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REVIEW ARTICLE

Antioxidants from black and green tea: from dietary modulation of oxidative stress to pharmacological mechanisms

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The consumption of tea (*Camellia sinensis*) has been correlated with a low incidence of chronic pathologies, such as cardiovascular disease and cancer, in which oxidative stress plays a critical role. Tea catechins and theaflavins are, respectively, the bioactive phytochemicals responsible for the antioxidant activity of green tea (GT) and black tea (BT). In addition to their redox properties, tea catechins and theaflavins could have also pharmacological activities, such as the ability to lower glucose, lipid and uric acid (UA) levels. These activities are mediated by pharmacological mechanisms such as enzymatic inhibition and interaction with transporters. Epigallocatechin gallate is the most active compound at inhibiting the enzymes involved in cholesterol and UA metabolism (hydroxy-3-methyl-glutaryl-CoA reductase and xanthine oxidase respectively) and affecting glucose transporters. The structural features of catechins that significantly contribute to their pharmacological effect are the presence/absence of the galloyl moiety and the number and positions of the hydroxyl groups on the rings. Although the inhibitory effects on α-glucosidase, maltase, amylase and lipase, multidrug resistance 1, organic anion transporters and proton-coupled folate transport occur at higher concentrations than those apparent in the circulation, these effects could be relevant in the gut. In conclusion, despite the urgent need for further research in humans, the regular consumption of moderate quantities of GT and BT can effectively modulate their antioxidant capacity, mainly in people subjected to oxidative stress, and could improve the metabolism of glucose, lipid and UA.

LINKED ARTICLES

This article is part of a themed section on Principles of Pharmacological Research of Nutraceuticals. To view the other articles in this section visit http://onlinelibrary.wiley.com/doi/10.1111/bph.v174.11/issuetoc

Abbreviations

BT, black tea; BTE, black tea extract; CYP450, cytochrome p450; DNMT, DNA-methyltransferase; EC, epicatechin; ECG, epicatechin gallate; EGC, epigallocatechin; EGCG, epigallocatechin gallate; GLUT1, sodium-independent glucose transporter; GST, glutathione S-Transferase; GT, green tea; GTE, green tea extract; HMGR, hydroxy-3-methyl-glutaryl-CoA reductase; IsoP, isoprostanes; MDR1, multidrug resistance 1; NEAC, non enzymatic antioxidant capacity; Nrf2, nuclear factor-erythroid 2-related factor 2; OAT, organic anion transporters; OCT, organic cation transporters; OSRRF, oxidative stress-related risk factors; OT, oolong tea; PCFT, proton-coupled folate transport; RNase A, ribonuclease A; SGLT1, sodium-dependent glucose transporter; TrxR, thioredoxin reductase; UA, uric acid; XO, xanthine oxidase

DOI:10.1111/bph.13649

Tables of Links

TARGETS		
Enzymes[a]	Glucosidase	**Transporters**[b]
Amylase	Glutathione reductase	GLUT1
COX-1	HMGR	MDR1
Cytochrome p450 1	Lipase	OAT
Cytochrome p450 2	Maltase	OCT1
Cytochrome p450 3	Xanthine oxidase	OCT3
DNA methyltransferase		PCFT
DNA polymerase		SGLT1

LIGANDS
Epigallocatechin gallate (EGCG)
Uric acid

These Tables list key protein targets and ligands in this article which are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Southan *et al.*, 2016) and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 ([a,b]Alexander *et al.*, 2015a,b).

Introduction

The consumption of tea (*Camellia sinensis*) has been correlated with low incidence of chronic pathologies, such as cardiovascular disease and cancer (Tang *et al.*, 2015). However, although the molecules involved in this effect have been shown to have anti-inflammatory and antioxidant effects, and to improve endothelial function, no clear-cut conclusion has been reached on their mechanism of action. The health benefits ascribed to the consumption of teas are thought to be associated with their high content of bioactive ingredients such as polyphenols. The latter are secondary plant metabolites and include the subclasses of flavonoids, flavones, flavonols, flavanols, isoflavones, flavanones and anthocyanidins (Del Rio *et al.*, 2013). Within the polyphenols, the tea flavanols, catechins and theaflavins, have been identified as the bioactive phytochemicals of green tea (GT) and black tea (BT) respectively, and shown to be responsible for their antioxidant activity (Serafini *et al.*, 2011). The antioxidant properties of GT and BT in humans were discovered in 1996 (Serafini *et al*. 1996), where in healthy subjects, the non enzymatic antioxidant capacity (NEAC) of plasma was shown to significantly increase after the ingestion of 300 mL of either BT or GT (Serafini *et al*. 1996). However, when GT and BT were consumed with milk, the antioxidant activity was drastically reduced or totally inhibited (Serafini *et al.*, 1996).

Apart from their antioxidant activity, tea flavanols could also have other activities of pharmacological interest, such as the ability to lower glucose (Liu *et al.*, 2013; Zheng *et al.*, 2013), lipid (Zheng *et al.*, 2011; Hartley *et al.*, 2013; Onakpoya *et al.*, 2014) and uric acid (UA) (Peluso *et al.*, 2015a) concentrations. These activities could be mediated by their effects on various enzymes and transporters (Peluso *et al.*, 2015b). One of the most important mechanisms of food–drug interactions has been suggested to be mediated by effects on transporters (Shang *et al.*, 2014; Werba *et al.*, 2015). With the increasing interest in the health promoting properties of tea, in this review we have evaluated the role of teas in modulating oxidative stress in humans and the mechanisms involved in the pharmacological effects of tea flavanols.

Flavanols in teas and their pharmacokinetics in humans

GT and BT are the two types of tea mostly consumed throughout the world, and they contain different phytochemicals endowed with biological activities, such as flavanols (Serafini *et al.*, 2011). The processing or harvesting times of the leaves of *C. sinensis* leads to the different composition of flavonoids between GT and BT (Serafini *et al.*, 2011). In the case of GT, the leaves are steamed quickly after harvesting. Home tea preparation has also an impact on the flavonoid content of tea; brews of 5 min at temperatures of 100°C result in infusions with greater antioxidant capacity than teas with a shorter brewing time (2 min) at lower temperatures (60–80°C) (Sharpe *et al.*, 2016).

