbed into the blood and excreted in the urine (4.22±0.28 mmol/24 hours), when compared to non-consumption (1.89+0.28 mmol/24 hours) [37].

6. Health benefits

6.1. Health promotion

The potential health effects of green tea catechins depend not only on the amount consumed, but also on their bioavailability, which appears to be substantially varied. Following the oral administration of tea catechins to rats [38] and mice [39], the four principal catechins have been identified in the portal vein, indicating that tea catechins are absorbed intestinally. There appear to be species-related differences in the bioavailability of EGCG compared to other tea

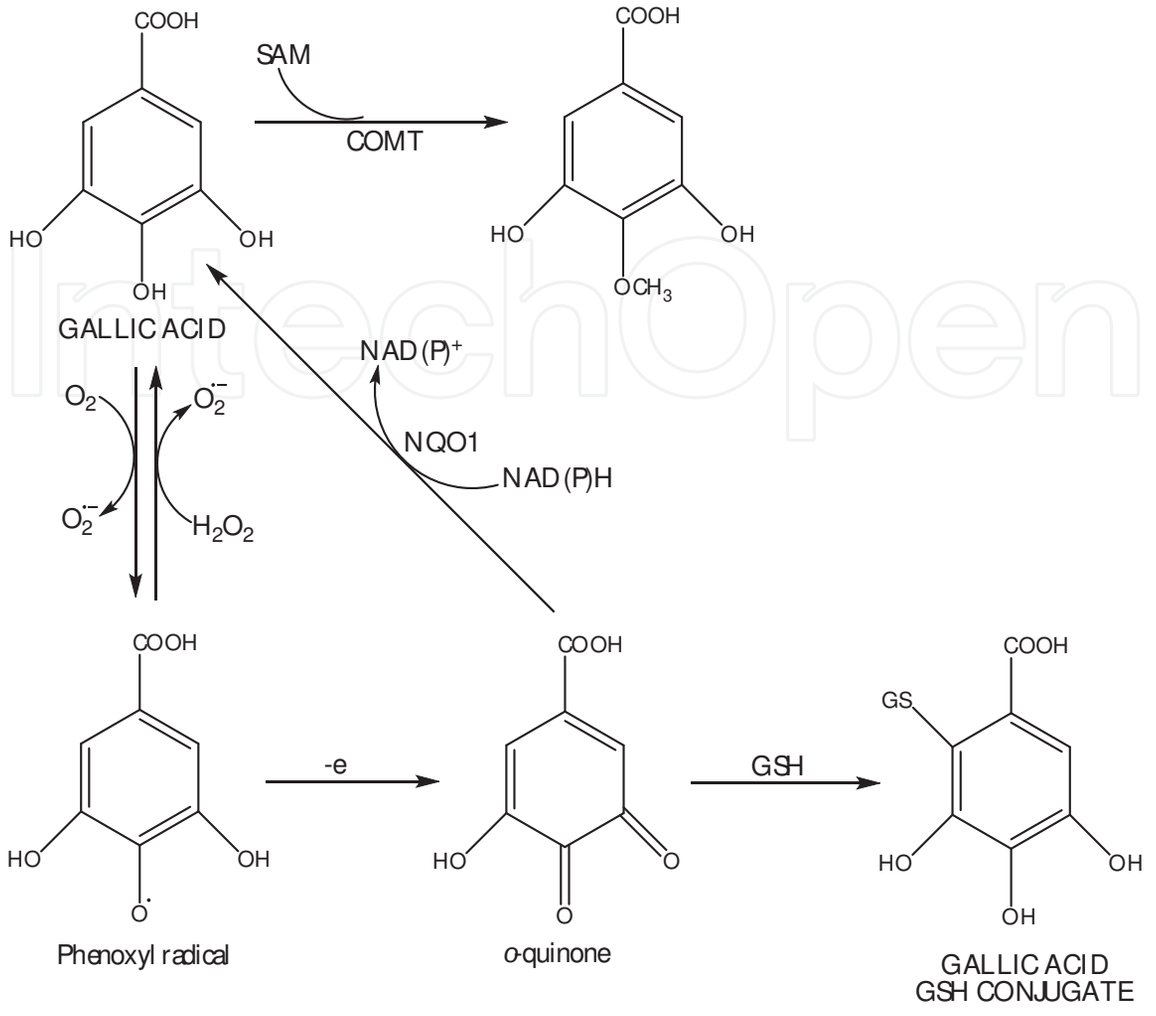

Figure 2. Possible mechanism for the hepaticgalloyl ring metabolism (Redrawn from [36]). Abbreviations: COMT=catechol-*O*-methyltransferase; GSH=reduced glutathione;NAD(P)$^+$=nicotinamide adenine dinucleotide phosphate; NAD(P)H=reduced nicotinamide adenine dinucleotide phosphate; NQO1=NAD(P)H:quinone oxidoreductase-1; SAM=*S*-adenosyl methionine

