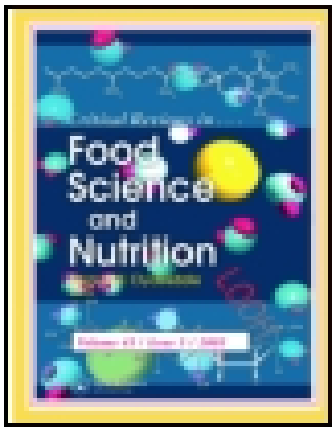

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Green Tea and Bbone Marrow Transplantation: From Antioxidant Activity to Enzymatic and Multidrug-resistance Modulation

Ilaria Peluso[a], Maura Palmery[a] & Annabella Vitalone[a]
[a] Department of Physiology and Pharmacology "V. Erspamer", "Sapienza" University of Rome, P.le Aldo Moro 5, 00185 Rome, Italy.
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Green tea and bone marrow transplantation: from antioxidant activity to enzymatic and multidrug-resistance modulation

Ilaria Peluso[1], Maura Palmery[1] and Annabella Vitalone[1]*

[1]Department of Physiology and Pharmacology “V. Erspamer”, "Sapienza" University of Rome , P.le Aldo Moro 5, 00185 Rome, Italy.

Corresponding author’s:

Annabella Vitalone, PhD

Department of Physiology and Pharmacology "V. Erspamer"

"Sapienza" University of Rome ,

P.le Aldo Moro 5, 00185 Rome, Italy.

annabella.vitalone@uniroma1.it

Short title for the running head: Green tea and bone marrow transplantation

Abstract

Epigallocatechin-3-gallate (EGCG), the main flavonoid of Green Tea (GT), could play an active role in the prevention of oxidative stress related diseases, such as hematological malignancies.

Some effects of EGCG are not imputable to the antioxidant activity, but involve modulation of antioxidant enzymes and uric acid (UA) levels. The latter is the major factor responsible of the plasma Non-Enzymatic Antioxidant Capacity (NEAC). However, hyperuricaemia is a frequent clinical feature caused by tumor lysis syndrome or cyclosporine side effects, before and after bone marrow transplantation (BMT). Besides, food-drug interactions could be associated with GT consumption and could have clinical implications.

The molecular mechanisms involved in the redox and drug metabolizing/transporting pathways was discussed with particular reference to the potential role of GT and EGCG in BMT.

Moreover, reviewing data on NEAC, isoprostanes, uric acid and various enzymes, from human studies on GT, its extract or EGCG, an increase in NEAC, no effect on isoprostanes and contrasting results on UA and enzymes were observed.

Currently, few and contrasting available evidences suggest caution for GT consumption in BMT patients and more studies are needed in order to better understand the potential impact of EGCG on oxidative stress and metabolizing/transporting systems.

Keywords: Green tea; bone marrow transplantation, antioxidant, multidrug-resistance, hyperuricaemia.

Introduction

Green tea (GT), produced from the leaves of the *Camellia sinensis*, is one of the most popular beverages worldwide, due to the fact that its consumption has been correlated with low incidence of some kind of cancer (e.g. hematological malignancies) (Zhang et al., 2008). In order to understand this epidemiological evidence many mechanisms have been suggested, in particular antioxidant property (Yang et al., 2009). This attracted a great deal of interest over the last years, considering that the haematological malignancies are associated to oxidative stress and to an increase of the lipoperoxidation products isoprostanes (IsoP) (Hole et al., 2011; Battisti et al., 2008).

Among all tea polyphenols, epigallocatechin-3-gallate (EGCG), a flavonoid of the flavanols subgroup, has been found to be responsible for much of the antioxidant activity of GT (Khan et al., 2006). However, recently data suggest that some effects of EGCG are not imputable to its antioxidant activity (Yokozawa et al., 2004; Patra et al., 2008; Na and Surh, 2008; Park and Dong, 2003). Besides, antioxidant defenses of the body are composed of molecular and enzymatic players; the latter supply protection at the cellular level, together with glutathione (GSH), and include superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), glutathione reductase (GSR) and glutathione S-Transferase (GST), whereas in plasma non-enzymatic antioxidants play the major role (Serafini et al., 2011). Plasma Non-Enzymatic Antioxidant Capacity (NEAC) is due to endogenous uric acid (UA), bilirubin and thiols, as well as to dietary-derived molecules such as vitamin E, ascorbic acid, carotenoids, and polyphenols (Serafini et al., 2011). Some of the protective effects of EGCG have been ascribed to its capability to reduce high UA level (Yokozawa et al., 2004). This is an interesting finding,