The major active flavonoids in GT are epicatechin (EC), epicatechin gallate (ECG), epigallocatechin (EGC) and epigallocatechin gallate (EGCG), as displayed in Table 1. The structure of EGCG includes a benzenediol ring joined to a tetrahydropyran moiety, a pyrogallol ring and a galloyl group (with the pyrogallol ring) (Figure 1) (Serafini *et al.*, 2011). ECG lacks a hydroxyl group on the pyrogallol ring; while in EGC, the galloyl group is replaced by a hydrogen atom (Figure 1). These flavonoids are present in lower amounts in BT where they are in part converted, during the enzymatic fermentation process driven by polyphenol oxidase, to complex condensation products, such as theaflavins (Figure 1) and thearubigins (Serafini *et al.*, 2011; Stodt *et al.*, 2014). The latter are known to be heterogeneous polymers, but their formation and characterization have yet to be elucidated, whereas the former possess a characteristic benzotropolone moiety that is produced by condensation between a catechol-type ring of EC and a pyrogallol-type ring of EGC (Tanaka *et al.*, 2009).

Table 1

Flavanol content of GT, BT and OT

	GT infusion mg·100 mL^{-1} ± SD	BT infusion mg·100 mL^{-1} ± SD	OT infusion mg·100 mL^{-1} ± SD	References
EC	7.93 ± 13.74	3.94 ± 4.27	2.7 ± 3.77	Arts *et al.*, 2000; Begona Barroso and Werken van de, 1999; Bronner and Beecher, 1998; Ding *et al.*, 1992; Ding *et al.*, 1999; Khokhar and Magnusdottir, 2002; Kilmartin and Chyong, 2003; Kuhr and Engelhardt, 1991; Lee and Ong, 2000; Liang *et al.*, 2003; Lin *et al.*, 1996; Lin *et al.*, 1998; Long *et al.*, 2001; Luximon-Ramma *et al.*, 2005; Pascual-Teresa *et al.*, 2000; Pelillo *et al.*, 2002; Price and Spitzer, 1993; Rechner *et al.*, 2002; Stewart *et al.*, 2005; Wang *et al.*, 2000; Zhang *et al.*, 1997
ECG	7.50 ± 10.19	7.34 ± 7.10	4.99 ± 6.55	
EGC	19.68 ± 25.11	7.19 ± 10.87	9.65 ± 14.16	
EGCG	27.16 ± 39.91	9.12 ± 12.67	17.89 ± 27.41	
TF	–	3.27 ± 3.31	–	Liang *et al.*, 2003; Stewart *et al.*, 2005; Ding *et al.* 1992
TF3G	–	1.58 ± 2.97	–	
TF3′G	–	4.08 ± 4.08	–	
TFDG	–	3.52 ± 3.89	–	

TF, theaflavin; TF3G, theaflavin 3-O-gallate; TF3′G, theaflavin 3′-O-gallate; TFDG, theaflavin 3,3′-O-digallate. (Source: http://phenol-explorer.eu/, values calculated by combining the data from the publications listed).

Oolong tea (OT) also originates from *C. sinensis* and is produced using a shorter fermentation time than BT and contains fewer flavanols (35.72 mg · 100 mL^{-1} infusion) than BT and GT (76.46 mg·100 mL^{-1} GT infusion, 82.6 mg·100 mL^{-1} BT infusion) (Table 1). In addition, a new group of polymeric oxidized flavanols have been isolated and identified from OT and are known as theasinensins (Weerawatanakorn *et al.*, 2015). Theasinensins are quinone dimers of EGC and EGCG produced by these two catechin quinone monomers and have been suggested to contribute to biological activities of OT (Weerawatanakorn *et al.*, 2015) despite there being no data available on their content and absorption.

At present the data published on the absorption of green tea phenolics vary considerably and are controversial (Manach *et al.*, 2005). Analytical limitations have drastically biased the identification and characterization of flavan-3-ol catabolites, but also a lack of available pure standards for each specific catabolite has significantly reduced the quality of absorption studies. The liver and intestines play a major role in the first-pass metabolism and absorption of catechins (Feng, 2006). After ingestion of GT, ECG is generally absent from plasma, whereas EGCG, EGC and EC are found in various forms, free or conjugated with glucuronide, sulfate or methyl groups (Table 2). Williamson *et al.* (2011), Clifford *et al.* (2013) and Del Rio *et al.* (2013) reviewed the pharmacokinetic data of the consumption of GT in humans (Table 2).

Although the *F* values of bioavailability were not estimated in humans, after the consumption of a cup of GT containing 112 mg of EGCG, 51 mg of EGC and 15 mg of EC in 200 mL, the predicted peak-plasma concentrations (Cmax) values (total free and sulfate/glucuronide conjugates) are 125, 181 and 76 nM, respectively, together with 94 nM methyl-EGC and 51 nM methyl-EC (Williamson *et al.*, 2011); these Cmax values occurred 1.3–2.7 h after ingestion (Table 2). After the ingestion of 500 mL of GT, the reported $t_{1/2}$ of flavanols' conjugates ranged between 1 and 3.1 h (Clifford *et al.* (2013).

The serum metabolites of GT (GTM, sulfates/glucuronides of EC, EGC, ECG and EGCG: 32.47, 33.29, 0.13 and 0.40 μM respectively), prepared from rats given an infusion of GT, significantly inhibited the activity of the organic anion transporters (OAT) in CHO cells expressing OAT1 and in HEK293 cells expressing OAT3 (Peng *et al.*, 2015).

Urine collected 0–24 h after GT ingestion contained flavan-3-ol metabolites similar to those detected in plasma (Del Rio *et al.*, 2013). The percentage of metabolites excreted in urine range from 8.1 to 28.5% of the ingested GT flavanols (Del Rio *et al.*, 2013).

Only limited data are available on the pharmacokinetic of theaflavins in humans: after the consumption of 700 mg theaflavins, equivalent to about 30 cups of black tea, the maximum concentration detected in blood plasma was around 1.0 μg·L^{-1} in a sample collected after 2 h and also the concentration in urine peaked after 2 h at 4.2 μg·L^{-1} (Mulder *et al.*, 2001), as shown in Table 2.