catechins [7]. The epicatechin isomers purified from green tea were effective agents in protecting human low-density lipoproteins (LDL) and red blood cell (RBC) membranes from oxidative modification [40]. These effects are partly due to their free-radical scavenging abilities [20] and their iron-chelating properties, which are capable of binding any available iron, thus greatly reducing their bioavailability. They also have many pharmacological properties, including anti-hypertensive [41], anti-atheroslcerotic [42], anti-carcinogenic [43-45] and hypocholesterolemic effects [46, 47]. Health benefits of green tea consumption were achieved in the rodents within relatively short periods: three weeks [48], four weeks [49, 50], five weeks [51, 52] and eight weeks [53, 54].

Surprisingly, catechins inhibited xanthine oxidase (XO) activity *in vitro* [55– 58] and the XO inhibition constant (K_i) of EGCG was comparable to that of the common XO inhibitor allopurinol (0.76 versus 0.30 μmol) [56]. GTE consumption was found to decrease levels of serum uric acid concentrations observed in human subjects [59-61]; for instance, by decreasing serum uric

acid levels from 4.54 to 4.22 mg/dl (p<0.05) within 7 days [59]. Our group has currently found that the consumption of GTE (2, 4 and 6 g/day), of which the 2 g/day dose was found to be the most effective, lowered levels of serum uric acid (3.53%) and also increased serum trolox-equivalent antioxidant capacity (TEAC) values in healthy volunteers (n=11) (unpublished data), suggesting an hypouricemic effect by XO inhibition or an increase of urinary uric acid excretion.

6.2. Hematologic disorders

In consideration of the evidence for its iron chelating properties, strong antioxidant capacity, low toxicity, and orally available administration, green tea has potential to be used as a pharmacological agent in the management of diseasesrelated to iron overload. Hypothetically, the removal of iron could reduce oxidative damage to the cellular biomolecules, including lipids, proteins, carbohydrates and nucleic acids, and this can consequently prevent, as well as improve the vital organ dysfunctions. DFP, known to readily permeate and mobilize nonheme iron from β-thalassemic patient erythrocytes, serves as a benchmark against which orally effective agents; catechins in GTE and purified EGCG products have been compared. Our studies have paid particular attention to the efficacy of GTE and EGCG in terms of the aspects of anti-oxidation and the potential for iron chelation in order to alleviate oxidative stress and iron overload in β-thalassemic mice in the past experiments, and in Thai β-thalassemia patients with regard to the near future.

Though the pathological role of redox iron in the hemosiderosis (such as hereditary hemochromatosis and thalassemia) is well characterized, excessive accumulation of the iron can result in significant organ dysfunction and abnormality. Recognition of the role of iron in conditions beyond transfusion-dependent iron overload may bring significant implications for the management of metabolic, infectious, and degenerative diseases. New findings obtained during the past years, especially in terms of the discovery of mutations in the genes associated with brain iron metabolism, have provided key insights into the mechanisms of brain iron homeostasis and the pathological mechanisms responsible for neurodegenerative diseases. Increased iron in the brain, which is rich in oxygen and fatty acids, provides an ideal environment for oxidative stress and possible irreparable tissue damage. Oxidative stress, resulting from increased brain iron levels, and possibly also from defects in antioxidant defense mechanisms, is widely believed to be associated with neuronal death in brain disorders.

The interaction between iron overload and dietary antioxidants has been well characterized; especially, with respect to vitamins E and C. Vitamin E has been extensively studied with respect to its capacity to protect molecules from the *in vitro* and *in vivo* effects of iron toxicity [62, 63]. Elevated levels of ROS tended to normalize in response to oral therapy with vitamin E, with patients exhibiting improvement in the antioxidant–oxidant balance in plasma and decreased lipid peroxidation in erythrocytes [64]. However, prolonged administration of vitamin E did not result in any significant changes in Hb levels in patients with β-thalassemia intermedia [65]. Therefore, vitamin E by itself is probably insufficient in inducing major

changes in the rate of RBC hemolysis and in prolonging their survival, resulting in increased Hb levels.