considering that UA is not only an endogenous antioxidant but can also be a dangerous signal for immune system in the Graft-Versus-Host Disease (GVHD) (Zeiser et al., 2011). Hyperuricaemia has been associated to oxidative stress (Lahera et al., 2006) and to condition occurring in hematologycal malignancies, such as Tumor Lysis Syndrome (TLS) (Montesinos et al., 2008; Yamazaki et al., 2004) and renal injury (Saddadi et al., 2010; Hale et al., 2005). EGCG is also the major biologically active component in the inhibition of growth and induction of apoptosis in cancer cells (Shammas et al., 2006; Lee et al., 2004), also through Reactive Oxigen Species (ROS) production (Noda et al., 2007). On the other hand, GT promotes the proliferation of human bone marrow hematopoietic CD34(+) and CD133(+) progenitors (Bickford et al., 2006). Moreover, should be kept in mind that despite the *in vitro* chemosensitizing activity of EGCG in human leukemia cells (Davenport et al., 2010) and in multiple myeloma cells (Wang et al., 2009), EGCG inhibits also the therapeutic activity of bortezomib (an anticancer drug), in mice (Golden et al., 2009). This suggests that patients undergone this therapy should be informed to refrain self-administration of GT or GT-derived supplements. Besides, caution in green tea extracts (GTE) use is suggested also by reported cases of acute liver failure (Mazzanti et al., 2009). Liver and intestine play a major role in the first pass metabolism of both catechins and drugs bioavailability (Feng, 2006; Guastaldi et al., 2011). Therefore, food and drug interaction could be particularly relevant in patients with haematological cancer, before and after Bone Marrow Transplantation (BMT) (Guastaldi et al., 2011).

Considering that oxidative stress is involved in the regulation of normal and neoplastic hematopoiesis (Hole et al., 2011), and antioxidant intervention may improve hematopoietic reconstitution capacity of stem cells (Hao et al., 2011), the aim of the present work was to

evaluate the effects of GT, GTE and EGCG on the antioxidant status and its relationship with catechins bioavailability, reviewing the available evidence from human intervention studies. The effects of GT, GTE and EGCG on drug metabolizing/transporting systems was also discussed with particular emphasis to their potential role during cyclosporine treatment after BMT.

The potential effect of EGCG in BMT: modulation of enzymes and drug transporting systems

Molecular mechanisms

Various molecular pathways, including the nuclear factor-erythoroid 2 p45-related factor 2 (Nrf2) / antioxidant responsive elements (ARE) (Patra et al., 2008; Na and Surh, 2008; Zheng et al., 2011; Köhle and Bock, 2007), the nuclear factor κB (NF-κB) (Park and Dong, 2003; Tian, 2009; Martinez-Hervas et al., 2010) and the aryl hydrocarbon receptor (AhR) (Sugihara et al., 2001; Yin et al., 2009; Palermo et al., 2005; Han et al., 2012), have been shown to be a key regulators of antioxidant genes (Patra et al., 2008; Na and Surh, 2008; Park and Dong, 2003; Zheng et al., 2012), xanthine oxidase (XO) (Martinez-Hervas et al., 2010; Sugihara et al., 2001) phase I and phase II metabolizing enzymes, as well as phase III transporters (Köhle and Bock, 2007; Tian, 2009; Yin et al., 2009; Palermo et al., 2005) (Figure 1). Various connections between AhR and NF-κB (Tian, 2009) or Nrf2 (Köhle and Bock, 2007) pathways have been suggested and they are potentially important in the alteration of xenobiotic metabolism and disposition. Flavonoids are substrates of drug metabolism/transport systems (Feng, 2006), acting as competitors for drug absorption. At transcriptional level, they could also regulate their own

bioavailability and metabolism, and could interact with drugs. In particular, EGCG activates Nrf-2 (Na and Surh, 2008; Han et al., 2012; Tsai et al., 2011) and inhibits NF-κB (Park and Dong, 2003; Tsai et al., 2011) and AhR (Yin et al., 2009; Palermo et al., 2005; Han et al., 2012) response-pathways. Some of these effects seem to be mediated by the interactions with mitogen-activated protein kinases (extracellular regulated kinase [ERK]1/2, p38 MAPK) and protein kinase C (PKC) (Park and Dong, 2003). The not specific binding of EGCG in membrane lipid rafts destabilizes the rafts structure and inactivates MAPK signaling (Patra et al., 2008) (Figure 1). The structure–activity relationship analysis of major GT catechins on cell-surface binding suggests that binding activities of pyrogallol-type catechins (EGCG and Gallocatechin 3-O-gallate, GCG) are higher than those of catechol-type catechins (Epicatechin 3-O-gallate, ECG and Gallocatechin, CG) (Patra et al., 2008). It is reasonable to believe that laminin receptor (LamR), in association with rafts, is involved in this effect (Patra et al., 2008). However, an interactions with caveolae plasma membrane microdomains and a displacement of caveolin-1 have been recently suggested as mechanisms of induction by EGCG of Nrf2-induced antioxidant enzymes expression (Zheng et al. 2012) (Figure 1).