In addition to the intestinal or hepatic metabolites, metabolites derived from colonic bacteria have been identified (Sang *et al.*, 2008). In particular, the action of the microbiota results in their conversion to C-6-C-5 phenylvalerolactones and phenylvaleric acids, which undergo side-chain shortening to produce C-6-C-1 phenolic and aromatic acids that

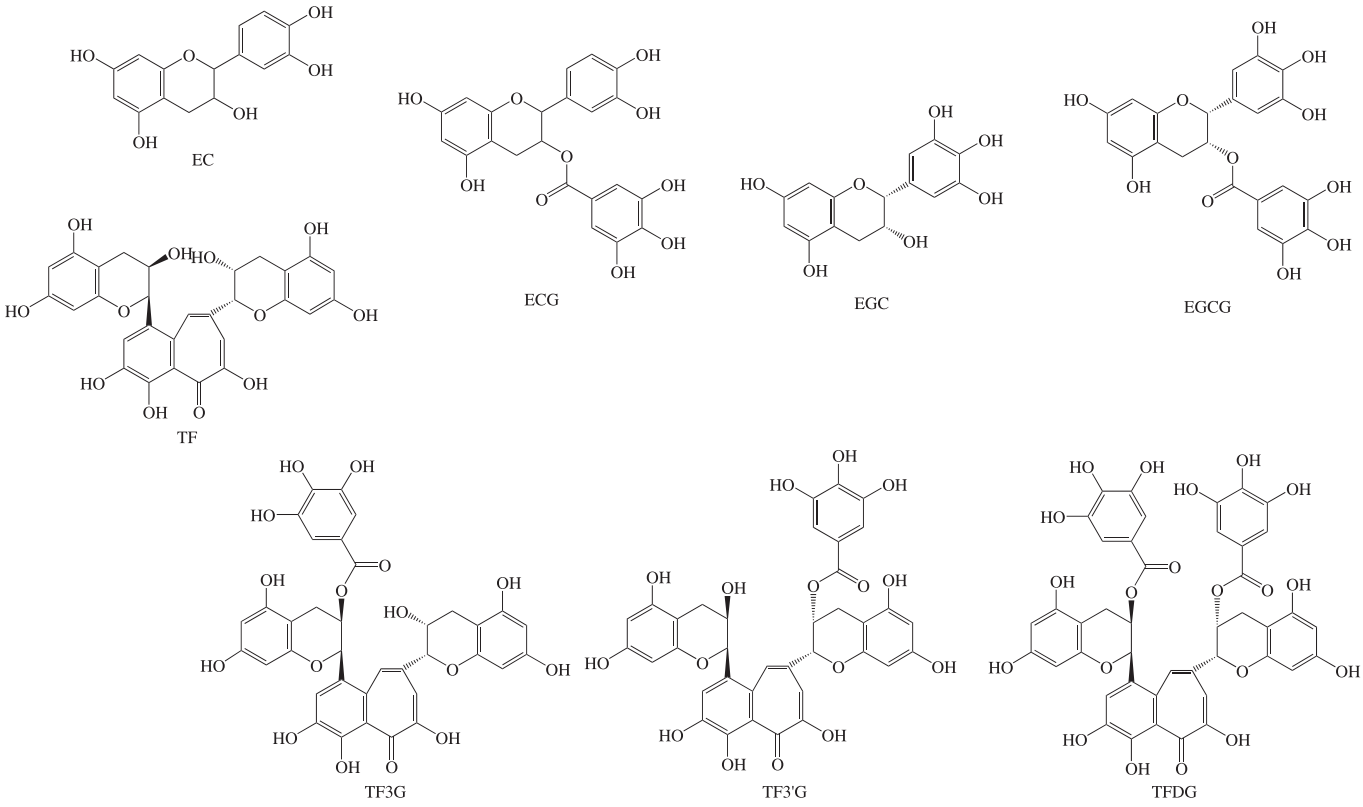

Figure 1
Chemical structures of bioactive ingredients in green and black tea. TF, theaflavins; TF3G, theaflavin 3-O-gallate; TF3'G, theaflavin 3'-O-gallate; TFDG, theaflavin 3,3'-O-digallate.

enter the bloodstream and are excreted in urine in amounts equivalent to 36% of flavanol intake (Clifford *et al.*, 2013). It has recently been observed that the microbial metabolite 5-(3′,5′-dihydroxyphenyl)-γ-valerolactone (EGC-M5) and the 5-(3′,5′-dihydroxyphenyl)-γ-valerolactone-3′-O-glucuronide (EGC-M5-glucuronide) significantly increase CD4+ activity (ATP level), having immunostimulatory activity, whereas EGC and EGCG decreased the CD4+ activity (Kim *et al.*, 2016).

Most polyphenols present in tea undergo drastic modifications due to the action of human and microbial enzymes leading to a wide array of metabolites. Moreover, as the gut micro flora vary significantly among subjects, this could result in different microbial catabolism and, consequently, diverse biological effects.

Antioxidant activity

The structural features of GT catechins that significantly contribute to their antioxidant action are the presence/absence of the galloyl moiety and the number and positions of the hydroxyl groups on the rings. The latter determine their ability to interact with biological matter through hydrogen bonding, or electron and hydrogen transfer processes within their antioxidant activities. In fact, the antioxidant mechanism implies hydrogen atom transfer or single electron transfer reactions, or both (Lambert and Elias, 2010). Tea catechins are thought to display antioxidant activity, scavenging lipid alkoxyl and peroxyl radicals by acting as chain-breaking antioxidants (Lambert and Elias, 2010). *In vitro*, a stoichiometric factor n of 4.16 ± 0.51 was obtained for EGCG, which is considered to be responsible for most of the antioxidant activity of GT (Khan *et al.*, 2006). In contrast, a factor of 2.20 ± 0.26 was found for EGC, during the reaction with peroxyl radicals generated by thermolysis of the azo initiator 2,2′-azobis(2,4-dimethylvaleronitrile) (Valcic *et al.*, 2000).