The interaction of another dietary antioxidant, vitamin C (ascorbic acid) and iron is less clear. Ascorbic acid can reduce 'free iron' (ferric) to a ferrous form, promoting the initiation and propagation of free radical reactions [66, 67]. In people under a risk of iron overload, in which the elevated levels of iron could lead to higher 'free iron' concentrations, an excess of vitamin C could have deleterious effects. Plant flavonoids (including rutin and curcumin) are another group of antioxidants, which may have therapeutic potential in thalassemia. However, despite their apparent salutary effects on erythrocytes, antioxidants have not yet been shown to ameliorate the anemia of the patients [68]. Antioxidants may be more effective if used in combination with an iron chelator. This approach, if successful, could be particularly useful in countries with limited financial resources.

The potential of green tea to prevent or ameliorate chronic disease is currently the subject of considerable scientific investigation. Although a number of mechanisms have been proposed as being responsible for green tea's beneficial effects, the radical scavenging and antioxidant properties of green tea catechins are frequently cited as important contributors. Emerging evidence has shown that catechins and their metabolites have many additional mechanisms of action [69] by affecting numerous sites, potentiating endogenous antioxidants and eliciting dual actions during oxidative stress. Much of the evidence supporting the antioxidant function for green tea catechins has been derived from assays of their antioxidant activity *in vitro*. However, evidence that green tea catechins are acting directly or indirectly as antioxidants *in vivo* is more limited [14]. Interestingly, green tea catechins can play a double role in reducing the rate of oxidation, as they can participate in: i) iron chelation [19]; and ii) trapping radicals [2, 20]. The catechins have been shown to protect culture cells from iron-mediated damage [21, 22]. In animal models of iron overload, they have been reported to ameliorate iron accumulation [17] and inhibit iron-induced lipid oxidation in the liver [23]. They also play a dual effect in decreased labile iron in the plasma and consequently depleting oxidative stress in iron-loaded rats [18]. Animal studies offer a unique opportunity to assess the contribution of the antioxidant properties of the catechins in terms of the physiological effects of tea administration in different models of oxidative-related diseases. Combining free-radical scavenging with iron-chelating properties, green tea catechins may have a capacity of chelating an excess of iron under iron-overloaded conditions and play the important preventive and/or protective roles in this unpleasant condition. None of the treatments over 2 months affected the levels of blood hemoglobin (Hb) in the WT, BKO and DH mice challenged by iron overload, there were fed a high iron-diet. Nonetheless, iron-induced oxidative stress as well as GSH content in the RBC cytoplasm, and lipid-peroxidation in the RBC plasma membrane were reversed by the GTE that was used in the testing, as well as the EGCG, when compared to the DW treatment (Table 3). We also found that these two green tea products increased the survival rate or half-life of the RBC of the WT and BKO mice significantly (Sakaewan Ounjaijen and Somdet Srichairatanakool, unpublished data). Our results suggest that GTE and EGCG treatment might directly increase the erythropoietic rate, either in normal mice or in thalassemic mice, but probably do protect red cells from ROS-induced hemolysis.