The mechanism of endocytosis of EGCG has not yet been experimentally analysed, but it is reasonable to believe that both LamR (in association with rafts) and caveolae-mediated vescicular transport play a role in the uptake of EGCG into the cytosol (Patra et al., 2008; Zheng et al. 2012).

It has been suggested that some derivatives of catechins can oxidize highly reactive cysteine thiol groups of kelch-like ECH-associated protein-1 (Keap1), resulting in disulfide bond formation and Nfr2 release (Na and Surh, 2008). Therefore, to induce cytoprotective enzymes, the

activation of Nfr2-ARE signaling by EGCG seems due to their pro-oxidant activity (Figure 1). Paradoxical is also the induction of antioxidant genes, that may involve a rapid phosphorylation of ERK1/2 and IκB, causing the translocation to the nucleus of the p50 subunit of NFκB (Park and Dong, 2003). Conversely, by counteracting the activation of IKK and the phosphorylation and degradation of IκBα, an inhibitory effects of EGCG on NFκB was also observed (Park and Dong, 2003) (Figure 1).

Several data are contrasting, regarding also the major transcription factors involved in phase I, II and III metabolism/transport systems. Recently, data suggest that EGCG inhibits AhR-mediated transcription by binding to hsp90, and stabilizing its complex with AhR (Yin et al., 2009; Palermo et al., 2005) (Figure 1). On the other hand, EGCG enhances CYP3A4 promoter activity without activating pregnane X receptor (PXR) (Dürken et al., 2000).

Uric acid and cyclosporine: oxidative stress in BMT

An impairment of total antioxidant capacity, a reduction of UA level, and the occurrence of an oxidative damage were found during chemiotherapy and radiotherapy preceding BMT (Dürken et al., 2000) and Stem Cell Transpantation (SCT) (Avivi et al., 2009) (Figure 2). However, during management of haematological malignancies, hyperuricaemia is a frequent clinical feature caused by TLS after chemiotherapy (Montesinos et l., 2008) and radiotherapy (Yamazaki et al., 2004). TLS (Saddadi et al., 2010) or haemolytic uraemic syndrome (Hale et al., 2005) occur also after BMT (Figure 2). Besides, the activation of XO by inflammatory cytokines (Deliliers and Annaloro, 2005) and cyclosporine side effects (Saddadi et al., 2010) contribute to hyperuricaemia following BMT (Figure 2).

Cyclosporine is one of the immunosuppressant used in the standard regime for the prevention of Graft Versus Host Disease (GVHD) after both BMT (Bolwell et al., 2004) and SCT (Mengarelli et al., 2003) in patient with haematological malignancy. The standard prophylaxis or treatment of hyperuricaemia in TLS consists of decreasing UA production with allopurinol, or by increasing uric acid conversion to allantoin with rasburicase (Tosi et al., 2008). Of note is that EGCG inhibits the hyperuricaemia (figure 2) induced by isoproterenol (Devika et al., 2008) and cyclosporine (Mohamadin et al., 2005) in rats, according with its inhibitory effects on XO *in vitro* (Lin et al., 2000). EGCG prevents *in vitro* free radical-mediated hemolysis by cyclosporine (Lin et al., 2000), and induces GPX (Na and Surh, 2008; Tsai et al., 2011) SOD (Na and Surh, 2008) and GST (Na and Surh, 2008; Han et al., 2012). This evidence is also confirmed by animal studies, where both GTE (Shin et al., 2012) and EGCG (Chang and Mun, 2004) reduce cyclosporine-induced nephrotoxicity, increasing the antioxidant enzyme activities of SOD and CAT (Shin et al., 2012), and decreasing lipoperoxidation and UA (Mohamadin et al., 2005) (figure 2). However, caution should be taken in considering the use of GTE to prolong allograft survival and to reduce cyclosporine nephrotoxicity (Tripathi et al., 2009). Indeed, GTE and/or EGCG could interact with several drugs in contrasting manner and at different levels, including GST phase-II detoxifying enzyme (Artali et al., 2009), P-glycoprotein (Pgp) (Li and Choi, 2008; Chung et al., 2009) and cytochrome P450 3A4 (CYP3A4) (Li and Choi, 2008; Chung et al., 2009; Nishikawa et al., 2004). In particular, the opposite effects of GTE on hepatic and intestinal CYP3A4 activity in rats (Nishikawa et al., 2004) could make unforeseeable the pharmacokinetic of cyclosporine in humans.