Despite the large body of evidence for the antioxidant effect of flavanols *in vitro*, the results from human trials are inconsistent and are related to ingested dose, measured biomarkers and the extent of oxidative stress in the subjects. As observed for healthy subjects (Serafini *et al.*, 1996; van het Hof *et al.*, 1997) the consumption of GT, but not BT, increased NEAC in subjects with risk factors. In particular, Bertipaglia de Santana *et al.* (2008) found increased of NEAC levels in hypercholesterolaemic subjects (n = 25) who consumed 500 mL of GT for 90 days. In contrast, the long-term consumption of five cups (21 days) (Davies *et al.*, 2003) or 900 mL (28 days) (Widlansky *et al.*, 2005) of BT did not increase plasma NEAC either in mildly hypercholesterolaemic subjects (Davies *et al.*, 2003) or in patients with coronary

Table 2

Pharmacokinetics of tea flavanols and their plasma metabolites in humans

	Ingested dose	Detected compound	Cmax	Tmax (h)	References
GT	EGCG 63–328.5 mg	EGCG	55–711 nM	1.3–2.7	http://phenol-explorer.eu/, Williamson *et al.*, 2011; Clifford *et al.*, 2013; Del Rio *et al.*, 2013
GT	EGC 32–306 mg	EGC	40–1791 nM	1.3–2.2	http://phenol-explorer.eu/, Williamson *et al.*, 2011; Clifford *et al.*, 2013; Del Rio *et al.*, 2013
GT	EC 12–113 mg	EC	29–655 nM	1.4–1.8	http://phenol-explorer.eu/, Williamson *et al.*, 2011; Clifford *et al.*, 2013; Del Rio *et al.*, 2013
GT	flavanols 32–154 mg	Methyl-EGC	62–5300 nM	2–2.3	http://phenol-explorer.eu/, Williamson *et al.*, 2011; Clifford *et al.*, 2013; Del Rio *et al.*, 2013
GT	flavanols 12–17 mg	Methyl-EC-sulfate	14–90 nM	1.3–1.7	http://phenol-explorer.eu/, Williamson *et al.*, 2011; Clifford *et al.*, 2013; Del Rio *et al.*, 2013
GT	Flavanols 648 μM in 500 mL	EC-glucuronide EC-sulfates EGC-glucuronide Met-EGC-glucuronide	29 nM 89 nM 126 nM 46 nM	1.7 1.6 2.2 2.3	http://phenol-explorer.eu/, Williamson *et al.*, 2011; Clifford *et al.*, 2013; Del Rio *et al.*, 2013
TFs	700 mg dissolved in 150 mL hot water: TF 123.9·700 mg^{-1} DW TF3G 222.6·700 mg^{-1} DW TF3′G 116.9·700 mg^{-1}DW TFDG 219.8·700 mg^{-1}DW	Theaflavins	≈1 $\mu g \cdot L^{-1}$	2	http://phenol-explorer.eu/, Mulder *et al.*, 2001

Cmax, peak-plasma concentrations; DW, dry weight; TF, theaflavin; TF3G, theaflavin 3-O-gallate; TF3′G, theaflavin 3′-O-gallate; TFDG, theaflavin 3,3′-O-digallate; Tmax, time at which the Cmax is observed.

artery disease (Widlansky *et al.*, 2005). In a randomized cross-over study that investigated the dose–response effect of 500 mL of GT with different solid contents (1.4, 1.6, 1.8 and 2.0 $g \cdot L^{-1}$), a linear increase in NEAC was observed when the amount of tea solids present in GT was increased. This highlights the presence of a linear association between the amount of flavonoids ingested and the extent of the antioxidant response in humans (Pecorari *et al.*, 2010). Only one human study has investigated the ability of a ready-to-drink OT to modulate plasma antioxidant status; it showed that ingestion of 500 mL of OT significantly increased plasma and urinary NEAC levels (Villaño *et al.* 2012).

The picture is even more complicated if we select intervention studies looking at isoprostanes (IsoP), a reliable marker of oxidative stress. The consumption of BT, GT, green tea extract (GTE) or catechins did not change IsoP levels either in healthy subjects or in disease patients (Table 3). Of the 17 interventions, from 13 studies, only one reported a decrease in plasma and serum IsoP after 4 weeks consumption of BT (500 $mL \cdot day^{-1}$) in 12 healthy volunteers, whereas no effect was observed after acute drinking of a single dose (Wolfram *et al.*, 2002). The consumption of GT (Müller *et al.*, 2010) or catechins (Loke *et al.*, 2008) did not change the levels of IsoP in an acute intervention study, despite the increase in NEAC and/or markers of absorption of polyphenols (Table 3). Similarly, Braga *et al.* (2012) found increased levels of NEAC after 2 days of GTE consumption in pancreatic cancer patients, whereas IsoP levels were unchanged. No changes in IsoP levels were observed after the repeated consumption of GT, GTE or catechins (7–112 days) in either healthy (Table 3) or hypertensive subjects (Hodgson *et al.*, 2002a), even when consumed in association with onions (O'Reilly *et al.*, 2001) or lutein (Li *et al.*, 2010). Moreover, there is a clear discrepancy between effects on antioxidant capacity and on oxidative stress markers, as demonstrated in Table 3. The effect of teas on plasma NEAC was described in a meta-analysis by Lettieri-Barbato *et al.* (2013), who investigated the antioxidant effect of plant food ingestion in humans. The main result from the 17 interventions showed that tea consumption induced a similar increase in

Table 3

Human intervention studies with BT, GT, EC and EGCG: effect on absorption of IsoP, NEAC and polyphenols