Mice	Fe diet (0.2% ferrocene, w/w)								
	+DW			+GTE (90 mg/kg/day)			+EGCG (50 mg/kg/day)		
	Month 0	Month 1	Month 2	Month 0	Month 1	Month 2	Month 0	Month 1	Month 2
Blood Hb concentration (g/dl)									
WT (n = 24)	14.80±1.14	15.19 ±1.11	15.15±1.06	15.22±1.23	15.37±1.23	15.32±1.14	15.29±1.25	15.40±1.13	15.41±1.00
BKO (n = 16)	9.45 ±0.56	9.35 ±0.40	9.28 ±0.31	9.55 ±0.59	9.60 ±0.45	9.54 ±0.48	9.45 ±0.56	9.53 ±0.36	9.56 ±0.39
DH (n = 10)	15.97±1.09	15.80±1.01	15.85±0.88	16.11±0.84	16.25±0.85	16.17±0.77	16.33±0.76	16.41±0.72	16.29±0.71
Erythrocyte ROS (Fluorescent intensity unit)									
WT (n = 10)	38.46±9.17	38.29 ±10.93	42.62±9.63	31.74±9.14	23.29±3.99†	22.45±3.39†	33.07±8.08	26.87±3.72†	23.26±3.02†
BKO (n = 10)	48.29±8.01	53.92 ±9.69	59.81±8.96	35.07±7.68	33.69±7.83†	38.50±6.90†	33.88±7.08	31.47±8.93†	36.67±5.16†
DH (n = 10)	43.08±4.38	44.38 ±3.78	49.60±4.25	31.97±4.23	31.57±4.31	27.88±3.65†	31.51±5.38	31.50±4.38	28.17±4.64†
Erythrocyte MDA (pmol/g Hb)									
WT (n = 8)	ND	ND	48.23±6.15	ND	ND	36.80±3.23†	ND	ND	36.82±2.71†
BKO (n = 8)	ND	ND	60.63±3.28	ND	ND	44.26±2.87†	ND	ND	44.74±2.79†
DH (n = 8)	ND	ND	50.86±1.90	ND	ND	42.00±2.85†	ND	ND	40.36±2.83†
Erythrocyte GSH (μmol/g Hb)									
WT (n = 8)	ND	ND	2.80 ±0.52	ND	ND	3.61 ±0.32†	ND	ND	3.73 ±0.29†
BKO (n = 8)	ND	ND	2.56 ±0.22	ND	ND	3.31 ±0.40†	ND	ND	3.24 ±0.36†
DH (n = 8)	ND	ND	2.76 ±0.18	ND	ND	3.49 ±0.22†	ND	ND	3.46 ±0.19†

†p <0.05 compared to DW.

Table 3. Levels of blood Hb, erythrocyte ROS, GSH and MDA (mean±SD) in WT, BKO and DH mice fed with an Fe diet (iron content 780 mg/kg) and treated with DW, GTE and EGCG for 2 months.†p <0.05 compared to DW treatment. ND=not done.

The inhibition of the growth of blast cells from patients with acute myelocytic leukemic (AML) by EGCG affected hematopoietic growth factors (HGF), granulocyte colony stimulating factor (G-CSF), granulocyte macrophage colony stimulating factor (GM-CSF) or interleukin-3 (IL-3), was useful in terms of the stimulation of leukemic cell proliferation. EGCG dosage and time dependently reduced the survival of NSF60 leukemic cell lines [69, 70]. These factors can lead to an induction of cell apoptosis, including endonuclease activation, p53 induction, caspase 3 protease activation *via* a Bcl-2-insensitive pathway, free-radical production and sphinganine accumulation. Chemopreventive effects in multi-step carcinogenesis by EGCG have also been mentioned [71]. From in vitro studies, green tea and EGCG (dose 9-27 μg/ml) displayed a significant level of inhibition of the peripheral blood T-lymphocytes of adult T-lymphocytes patients, along with a moderate level of inhibition of human T-cell lymphotropic virus type I (HTLV-I)-infected T-cell line, but not of T-lymphocytes in the healthy controls. This was possibly due to a suppression of HTLV-I pX gene expression and induction of cell apoptosis [72].Consistently, Japanese HTLV-1 carriers who had taken green tea extract powder (9 capsules/day equivalent to 10 cups of regular green tea drinking) for 5 months showed a significant decrease in the HTLV-1 provirus load, suggesting that green tea drinking could inhibit the proliferation of HTLV-1-infected lymphocytes [73].

Surprisingly, EGCG diminished the phosphorylation of vascular endothelial growth factor (VEGF) receptors, potent angiogenic cytokines that are essential for the survival of tumor cells in the autocrine pathway, in chronic lymphocytic leukemia B cells that have been isolated from leukemic patients, leading to cell apoptosis [74]. EGCG decreased human telomerase reverse transcriptase (hTERT) promoter methylation and histone H_3 Lys9 acetylation, but increased hTERT repressor E_2F-1 binding at the promoter of MCF-7 breast cancers and HL60 promyelocytic leukemia cell cultures [75]. EGCG treatment induced death-associated protein kinase 2 (DAPK2) in multiple myeloma cells and dose dependently increased levels of the DAPK2 in HL60 and NB4 AML cells, while a combined treatment of EGCG (0 – 40 μM) with all-*trans* retinoic acid (ATRA) (1 μM) cooperatively induced and potentially differentiated the DAPK2 enzyme [76]. After ten patients with stage-0 chronic lymphocytic leukemia (CLL) had been orally given GTE for 6 months; eight patients showed decreases in lymphocytosis and circulating regulatory T cells (T_{reg}) numbers, while one patient revealed stable lymphocytosis with decreased T_{reg} numbers, and one patient showed increased lymphocytosis and T_{reg} numbers [77].