Effect of GT, GTE and EGCG: human evidence.

A review of 48 interventions, from 42 studies (table 1) has been performed. Of these interventions, 20 studies regard a single ingestion (bolus) and the others 28 were related to a repeated supplementations. These studies reported measurements of NEAC (n=32), of IsoP (n=8), UA (n=17), and various enzymes [e.g. SOD (n=5), CAT (n=2), GPX (n=3), GST (n=1), GSR (n=1), XO (n=1), CYP450 (n=6)], obtained from 28, 8, 13 and 10 studies, respectively. Only 23 of the 48 intervention reported data of bioavailability of catechins.

Isoprostane, Non-Enzymatic Antioxidant Capacity, and uric acid

IsoP levels were not affected by either treatments (e.g., GT, GTE and EGCG), nor by study design (e.g. bolus or repeated administration), also when other parameters, such as NEAC (Braga et al., 2012; Loke et al., 2008) or catechins (Hirano-Ohmori et al., 2005; Loke et al., 2008; Müller et al., 2010), increased after treatment. On the other hand, the majority of the interventions with GT and its supplements pointed out an increase of NEAC (69%, n=22/32); the percentage of interventions reporting consistent results with markers of catechins bioavailability were 61% (n=11/18) (Table 1). Thus, there is a clear discrepancy between catechins concentration in body fluids and the effect on IsoP, compared with data on NEAC. Probably, the preferential compartmentalization in the hydrophilic environment of catechins may account of the difference in the effects on NEAC and IsoP, in humans. After consumption of tea, the catechins were mainly found in the protein-rich fraction of plasma, while their low concentration in LDL was not sufficient to enhance their resistance to oxidation (van het Hof et al., 1999).

Human intervention studies on NEAC, after the exposure to GT or dietary supplements (i.e.,

GTE and EGCG) are summarized in Table 1. GT, both in bolus and repeated administration, has produced significant increments of NEAC in 9 of 10 (90%) and in 5 of 7 (71%) interventions, respectively. On the other hand, only one of the two bolus treatments (50%) of EGCG increased NEAC, and only 4 of seven of the single ingestion of GTE (57%) induced increases in NEAC, while repeated supplementation with GTE resulted in a positive NEAC effect in 5 out of 6 interventions (83%). Considering that the extraction conditions may affect also the antioxidant capacity *in vitro* (Rusak et al., 2008), the lack of standardization in tea extraction procedures could justify the difficulty in comparing data from the various (and few) studies with GTE. Moreover, in two studies, GTE was administered in association with other antioxidants such as pomegranate extract (Fenercioglu et al., 2010), vitamin C (Braga et al., 2012; Fenercioglu et al., 2010), vitamin E (Braga et al., 2012) and β-carotene (Braga et al., 2012). One of these interventions (Braga et al., 2012) was a placebo-controlled trial involving 36 subjects undergoing pancreatic-duodenectomy (PD) for either pancreatic cancer or periampullary cancer. These patients received three doses of a supplement containing 1g of GTE, preoperatively. The first dose the day before operation at 3 PM; the second 6 h later, and the third dose 3 h before surgery. The authors reported a NEAC increase on postoperative day 1, 3 and 7, while unchanged levels of IsoP were found in both placebo and treatment groups.

In all acute interventions with GT, total phenols, flavonols and catechins were detected in plasma associated with an increase of NEAC (Table 1).

In particular, Henning et al. (2004; 2005) have found an increase in plasma catechins concentration and NEAC, after acute ingestion of both GT (Henning et al., 2004) and EGCG (Henning et al., 2005), either in purified form or as GTE (Henning et al., 2004; 2005).