	Subjects	Dose day^{-1} (n° days)	IsoP	NEAC	PC§	Reference
BT	10 (mildly dyslipidaemic)	10 g in1250 mL (28)	↔	–	–	Hodgson *et al.*, 2002b
BT	12	500 mL (1)	↔	–	–	Wolfram *et al.*, 2002
BT	12	500 mL (28)	↓	–	–	Wolfram *et al.*, 2002
BT	13 (hypertensive)	10 g in 1000 mL (7)	↔	–	–	Hodgson *et al.*, 2002a
BT	15 (mildly dyslipidaemic)	Five cups (21)	↔	↔	–	Davies *et al.*, 2003
BT	22 (mildly dyslipidaemic)	10 g in 1250 mL (28)	↔	–	–	Hodgson *et al.*, 2002a
BT	66 (coronary artery disease)	900 mL (28)	↔	↔	–	Widlansky *et al.*, 2005
BT + Onions	32	300 mL + 150 g of onion cake (14)	↔	–	–	O'Reilly *et al.*, 2001
GT	13 (hypertensive)	10 g in 1000 mL (7)	↔	–	–	Hodgson *et al.*, 2002a
GT	22	6.3 g in 700 mL (14)	↔	–	↑	Hirano-Ohmori *et al.*, 2005
GT	33	600 mL (1)	↔	↑	↑	Müller *et al.*, 2010
GTE	20	3 g (28)	↔	–	–	Freese *et al.*, 1999
GTE	36 (pancreatic cancer)	1000 mg (2)	↔	↑	–	Braga *et al.*, 2012
GTE	9	844 mg (catechins) (14)	↔	–	–	Donovan *et al.*, 2005
GTE + lutein	40	200 + 12 mg lutein (112 days)	↔	–	↔	Li *et al.*, 2010
EC	12	200 mg (1)	↔	–	↑	Loke *et al.*, 2008
EGCG	12	200 mg (1)	↔	–	↑	Loke *et al.*, 2008

IsoP, isoprostanes; NEAC, non-enzymatic antioxidant capacity; PC, polyphenols concentration, §reported as the plasma or urinary concentrations of a single cathechin, total catechins or total phenols or their metabolites; ↔, unchanged; ↑, increased; ↓, decreased.

plasma NEAC after both acute and chronic ingestion (Lettieri-Barbato *et al.*, 2013) and that GT had a stronger antioxidant effect than BT (Lettieri-Barbato *et al.*, 2013). When participants were divided into healthy subjects and subjects exposed to oxidative stress-related risk factors (OSRRF), in the beverage category including teas, an effect on plasma NEAC was clearly detected in the OSRRF category, whereas no changes in plasma NEAC were observed in healthy subjects (Lettieri-Barbato *et al.*, 2013). Biomarkers of oxidative stress such as isoprostanes increase significantly only when an ongoing oxidative stress is present, following that, antioxidant modulation might occur only if levels are significantly high; unfortunately, there are no data available on the physiological level of isoprostanes in healthy humans. Moreover, NEAC represents the overall molecular antioxidant defences of plasma and, despite being regulated endogenously, might be more liable to increase after the consumption of tea or plant food supplements compared with the reducing markers of oxidative stress. In intervention studies, it is highly recommended that different markers of oxidative stress, antioxidant status and redox enzymes should be measured in order to have a complete picture of the phenomenon and define the results according to the different aspects of the redox mechanism. Overall, it is possible that the antioxidant activity of teas is strictly associated with the presence of chronic oxidative stress, when an increase in antioxidant activity from dietary sources is required to improve the antioxidant defences. In this regard, more evidence is needed to identify differences in the level of markers of oxidative stress and antioxidants status between healthy and pre-pathological conditions.

Enzymatic inhibition

In vitro GTE, black tea extract (BTE), catechins and theaflavins have been shown to inhibit various enzymes involved in glucose and lipid metabolism, such as amylase, maltase, glucosidase and lipase and the enzyme involved in cholesterol synthesis hydroxy-3-methyl-glutaryl-CoA reductase (HMGR). As shown in Table 4, the IC_{50} values range between 10^{-8} and 10^{-5} M. In the majority of the cases, GTE, BTE, catechins and theaflavins inhibit the enzymes in a non-competitive manner with respect to substrate concentration. EGCG potently inhibits the *in vitro* activity of HMGR (K_i in the nanomolar range) by competitively binding to the co-factor site of the reductase (Cuccioloni *et al.*, 2011). In contrast, EGCG interacts with Val^{21}, Glu^{188} and Glu^{220} of lipase, inducing conformational alterations and decreasing the enzyme's catalytic activity (Wu *et al.*, 2013). The galloyl moiety seems to be involved in the inhibitory effect on pancreatic lipase, because theaflavins and catechins without galloyl moieties did not inhibit this enzyme (Ikeda *et al.*, 2005; Kobayashi *et al.*, 2009).

However, the results in humans are contrasting as highlighted by different meta-analyses on human interventions with GT, BT or catechins. In particular, Zheng *et al.* (2013) and Liu *et al.* (2013) found decreased glucose levels, whereas no significant effects on glucose were observed in a recent meta-analysis (Khalesi *et al.*, 2014; Li *et al.*, 2016). Similarly, a different meta-analysis reported a reduction in cholesterol levels (Zheng *et al.*, 2011; Hartley *et al.*, 2013; Khalesi *et al.*, 2014; Onakpoya *et al.*, 2014), but this was not confirmed by Li *et al.* (2016) and Zhao *et al.* (2015).

Table 4

Inhibitory effect *in vitro* of tea flavanols on selected enzymes

	Enzyme	IC_{50} or K_i	References
GTE	α-glucosidase, maltase or amylase	2.82 μg·mL^{-1}	Forester *et al.*, 2012; Nguyen *et al.*, 2012; Simsek *et al.*, 2015; Yang and Kong, 2016.
BTE		2.25 μg·mL^{-1}	
EGCG		10^{-5} M	
BTE	Lipase	0.9–1.3 μg·mL^{-1}	Grove *et al.*, 2012; Kobayashi *et al.*, 2009; Wang *et al.*, 2014; Yuda *et al.*, 2012.
TFDG, EGCG		10^{-6} M	
EGCG	HMGR	10^{-8} M	Cuccioloni *et al.*, 2011.
BTE	XO	5.8%	Aucamp *et al.*, 1997; Lin *et al.*, 2000; Dew *et al.*, 2005.
TFDG		10^{-6}–10^{-5} M	
EC, EGC		10^{-5} M	
ECG		10^{-6} M	
EGCG		10^{-7} M	
EGC, GCG and EGCG	GST	10^{-6} M	Boušová *et al.*, 2012.
GTE	TrxR	256 μg·mL^{-1}	Wang *et al.*, 2008; Du *et al.*, 2009.
EGCG, ECG		10^{-5} M	
TF3G, TF3'G and TFDG		10^{-5} M	
EGCG	COX-1	10^{-6} M	Lee *et al.*, 2013.
EGC and ECG	DNA-pol	10^{-4} M	Mizushina *et al.*, 2005.
EGCG		10^{-6} M	
ECG > Met-EGCG > EGC > Di-Me-EGCG > EC	DNMT	10^{-6}–10^{-5} M	Fang *et al.*, 2003; Rajavelu *et al.*, 2011.
EGCG		10^{-7}–10^{-6} M	
TFDG		10^{-5} M	
GTE	RNase A	10^{-4} M GAE	Ghosh *et al.*, 2004.
EGCG		10^{-5} M	