The results of the phase 2 clinical study demonstrated that patients with early stage CLL consumed GTE (Polyphenon E preparation, dose of 2000 mg/day, twice daily) for 6 months showed decreases in the absolute lymphocyte counts and lymphadenopathy [78].

6.3. Cardiovascular diseases

Epigenetics, hypercholesterolemia, diabetes, hypertension, heavy smoking, physical inactivity, stress and obesity are all risk factors for atherosclerosis and cardiovascular diseases (CVD). Green tea catechins have been reported to exert anti-obesity effects, including a reduction of adipocyte differentiation and proliferation; decreases in lipogenesis, fat mass, body weight,

fat absorption, plasma levels of triglycerides, free fatty acids, cholesterol, glucose, insulin and leptin; and increases in β-oxidation and thermogenesis.

Yang and Koo reported that the ECG and EGCG that are present in Chinese green tea reduced lipid deposition-caused weight, as well as the cholesterol content of the liver, importantly lowered levels of serum cholesterol levels and the atherogenic index in the rats fed with a cholesterol-enriched diet [54]. Rats fed with the green tea powder (20 g/kg)-enriched diet showed a significant increase in the lag-phase oxidation of plasma with very low density in lipoproteins (VLDL) and LDL by 33% when compared to the control diet [48]. EGCG was proposed to be a competitive inhibitor of β-ketoacyl reductase of the FAS enzyme complex in the liver [79]. EGCG and ECG lowered FAS and malate enzymes in rat liver cytosol, resulting in a significant decrease in visceral fat deposition and hepatic triglyceride content [80]. Nonetheless, experiments showed that GTE lowered serum cholesterol and triglyceride concentrations in the hamsters fed with high fat diet (200 g lard and 1 g cholesterol/kg) in a concentration-dependent manner, for which the mechanism was most likely due to its influence on the absorption of dietary fat and cholesterol, but not on the inhibition of the synthesis of cholesterol or fatty acid [49]. Another study supports the evidence that Chinese green tea lowered plasma cholesterol levels by increasing fecal bile acids and cholesterol excretion, but not by inhibiting activities of three major lipid metabolizing enzymes, including 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-Co A) reductase, cholesterol 7α-hydroxylase and FAS [53]. More importantly, high plasma cholesterol levels, fatty liver, renal dysfunctions and severe atherosclerotic aorta were observed in the LDL knockout mice fed with a normal diet, but not in those fed with a 4% green tea catechins-enriched diet for 35 weeks [81].

GTE, which had greater effects than oolong tea and black tea, decreased high serum triglyceride (195 vs. 119 mg/dl) and cholesterol (104 vs. 73 mg/dl) levels to normal levels, and also decreased hepatic triglyceride content in sucrose-induced hyperlipidemic rats (8.4±1.5 vs. 27.7±7.9 mg/g wet weight (p<0.05); possibly by limiting the intestinal absorption of dietary fat and storage of fat in the liver [52]. EGCG (dose of 0.5 g/kg for 4 weeks) can interfere with the micellar solubilization of dietary cholesterol in the gastrointestinal tract and subsequently reduce cholesterol absorption in the rats fed with a high cholesterol diet [50].

Green tea catechins functioned against membrane phospholipid peroxidation [82], showed a strong synergistic anti-oxidative activity with α-tocopherol in micelles [83],as well as in human LDL levels [84], and had a protective effect of high-density lipoprotein (HDL) on endothelial cell-dependent vasodilatation [85]. They have many pharmacological activities, including anti-hypertensive [41] and anti-atherosclerotic [86, 87] effects. Clearly, green tea catechins; especially EGCG, has a potential hypolipidemic effect, possibly by interfering with the emulsification, digestion, and micellar solubilization of lipids in the critical steps of intestinal absorption of dietary lipids [88]. Bursill and coworkers found that GTE (2% catechins, w/w) decreased the levels of total cholesterol (-60%), VLDL-and intermediate density lipoprotein (IDL)-cholesterol (-70%), LDL-cholesterol (-80%) in plasma, total cholesterol (622 versus 800 μmol/g,-10%) and unesterified cholesterol (323 versus 399 μmol/g,-15%) in the liver, and cholesterol (-25%) in the thoracic aorta (0.73 versus 0.98 μmol/g,-25%) and aortic arch fatty streak (1.93 versus 2.35 μmol/g) of the rabbits fed with a high cholesterol (0.25%, w/w) diet

compared with the placebo group, possibly due to a decrease in cholesterol synthesis and an upregulation of hepatic LDL receptor gene expression [89, 90]. Controversial data has indicated that the consumption of high doses of green tea polyphenols (714 mg/day) for 3 weeks resulted in decreases in the total cholesterol:HDL-cholesterol ratio, but had no effects on the risk biomarkers of CVD [91].