Analogously, after acute ingestion of GT, Pietta et al. (1998a) have found an increases in NEAC, EGCG plasma levels and urinary catechins metabolites. An increase in plasma catechins were also found by the same author, after administration of GTE or its phospholipid complex (Pietta et al., 1998b). The catechins levels resulted higher (4.0±0.6μM *vs* 2.0±0.2μM) in the phospholipid complex than in GTE, showing an increased absorption with this kind of formulation. However, in both cases, the increase in plasmatic level of NEAC was similar: 17±5% for GTE and 18±7% for the phospholipid complex. An increase in NEAC was also found following 42-days supplementation with GT, without any change in plasma total phenols (Erba et al., 2005). Therefore, there is not a concentration dependent relationship between EGCG and NEAC levels. Considering that an increase in NEAC was frequently found after bolus intervention rather than after repeated consumption, some considerations could be made. First, in chronic interventions many factors, such as study design, subjects randomization and compliance, could interfere with the results. Secondly, flavonoids may also self-regulate their own bioavailability and their metabolism in chronic intervention, by modulating the drug metabolizing/transporting systems (figure 1) as well as by affecting their microbial metabolism, due to their antibacterial properties (Taguri et al., 2004). Finally, NEAC assays evaluate both endogenous and exogenous antioxidants, thus if tea affects the levels of endogenous antioxidants it could have both direct and indirect effects on NEAC. In particular, the inhibitory effects of EGCG on XO could decrease UA circulating levels (figure 1). In accordance to the hypothesis that chronic consumption of tea may regulate UA circulating levels are the results of Panza et al. (2008), that reported a decrease of UA levels, after 7 days of ingestion of GT (600ml), and an inhibition of the exercise-induced activation of XO. Thus, the inhibition of XO (enzyme producing UA) by

consumption of GTE or EGCG could profoundly affect the NEAC values. These effects should be taken into account, because UA is the major antioxidant that contributes to NEAC values.

A lower level of UA was also observed by Kimura et al. (2002), after 7 days of GTE ingestion (when EGCG concentration was significantly higher compared with pre-ingestion levels), as well as after 7 days of withdrawal (when catechins decreased to baseline levels).

The effect of GTE ingestion on UA reduction could hide the expected improvement of NEAC, due to the increase in catechins plasmatic levels (Kimura et al., 2002). The indirect effect of GTE on NEAC is more evident when catechins disappeared from circulation, 7 days after withdrawal, and NEAC decrease (Kimura et al., 2002).

With regard to studies analyzing the effect of GT, GTE and EGCG on UA, conflicting data are available. In particular, decreased, increased or unchanged UA levels were found (table 1).

Antioxidant and CYP enzymes

Considering the results on antioxidant enzymes after GT, GTE or ECGC consumption (table 1), more studies are needed, taking also into account the great variability of the various samples analyzed [such as erythrocytes (Jówko et al., 2011; Jówko et al., 2012; Young et al., 2002), plasma (Gomikawa et al., 2008) or lymphocytes (Chow et al., 2006; Erba et al., 2005)] and the different methods utilized [e.g. enzymatic activity (Chow et al., 2006; Erba et al., 2005; Gomikawa et al., 2008 Young et al., 2002) or level (Emara and El-Bahrawy, 2008)]. For example, the SOD activity in plasma (Gomikawa et al., 2008) and in erythrocytes (Jówko et al., 2011; Jówko et al., 2012; Young et al. 2002) remained unchanged after GT (Gomikawa et al., 2008) or GTE consumption (Jówko et al., 2011; Jówko et al., 2012; Young et al. 2002). On the

contrary, tea abrogated the benzene-induced reduction of SOD (as well as GPX and catalase) in pump male workers (Emara and El-Bahrawy, 2008). A decrease in GPX activity in lymphocytes of healthy subjects consuming GT was conversely reported (Erba et al., 2005).

As regards GST activity, after EGCG consumption, an increase in its activity was found in healthy volunteers with low baseline level (Chow et al., 2006).

Concerning data on drug metabolizing enzymes, only two intervention studies have been conducted. In a crossover design, 42 healthy volunteers underwent a 4-week washout period, by refraining from tea or tea-related products (Chow et al., 2007). At the end of the washout period, study participants received a cocktail of CYP metabolic probe drugs, including caffeine, dextromethorphan, losartan, and buspirone for assessing the activity of CYP1A2, CYP2D6, CYP2C9, and CYP3A4, respectively. To measurements of CYP enzyme activities, blood and urine samples were collected and probe drug and metabolite concentrations were determined. After 4 weeks of EGCG consumption, a significant increase of buspirone concentration was found, suggesting a reduction in CYP3A4 activity (Chow et al., 2007). On the contrary, despite the EGCG increase in plasma, no effect on CYP3A4 activity was found using alprazolam as probe drug (Donovan et al., 2004). Of note is the case report documenting the interaction of GT and an immunosuppressant (i.e. Tacrolimus), a substrate for the CYP3A4 and P-glycoprotein. 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. 1mg/24 h). After GT ingestion, an increase in tacrolimus levels has been observed, and a positive dechallenge of the tea was performed (Vischini et al., 2011).