TF, theaflavin; TF3G, theaflavin 3-O-gallate; TF3'G, theaflavin 3'-O-gallate; TFDG, theaflavin 3,3'-O-digallate; DNA-pol, DNA-polymerase; GAE, gallic acid equivalents.

As shown in Table 4, theaflavins and catechins inhibit xanthine oxidase (XO) activity and UA production *in vitro*: theaflavin 3,3'-O-digallate (10^{-6} M) and EGCG (10^{-7} M) act as competitive inhibitors (Aucamp *et al.*, 1997; Lin *et al.*, 2000). Despite the effect of theaflavins and catechins as XO inhibitors, in a meta-analysis reviewing human intervention studies that measured UA after tea products, no significant differences were observed between BT, GT and GTE (Peluso *et al.*, 2015a). However, it must be taken into account that many studies had UA as secondary outpoint and did not consider the fact that the normal range of UA differs in males and females. Only the study of Bahorun *et al.* (2010) had UA as primary outpoint and BT as a treatment and reported data for men and women separately, stratifying them according to baseline levels. It showed a decrease of UA only in subjects with high baseline levels and in men with baseline UA concentrations above 80 mg·L^{-1}, with the latter lowered after washout (BT 73 ± 17 mg·L^{-1} and water 80 ± 20 mg·L^{-1}) suggesting an inhibitory effect on XO that persists after discontinuation of consumption (Bahorun *et al.*, 2010). In accordance with the hypothesis of a persistent inhibitory effect on XO, in an uncontrolled trial, GTE (164 mg tea catechins) decreased UA after 7 days of washout, subsequent to 7 days of supplementation (Kimura *et al.*, 2002). Panza *et al.* (2008) reported a decrease in UA levels after 7 days of ingestion of GT (600 mL) and an inhibition of the exercise-induced activation of XO. Moreover, in an uncontrolled trial, decreases in UA after 9 weeks of GT (100 mg·day^{-1} of total catechins) and increases in UA with catechin-enriched GT (400 mg·day^{-1} of total catechins) were observed, but these effects were not statistically significant (Sone *et al.*, 2011). Furthermore, treatments of 2 weeks with GT (1.5 g, three times a day with total catechins 183 mg·g^{-1}: 823.5 mg·day^{-1}) (Gomikawa *et al.*, 2008) or 16 weeks with GTE (200 mg·day^{-1}) plus lutein (12 mg·day^{-1}) (Li *et al.*, 2010) were unable to change the UA concentration. Therefore, longer or higher consumptions of tea catechins do not seem to be associated with a greater effect, in contrast to the results of Kimura *et al.* (2002).

As shown in Table 4, catechins and theaflavins inhibit glutathione S-transferase (GST) and thioredoxin reductase (TrxR) with IC_{50} values between 10^{-6} and 10^{-5} M (Table 4). However, catechins are also able to stimulate the transcription of antioxidant enzymes, including SOD, catalase, glutathione peroxidase, glutathione reductase and GST, through the nuclear factor-erythroid 2-related factor 2

(Nrf2)/antioxidant responsive elements pathway (Na and Surh, 2008). In particular, it has been suggested that some derivatives of catechins can oxidize highly reactive cysteine thiol groups of kelch-like ECH-associated protein-1, resulting in disulfide bond formation and Nfr2 release (Na and Surh, 2008). In mice, a repeated (5 days) non-lethal toxic dose (55 or 75 mg·kg^{-1}) of EGCG decreased the expression of Nrf2 in the cytosol and increased it in the nucleus. As a result, mRNA expression and activities and/or protein levels of Nrf2-target genes including GST and TrxR were increased (Wang *et al.*, 2015).

Regarding the reported inhibition of COX-1 activity in platelets (Lee *et al.*, 2013; Table 4), this effect is not supported by the results of a human study conducted by Hirano-Ohmori *et al.* (2005). After the consumption of seven cups of GT a day for 2 weeks by healthy subjects, no significant changes in the aggregation of platelets were observed, despite a significant decrease in the serum low density lipoproteins (MDA-LDL).

Some catechins inhibited mammalian DNA-polymerase, DNA-methyltransferase (DNMT) and ribonuclease A (RNase A) (Table 4), with EGCG being the strongest inhibitor with IC_{50} values ranging between 10^{-7} M (DNMT9) and 10^{-5} M (RNase A). Among these enzymes, DNMT is involved in the hypermethylation of the promoter regions, which is an important mechanism for silencing the expression of many significant genes in cancer (Yiannakopoulou, 2015). However, data from meta-analyses provided contrasting results and indicated that the associations differ according to sex, ethnicity, cancer and tea types (Zeng *et al.*, 2014; Ma *et al.*, 2015; Zhu *et al.*, 2015; Huang *et al.*, 2016; Zhou *et al.*, 2016).