6.4. Neurological diseases

The errors in brain iron metabolism found in neurological disorders are found to be multifactorial, however treatment conditions seem to be particularly important. Epilepsy, an oxidative related disorder of the brain, has served as a model for the investigation in the role of iron, especially NTBI in neurological disorders. The effect of antiepileptic drug treatment on changes of iron status and oxidative stress parameters were determined [92]. Recent genetic and biochemical manipulations of iron overload have placed iron at the centre of research into neurodegenerative diseases. This is supported by the discovery of genetic and non-genetic misregulations of the iron metabolism in these disorders. In many neurodegenerative disorders, abnormally high levels of iron in specific regions of the brain have been reported [93]. Evidence for iron contribution to diseases by augmentation of oxidative stress have led to an examination of the contribution of iron to other diseases, in which oxidative stress may be involved, including epilepsy [94]. It has not been possible to determine whether the accumulated iron is in the labile iron pool (LIP), which can participate in the Fenton reaction to generate the reactive hydroxyl radical. The reduction in GSH during disease progression and in response to neurotoxins, together with increased iron accumulation and ROS generation, might be taken as evidence for the presence of free iron [95].

Oxidative stress, resulting from increased brain iron levels, and possibly also from defects in antioxidant defensive mechanisms, is widely believed to be associated with neuronal death in these disorders [96, 97], along with a reduced availability of GSH and other antioxidant substances in the brain. Changes in the integrity of the blood brain barrier (BBB) due to altered vascularization of the tissue or inflammatory events could be another initial cause. However, neuronal death by any initial cause could lead to large amounts of iron release and increased ROS formation [98]. Therefore, iron and iron-induced oxidative stress could possibly be a common mechanism involved in the development of neurodegeneration [99] (Figure 3). Available data strongly support this hypothesis [100, 101]

Based on this hypothesis, therefore, therapeutic efforts should be devoted to reducing brain iron levels and inhibiting the generation of ROS. A few recent studies have shown that the iron chelator, deferrioxamine, may be a significant factor in an effective therapy for the prevention and treatment of brain disorders [102]. One possible non-toxic approach with natural metal chelators could make use of green tea catechins, especially EGCG. This compound comprising antioxidant, iron chelating and anti-inflammatory activities; has been shown to be neuroprotective in animal models of Parkinson's disease (PD) and Alzheimer's disease (AD), and also regulates the processing of amyloid precursor protein (APP) through a non-amyloidogenic pathway [103, 104]. Understanding the timing of iron mismanagement in relation to the progression of neuronal losses would provide important information on pathogenesis, and