Conclusion

EGCG can influence enzymes involved in redox and drug metabolizing/transporting pathways, through modulation of NF-kB, Nrf2, AhR and MAPK pathways. Besides, not only the intrinsic antioxidant activity, but also the inhibitory effect on XO could influence NEAC. Despite the *in vitro* and animal model suggestions, limited human evidence are available on relationship between NEAC, IsoP, UA, CYP, antioxidant enzymes, and GT, GTE or EGCG consumption. From the reviewed human interventions, a clear antioxidant effect cannot be postulated, because no effect on IsoP (the *in vivo* lipo-peroxidation markers) was found, while data concerning NEAC were deeply influenced by UA levels. The latter seems to have complex interrelationship with GT or GT products. Therefore, the use of EGCG to reduce UA levels or to inhibit cyclosporine-induced lipo-peroxidative damage in patient undergoing BMT did not appear a novel therapeutic strategy as an "antioxidant approach". Moreover, the induction of antioxidant enzymes, reported by *in vitro* and in animal studies, is not confirmed by human evidence. Considering the potential advantages and disadvantages of both antioxidant and pro-oxidant therapeutic strategies in haematological malignancy (Hole et al., 2011), the unpredictable effect of GT or GT supplements on redox status could further complicate the patients' management. Furthermore, potential drug interactions suggest caution for GT consumption in BMT.

In conclusion, more studies and detailed bioavailability measurements are needed in order to better understand the potential impact of GT, GTE and EGCG on oxidative stress and metabolizing/transporting systems. Until that, GT consumption and its derived supplements should be used with caution in haematological/BMT patients.

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Table 1. Overview of the reviewed intervention studies in humans providing GT, GTE or EGCG.

Reference	n	Intervention	Dose	Bioavailability †	Iso P	NEA C	U A	Enzymes
Alexopoulos et al. 2008	14	GT (bolus)	6000 mg			↔		
Benzie et al. 1999	10	GT (bolus)	400 ml	↑		↑		
Bertipaglia de Santana et al. 2008	75	GT (90 days)	500 ml			↑		
Bogdanski et al. 2012	56	GTE (90 days)	379 mg			↑		
Braga et al. 2012	36 [a]	GTE (2 days)	1000 mg *		↔	↑		
Chow et al. 2006	42	EGCG (28 days)	800 mg					CYP1A2 ↔ CYP12D6 ↔ CYP12C9 ↔ CYP3A4

							↓
Chow et al. 2007	42	EGCG (28 days)	800 mg				GST ↑
Coimbra et al. 2006	34	GT (28 days)	100 ml		↔		
Donovan et al. 2004	11	GTE (14 days)	844 mg	↑			CYP3A4 ↔ CYP2D6 ↔
Donovan et al. 2005	9	GTE (14 days)	844 mg		↔		
Emara and El-Bahrawy 2008	60 [b]	GT (180 days)	6 cups		↑		SOD ↑ GPX ↑ CAT ↑
Erba et al. 2005	10	GT (42 days)	2 cups	↔	↑		GPX ↓
Fenercioglu et al. 2010	114 [c]	GTE (90 days)	300 mg**		↑		
Freese et al. 1999	20	GTE (28 days)	3000 mg		↔		
Gomikawa	5	GT (14	4500 mg	↔		↔	SOD ↔

et al. 2008		days)						
Henning et al. 2004	30	GTE (bolus)	462 mg	↑		↑		
Henning et al. 2004	30	GT (bolus)	426 ml	↑		↑		
Henning et al. 2005	20	EGCG (bolus)	580 mg	↑		↑	↑	
Henning et al. 2005	20	GTE (bolus)	1029 mg	↑		↑	↑	
Hirano-Ohmori et al. 2005	22	GT (14 days)	7 cups	↑	↔			
Hodgson et al. 2000	20	GT (bolus)	400 ml			↑		
Hodgson et al. 2002	13 [d]	GT (7 days)	5 cups		↔			
Hsu et al. 2008	41	GTE (84 days)	400 mg				↔	
Hsu et al. 2011	68 [c]	GTE (112 days)	856 mg				↔	
Jowko et al.	17	GTE (28	640 mg	↑		↑		SOD ↔