Flavanols are substrates of cytochrome p450 (CYP450) and are well-known to interfere with the pharmacokinetics of drugs in humans (Shang *et al.*, 2014; Werba *et al.*, 2015). However, only one case report has documented the interaction between GT and an immunosuppressant (tacrolimus), a substrate for CYP3A4. This case involved a 58-year-old male kidney transplant recipient, genotyped as 'poor metabolizer' and treated with a low dose of tacrolimus (i.e. 1 mg · 24 h^{-1}). After GT ingestion, an increase in tacrolimus levels was observed, and a positive dechallenge of tea was performed (Vischini *et al.*, 2011). In healthy volunteers, who received a cocktail of CYP450 metabolic probe drugs, including caffeine, dextromethorphan, losartan and buspirone for assessing the activity of CYP1A2, CYP2D6, CYP2C9 and CYP3A4, respectively, after 4 weeks of EGCG (800 mg) consumption, only a significant increase in the concentration of buspirone was found, suggesting a reduction in CYP3A4 activity (Chow *et al.*, 2006). In contrast, despite GTE (844 mg · day^{-1} for 14 days) inducing an increase in EGCG in plasma (1.3 ± 1.8 μM 2 h after treatment), no effect on CYP3A4 activity was found when alprazolam was used as the probe drug in healthy subjects (Donovan *et al.*, 2004). Therefore, the interaction of tea catechins with CYP450 depends on the substrate present.

Interaction with transporters

Catechins interact with transporters of the phase III drug detoxifying system, mainly the multidrug resistance 1 (MDR1), OAT and organic cation (OCT) transporters (Table 5). These transporters are characterized by low substrate specificity, and mediate the uptake of numerous drugs and xenobiotics into cells (Ayrton and Morgan, 2001). They are also involved in the absorption of flavonoids in the gastrointestinal tract and their subsequent tissue distribution (Passamonti *et al.*, 2009), as well as the extrusion of catechins (Vaidyanathan and Walle, 2003).

It is important to note that OAT (Sekine *et al.*, 2006; Wang *et al.*, 2010; Hu *et al.*, 2012) plays an important role in the renal excretion of urate. Therefore, the concentration of uric acid can be affected by the consumption of tea not only by its inhibition of XO (Table 4) but also its interaction with OAT (Table 5).

A recent review of the experimental studies in humans and/or clinical observations about interactions between GT

Table 5

Inhibitory effect *in vitro* of tea flavanols on selected transporters

	Transporter	IC_{50} or tested concentration	References
GT	MDR1	1% (v·v^{-1})	Kitagawa *et al.*, 2004; Knop *et al.*, 2015; Mei *et al.*, 2004; Qian *et al.*, 2005; Wang *et al.*, 2002.
GT polyphenols		40 μg·mL^{-1}	
EGCG		10^{-5}–10^{-6} M; 10 μg·mL^{-1}	
GT	OAT	0.39–2.6% (v·v^{-1})	Fuchikami *et al.*, 2006; Knop *et al.*, 2015; Misaka *et al.*, 2014; Roth *et al.*, 2011; Zhang *et al.*, 2013.
EGCG		10^{-6}–10^{-4} M	
ECG		10^{-5} M	
GT	OCT1/OCT2	1.4–7.0% (v·v^{-1})	Jaiyen *et al.*, 2015; Knop *et al.*, 2015.
GTE		1–3 mg·mL^{-1}	
EGC		10^{-3}–10^{-4} M	
EGCG		10^{-4} M	
EGCG	PCFT	10^{-6} M (competitive)	Kissei *et al.*, 2014.
ECG	GLUT1 /SGLT1	10^{-7}–10^{-3} M (competitive)	Johnston *et al.*, 2005; Kobayashi *et al.*, 2000; Naftalin *et al.*, 2003.
EGCG		10^{-7}–10^{-3} M (competitive)	

GLUT, sodium-independent glucose transporter; SGLT, sodium-dependent glucose transporter.

and cardiovascular drugs only yielded data for simvastatin and nadolol (Werba *et al.*, 2015). The authors suggested that these effects could be due to the inhibition of MDR1 and OAT exerted by GT catechins. Accordingly, the *in vitro* IC_{50} of tea flavanols on transporters, shown in Table 5, was lower for MDR1 and OAT than for OCT. Jaiyen *et al.* (2015) suggested that the consumption of GT could not interfere with cationic drugs secreted via renal OCT2 in humans because he found the interaction of GTE and ECG with OCT2 to be weak and reversible.

Kitagawa *et al.* (2004) reported that the effect of EGCG on MDR1 was more significant than that of verapamil (a well-known substrate for this transporter). The interaction of EGCG with MDR1 is at the level of the ATP-binding site (Wang *et al.*, 2002), in particular the ATP-binding site of the carboxyl-terminal nucleotide binding domain (Qian *et al.*, 2005), and it has been suggested that GT polyphenols and EGCG can reverse multidrug resistance through modulation of the ATPase activity of MDR1 (Mei *et al.*, 2004). Moreover, it has been suggested that the absorption of methotrexate can be reduced if it is consumed with GT, due to competitive inhibition of the proton-coupled folate transporter (PCFT) (Kissei *et al.*, 2014) (Table 5). However, while there are no data on this type of food and drug interaction, in an open-labelled randomized crossover study in healthy volunteers, it has been reported that GTE and BTE (0.3 g extract · 250 mL^{-1}) decrease the bioavailability of the vitamin folic acid (0.4 and 5 mg), reducing the Cmax of serum folate by 30–40% (Alemdaroglu *et al.*, 2008).

The glucose uptake pathways include sodium-independent (GLUT1) and sodium-dependent (SGLT1) transporters. Johnston *et al.* (2005) expressed both transporters in Caco-2 cells and showed that GT polyphenols (100 μM) decrease glucose uptake both in sodium-containing and sodium-free medium. It has been suggested that the antidiabetogenic effects of GT are, at least in part, due to the inhibition of the glucose transporter GLUT1 (Naftalin *et al.*, 2003). ECG and EGCG have high affinities for GLUT1 and competitively inhibit the uptake of glucose (ECG 0.14 μM; EGCG 0.9 μM) (Table 5). In particular, EGCG competitively inhibits the binding of glucose onto the external face of the carrier (Naftalin *et al.*, 2003). In contrast, the ungallated catechins, EC and EGC have only weak effects on glucose transport (Naftalin *et al.*, 2003). Similar results, but at higher concentrations compared with GLUT-1 inhibition, were obtained on SGLT1-mediated glucose transport that was competitively inhibited by ECG (390 μM) and EGCG (1 mM), whereas the inhibitory effects of EC and EGC were not significant (Kobayashi *et al.*, 2000) (Table 5). These data imply that a galloyl ester group may be important for blocking glucose uptake.