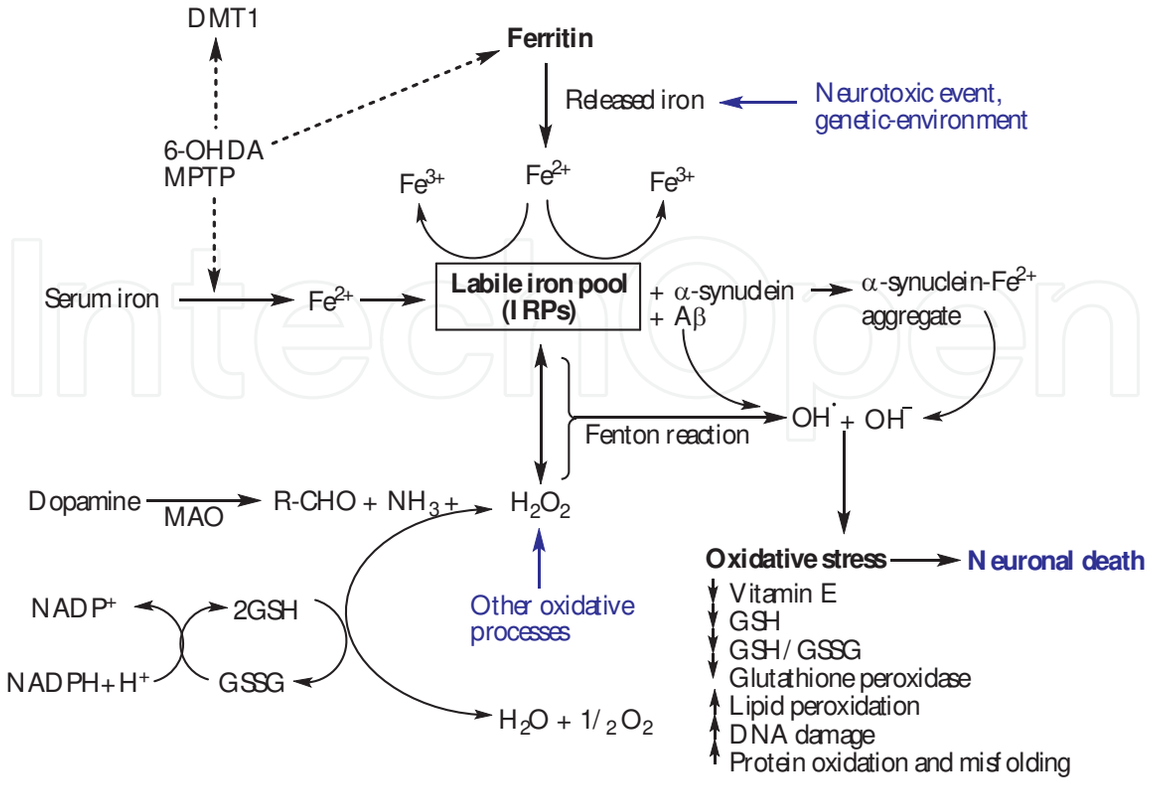

Figure 3. Mechanism of iron-induced neurodegeneration and its prevention [95]. Abbreviations: DMT1=divalent metal ion transporter-1; GSH=reduced glutathione; GSSG=oxidized glutathione; IRPs=iron regulatory proteins; MAO=monoamine oxidase; MPTP=1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine;$NADP^+$=nicotinamide adenine dinucleotide phosphate; NADPH=reduced nicotinamide adenine dinucleotide phosphate; 6-OHDA=6-hydroxydopamine

would raise the possibility of monitoring iron changes as a marker of disease progression, and perhaps even in a pre-clinical diagnosis in conditions where iron misregulation is an early event.

More *in vitro* and *in vivo* studies should be done to investigate how iron misregulation/accumulation synergizes with common endogenous and environmental toxins. Iron misregulation/accumulation alone can kill neurons only in genetic disorders where iron imbalance occurs rapidly and is extensive. However, in most cases, the amount of iron build-up is relatively low and the neurotoxic mechanism might involve a combination of iron and other toxins. Future investigations of iron in the brain, including how to best monitor iron deposition *in vivo*, the clinical relevance of excessive iron deposition, and the mechanistic relationship between iron deposition and disease pathophysiology, hold the promise of advancements in the field of neurotherapeutics.

6.5. Mutagenicity and cancinogenesis

Topical applications of green tea polyphenol fractions (such as EGCG, EGC and ECG) inhibitedbenz[a]-pyrene (BP)-and 7,12-dimethylbenz[a]-anthracene (DMBA)-initiated and 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-promoted tumorigenesis of mouse skin, possibly by inhibiting ROS production, inflammation and hyperplasia [105]. Green tea catechins can

counteract against tumorigenesis and DNA damage [106]. Mu and colleagues have identified an association between tea consumption and decreased cancer risk [107]. Surprisingly, EGCG in green tea exerted inhibitory effects on skin cancer, hepatocellular carcinoma and duodenal cancer, on metastasis of the melanoma cell line in lung cancer in mice, possibly by blocking the interaction of their tumor promoters with their own membrane receptors called sealing effects. Green tea significantly prevented growth of Namalwa, RAP1-EIO and HS-Sultan tumors transplanted intraperitoneally in the NOD/SCID mice; possibly by impairment of tumor invasion, anti-angiogenesis and by cell apoptosis induction [108]. EGCG decreased ornithine decarboxylase (ODC) and Ras and Jun oncogene levels, and also inhibited tyrosine kinase (TK) as well as mitogen-activated protein kinase (MAPK) activities in the transformed NIH-pATMras fibroblasts [109].