2011		days)						
Jówko et al. 2012	16	GTE (bolus)	640 mg	↑		↔	↔	SOD ↔
Kimura et al. 2002	5	GTE (bolus)	164 mg	↑		↔	↔	
Kimura et al. 2002	16	GTE (7 days)	492 mg	↑		↔	↓	
Leenen et al. 2000	21	GT (bolus)	300 ml	↑		↑	↔	
Li et al. 2010	40	GTE (112 days)	200 mg §	↔	↔			
Loke et al. 2008	12	EGCG (bolus)	200 mg	↑	↔			
Müller et al. 2010	33	GT (bolus)	600 ml	↑	↔	↑		
Panza et al. 2008	14	GT (7 days)	600 ml	↑		↑	↓	XO ↓
Pecorari et al. 2010	15	GT (bolus)	500 ml			↑		
Pietta et al. 1998a	6	GT (bolus)	300 ml	↑		↑		

Pietta et al. 1998b	6	GTE (bolus)	400 mg	↑	↑	
Pietta et al. 1998b	6	GTE (bolus)	400 mg ***	↑	↑	
Princen et al. 1998	13	GTE (28 days)	3600 g			↔
Princen et al. 1998	15	GT (28 days)	6 cups			↔
Rabovsky et al. 2006	5	GTE (bolus)	600 mg		↔	↓
Serafini et al. 1996	5	GT (bolus)	300 ml		↑	
Sone et al. 2011	25	GT (63 days)	400 mg catechins			↔
Sone et al. 2011	26	GT (63 days)	100 mg catechins			↔
Sung et al. 2000	10	GT (bolus)	450 ml		↑	
Sung et al.	12	GT (28	600 ml		↔	

2005		days)					
Van Amelsvoort et al. 2001	10	EGCG (bolus)	150 ml (of 1.5 mM)	↑		↔	↔
Van Het Hof et al. 1997	14	GT (28 days)	6 cups			↑	↔
Young et al. 2002	16	GTE (21 days)	100 mg/Kg	↑		↑	SOD ↔ GPX ↔ GSR↔ CAT ↔

IsoP, F2-isoprostanes; NEAC, Non Enzymatic Antioxidant Capacity; UA, uric acid. ↑, increase; ↔, no change; ↓, decrease. n, number of subjects ([a]cancer, [b]pump workers, [c]type 2 diabetes, [d]hypertensive). SOD, superoxide dismutase, GPX, glutathione peroxidase, GSR, glutathione reductase, GST, glutathione S-Transferases; XO, Xanthine Oxidase; CYP, Cytocrome P450. EGCG, Epigallocatechin Gallate. Supplement contained also *Vitamin. C 750mg, Vitamin. E 250mg and β-carotene 5mg; **pomegranate extract and ascorbic acid; ***phytosome. § both GTE treated and control subjects received also lutein. [†]Bioavailability is reported as the plasmatic or urinary concentrations of a single cathechin, total catechins or total phenols, or their metabolites.