Potential adverse effects

The Dietary Supplement Information Expert Committee (DSI EC) have systematically reviewed the safety information for GT products and indicated that the consumption of GTE could induce liver damage (Sarma *et al.*, 2008). In fact, there is an increasing number of case reports of hepatoxicity associated with the intake of GT dietary supplements (Schönthal, 2011, Stickel *et al.*, 2011, Teschke *et al.*, 2012, Mazzanti *et al.*, 2015). The patients showed clinical symptoms of different severity, ranging from a mild increase in serum aminotransferase levels to fulminant hepatitis requiring a liver transplant (Di Lorenzo *et al.*, 2015). The types of preparation responsible for these adverse effects were plant food supplements based on GTE, among these were a hydroalcoholic extract and an aqueous extract of GT consumed as tea or in capsules (Di Lorenzo *et al.*, 2015). The dose of the tea supplement ingested ranged between 320 mg·day^{-1} catechins (710 mg·day^{-1} polyphenols) for the decaffeinated extract and 1 g·day^{-1} catechins for the micronized powder (Mazzanti *et al.*, 2015). For patients who consumed the GTEs as infusions, the ingested dose ranged from two cups to 3 L·day^{-1}, corresponding to about 186 and 1395 mg polyphenols ·day^{-1} (Mazzanti *et al.*, 2015). The components most frequently indicated as responsible for hepatotoxicity are catechins and in particular EGCG supplements (Bunchorntavakul and Reddy, 2013, Di Lorenzo *et al.*, 2015).

Discussion and conclusion

In recent years, the attention of the scientific community has been focused on understanding the mechanisms of action of tea flavanols, due to evidence that the consumption of tea has beneficial effects on health (Serafini *et al.*, 2011). In addition to conventional antioxidant properties (Serafini *et al.*, 1996; Lettieri-Barbato *et al.*, 2013; Table 3), there is evidence from *in vitro* experiments that antioxidants in tea may act by pharmacological mechanisms, such as inhibiting various enzymes and interacting with transporters (Tables 4 and 5). In this context, some considerations should be taken into account. Firstly, the biological effect of flavanols depends on their absorption, which tends to be low in humans (Table 2). Secondly, once ingested, they are extensively metabolized into molecules with different chemical structures and activity compared with the ones originally present in the teas. Therefore, differences in microbiota (van Duynhoven *et al.*, 2014) and genetic polymorphism of metabolizing enzymes (Hursel *et al.*, 2014) could play a role in the inter-individual variability in the response to treatment. This implies that we must exercise caution when speculating about the effects of a cup of tea from *in vitro* data and results obtained in animals. Furthermore, the poor of absorption of flavonoids and the extensive metabolic activity they undergo during absorption lead to very low plasma concentrations and to the presence in the blood stream of a wide variety of known and lesser-known metabolites (Del Rio *et al.*, 2013). Also most of the *in vitro* evidence for the beneficial effects of flavonoids has been obtained with pure compounds, which are present at low concentrations in humans (Table 2). However, EGCG at concentrations similar to its Cmax (10^{-8}–10^{-7} M, Table 2) after the consumption of a cup of GT, can effectively inhibit the enzymes involved in cholesterol and UA metabolism (HMGR: IC_{50} 10^{-8} M; XO: IC_{50} 10^{-7} M, Table 4) and the glucose transporters (IC_{50} 10^{-7} M, Table 5). The structural features of catechins that significantly contribute to their pharmacological effect are the presence/absence of the galloyl moiety and the number and positions of the hydroxyl groups on the rings. This also accounts for the higher antioxidant activity

of GT than BT, both *in vitro* (Serafini *et al.*, 1996) and in human intervention studies (Lettieri-Barbato *et al.*, 2013).

At a pharmacological level, although the inhibitory effect on α-glucosidase, maltase, amylase and lipase, as well as on MDR1, OAT and PCFT, occurs at higher concentrations (IC_{50} 10^{-6}–10^{-5} M, Tables 4 and 5) compared to circulating levels (Table 2), these effects could be relevant in the gut. In particular, in humans, the GTE-induced decrease in the digestion and absorption of carbohydrates (Lochocka *et al.*, 2015) and lipids (Lisowska *et al.*, 2015) have been confirmed by the starch ^{13}C breath test and the ^{13}C-labelled mixed triglyceride breath test.

It has been suggested that the food–drug interactions with cardiovascular drugs could be due to the inhibitory effects of GT catechins on MDR1 and OAT (Werba *et al.*, 2015) and that their ability to reduce the bioavailability of the vitamin folic acid could be due to competitive inhibition of PCFT (Alemdaroglu *et al.*, 2008). Furthermore, as flavanols are substrates of CYP450, they interfere with the pharmacokinetics of many drugs in humans (Vischini *et al.*, 2011; Shang *et al.*, 2014; Werba *et al.*, 2015). Their extensive hepatic metabolism could also account for the case reports of hepatoxicity associated with an intake of GTE in humans. However, in a recent systematic review, it was found that liver-related adverse events were only reported in four out of the 34 trials examined (Isomura *et al.*, 2016). A meta-analysis of these four trials gave a summary odds ratio for liver-related adverse events in subjects who received green tea intervention versus placebo of 2.1 (Isomura *et al.*, 2016) and it was concluded that liver-related adverse events after the consumption of GTE are likely to be rare.

The antioxidant effect of tea ingestion requires more evidence to unravel the mechanism of action and the ingredients involved. Despite there being no convincing evidence from long-term intervention studies in humans, tea flavanols are still considered to be the major candidates involved in the biological activity of teas. Possible mechanisms of action, such as the induction of an endogenous redox pathway or direct effects of polyphenol metabolites, should be elucidated so that the molecules responsible for the effect can isolated and clear-cut evidence can be obtained from long-term intervention studies.

In conclusion, despite the urgent need for further research in humans, the regular consumption of moderate quantitities of GT and BT can effectively modulate the antioxidant capacity of individuals, mainly of people experiencing conditions of oxidative stress, and could improve glucose, lipid and UA metabolism.

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Author contributions

M.S. drafted the aspect related to antioxidant activity, planned and critically reviewed the manuscript. I.P. drafted the manuscript.

Conflict of interest

The authors declare no conflicts of interest.

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