7. Conclusions

Green tea has long been considered a refreshing beverage that is prepared from tea (*Camellia sinensis*) shoots. It exerts many beneficial health effects, including anti-oxidant, anti-diabetic, hypolipidemic, anti-aging, anti-gout, neuroprotective, cardioprotective, hepatoprotective, anti-inflammatory, anti-carcinogenesis properties, among others. Variations of strain, source, geographic area, altitude, climate, cultivation, duration of fermentation and the preparation process can give rise to differences in the amounts of catechins derivatives, nutritional values, biological activities and the pharmacological properties of green tea products. EGCG is the most abundant type of catechin found in green tea and also the most relevant phytochemical displaying an influencing in several diseases and disorders. Some green tea catechins are not absorbed, while some catechins are absorbed from the intestine into the blood, and then are biologically transformed in liver microsomes by glucuronidation, sulfation and methylation reactions and ultimately excreted through the bile and urine. In this article, we have focused on the efficacy of green tea crude extract and catechins fractions, particularly EGCG in 1) depleting free radicals in normal cells, 2) removing chelatable iron from vital organs with iron overload, 3) lowering the levels of the risk factors of cardiovascular diseases, 4) inhibiting growth and proliferation of leukemic cells and solid malignant tumors, and 5) scavenging ROS and a repletion in the reducing power in neuronal tissues. The recognized benefits of green tea are that it is 1) potent in antioxidation, 2) effective in iron chelation, 3) beneficial in the inhibition of fat digestion, absorption and synthesis, 4) apoptotic induction, and 5) neuroprotection, respectively. Green tea has played a prominent role in the lives of many over time as a beverage, as a component of the diet, and now a substance that can be applied in drugs. The benefits of which have now been evidently documented.

Abbreviations

AD=Alzheimer's disease

ALT=alanine aminotransferase

AML=acute myelocytic leukemia

APP=amyloid precursor protein

ATRA=all-*trans* retinoic acid

BBB=blood brain barrier

BKO=β-globin gene knockout

BP=benz[a]-pyrene

C=catechin

CLL=chronic lymphocytic leukemia

COMT=catechol-*O*-methyltransferase

CVD=cardiovascular diseases

DAPK2=death-associated protein kinase 2

DFP=deferiprone

DH=double heterozygous β-globin gene knockout carrying human β^E gene

DMBA=7,12-dimethylbenz[a]-anthracene

DMT1=divalent metal ion transporter-1

DW=deionized water

EC=epicatechin

ECG=epicatechin 3-gallate

EGC=epigallocatechin

EGCG=epigallocatechin 3-gallate

FAS=fatty acid synthase

GA=gallic acid

GC=gallocatechin

G-CSF=granulocyte colony stimulating factor

GM-CSF=granulocyte macrophage colony stimulating factor

GSH=reduced glutathione

GSSG=oxidized glutathione

GTE=green tea extract

Hb=hemoglobin

HDL=high-density lipoprotein

HGF=hematopoietic growth factors

HMG-Co A=3-hydroxy-3-methylglutaryl-coenzyme A

hTERT=human telomerase reverse transcriptase

HTLV-I=human T-cell lymphotropic virus type I

IDL=intermediate density lipoprotein

IL-3=interleukin-3

IRPs=iron regulatory proteins

K_i=inhibition constant

LD_{50}=lethal dose at 50%

LDL=low-density lipoprotein

LIP=labile iron pool

LPI=labile plasma iron

MAO=monoamine oxidase

MAPK=mitogen-activated protein kinase

MDA=malondialdehyde

MPTP=1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

MW=molecular weight

$NAD(P)^+$=nicotinamide adenine dinucleotide phosphate

NAD(P)H=reduced nicotinamide adenine dinucleotide phosphate

ND=not determined

NQO1=NAD(P)H:quinoneoxidoreductase 1

NTBI=non-transferrin bound iron

ODC=ornithine decarboxylase

6-OHDA=6-hydroxydopamine

PD=Parkinson's disease

PPO=polyphenol oxidase

RBC=red blood cell

RNS=reactive nitrogen species

ROS=reactive oxygen species

SAM=*S*-adenosyl methionine

SULT=sulfotransferases

$T_{1/2}\beta$=beta-elimination half-lives

TEAC=trolox-equivalent antioxidant capacity

TK=tyrosine kinase

TPA=12-*O*-tetradecanoylphorbol-13-acetate

T_{reg}=regulatory T cells

UGT=uridine diphosphate-glucuronosyltransferase

V_d=distribution volume

VEGF=vascular endothelial growth factor

WT=wild-type

XO=xanthine oxidase

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