Figure legends

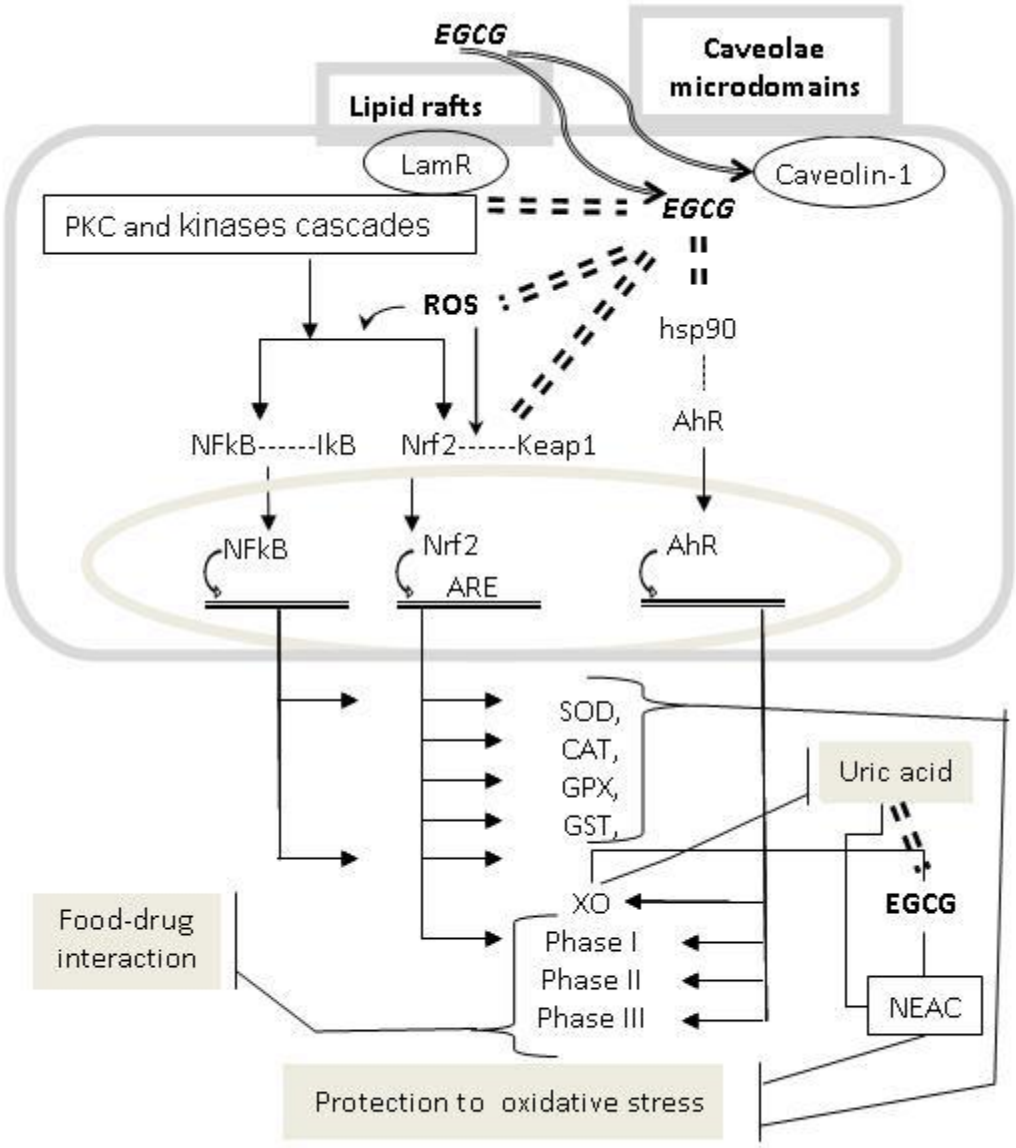

Figure 1.

Figure 1. Potential molecular mechanisms involved in the modulation by EGCG of redox pathway and metabolism/transport system.

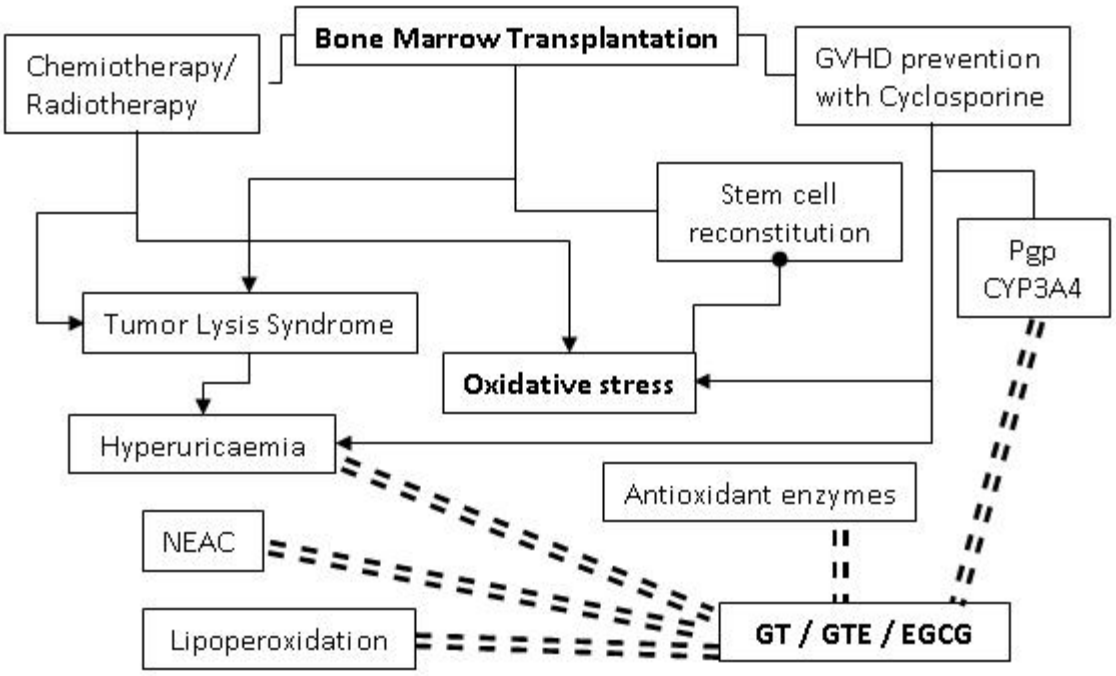

Figure 2.

Figure 2. Potential site of interaction between GT, GTE or EGCG and redox pathway or metabolism/transport system crucial before and after BMT.