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Nutritional contribution of coffee, cacao and tea phenolics to human health

H. M. Rawel and S. E. Kulling

University of Potsdam, Nuthetal, Germany

Correspondence to: PD Dr. Harshadrai M. Rawel, University of Potsdam, Institute of Nutritional Science, D-14558 Nuthetal, A.-Scheunert Allee 114 – 116, Germany, E-mail: rawel@uni-potsdam.de

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Abstract: The intention of this short overview is to contribute to a better understanding of the physiological effects of the coffee, cacao and tea phenolics to human health. The paper gives a short description of the principle phenolic compounds present in each of the food stuffs, their intake, summarises the data available on their bioavailability and metabolism and gives finally a short resume of their beneficial effects in biological systems *in vitro*, in animals, and in humans.

Zusammenfassung: Ziel dieser kurzen Übersicht ist es, zum besseren Verständnis der physiologischen Effekte der phenolischen Verbindungen von Kaffee, Kakao und Tee auf die menschliche Gesundheit beizutragen. Dazu werden die hauptsächlichen phenolischen Bestandteile in jedem dieser Lebensmittel beschrieben sowie deren Aufnahme. Es werden die verfügbaren Daten über die Bioverfügbarkeit vorgestellt und die positiven Effekte in biologischen Systemen *in vitro*, im Tierversuch und im Menschen diskutiert.

1. Introduction

Phenolic compounds as food components represent with more than 6000 identified substances the largest group of secondary metabolites in plant foods. They are characterized by a large range of structures and functions, but generally possessing an aromatic ring bearing one or more hydroxy substituents (Robards et al., 1999). Structure, classification, distribution of phenols in plant foods, intake and their physiological effects have been summarised by Kroll et al. (2003). Polyphenols are the most abundant antioxidants in the diet and the daily intakes of total polyphenols may range from less than 100 mg to in excess of 2 g. The critical importance of coffee and black tea as the major dietary sources has been documented (Clifford, 2004; Richelle et al., 2001). Only some 5% of the dietary polyphenols is absorbed in the duodenum, and of this only some 5%, mainly flavanols, reaches the plasma unchanged. Over 95% of the intake passes to the colon and is fermented by the gut microflora (Clifford, 2004). Experimental studies support a role of polyphenols in the prevention of cardiovascular diseases, cancers, neurodegenerative diseases, diabetes, or osteoporosis (Clifford, 2004; Scalbert et al., 2005).

However, it is very difficult to predict from these results the effects of polyphenol intake on disease prevention in humans (Scalbert et al., 2005). Firstly, estimation of dietary intake of polyphenols is difficult, due to limited availability of food composition data and bias inherent to dietary assessment methods, thus identifying a need for good biomarkers (Mennen et al., 2006). 4-O-methylgallic acid and isoferulic acid have been tested for potential biomarkers of exposure to polyphenols derived from tea and coffee respectively (Hodgson et al., 2004; Mennen et al., 2006). 4-O-methylgallic acid is derived from gallic acid in tea, and isoferulic acid is derived from chlorogenic acid in coffee (Hodgson et al., 2004). Secondly, most of the observed physiological effects are based on either *in vitro* models, cell / tissue culture studies, animal experiments or epidemiological data. The results thus obtained are generally projected to show if a strong association or correlation of activity in humans is possible or not, since data on basis of human investigations are relatively rare. Thirdly, these studies have often been conducted at doses or concentrations far beyond those documented in humans (Scalbert et al., 2005). More human studies are therefore needed to provide clear evidence of their health protective effects and to better evaluate the risks possibly resulting from too high polyphenol consumption (Scalbert et al., 2005).

2. Coffee phenolics

Coffee beans are one of the richest dietary sources of hydroxycinnamic acid derivatives (especially chlorogenic acid, Fig. 1) and for many consumers the major dietary source of phenolics (Clifford, 1999 and 2000). Depending on species, green coffee beans contain some 6–10% chlorogenic acids on a dry matter basis (Clifford, 1999). Besides the chlorogenic acid isomers (major component being 5-caffeoyl-quinic acid) and their di-esters, other hydroxycinnamic acid conjugates like feruloyl-quinic acids and caffeoyl-tyrosine were identified and their content in roasted coffee estimated (Clifford, 1999; Ky et al., 1997). A further study identified eleven chlorogenic acids including feruloyl-quinic acids, caffeoyltryptophan acid and *p*-coumaroyl-(L)-tryptophan in coffee beans by applying three-dimensional HPLC (Murata et al., 1995).

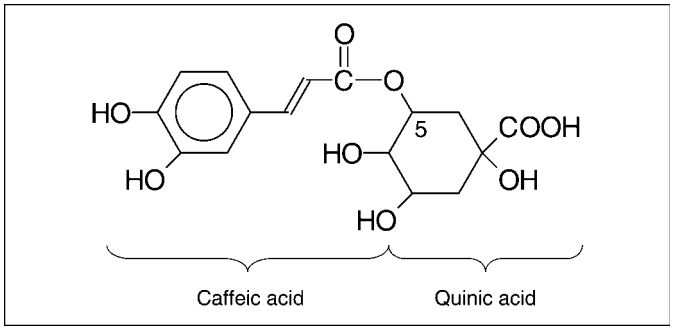


Fig. 1 Chemical formula of the chlorogenic acid (5-caffeoyl-quinic acid, IUPAC – numbering), the main phenolic compound of coffee.

During roasting there is a progressive destruction and transformation of chlorogenic acid and a parallel release of a series of reactive products. There still remains a substantial amount and the daily intake of total chlorogenic acids may vary substantially from a few mg to perhaps close to 1 g depending upon dietary behaviour (Clifford, 2000). In recent years this group of compounds has gained much importance in connection with its antioxidant and anticarcinogenic properties, which have been well established in animal studies (Gonthier et al., 2003b). This together with its high intake has invoked a series of research studies dealing with the absorption, metabolism and bioavailability of the hydroxycinnamic acid derivatives (Couteau et al., 2001; Gonthier et al., 2003b; Nardini et al., 2002; Olthof et al., 2001). A cross-over study with healthy ileostomy subjects documents the possibility of absorption of chlorogenic acid and caffeic acid in humans (Olthof et al., 2001). Recently, for the first time it was shown that chlorogenic acid is quickly absorbed in the rat stomach in its intact form (Lafay et al., 2006). But generally, ingested hydroxycinnamate esters normally reach the large intestine essentially unaltered, and may then be hydrolysed by esterases produced by the indigenous microflora (Couteau et al., 2001; Gonthier et al., 2003b; Lafay et al., 2006). The metabolites of microbial origin, namely *m*-coumaric acid and derivatives of phenylpropionic, benzoic and hippuric acids, represent the major compounds identified in both urine and plasma (Gonthier et al., 2003b).

With regard to beneficial effects of coffee phenolics it has been shown that both green and roasted coffee possess antiradical activity and that their more active component is 5-O-caffeoyl-quinic acid. Moreover the roasting process induces high MW components (later Maillard reaction products, i.e., melanoidins), also possessing antiradical activity in coffee (Daglia et al., 2004). These results could explain the neuroprotective effects found for coffee consumption in epidemiological studies (Daglia et al., 2004). Despite extensive research, the cardiovascular effects of coffee consumption in humans remain controversial (Mursu et al., 2005). Similarly, in this context chlorogenic acid has been shown to have antihypertensive actions, but epidemiologic data on the effects of coffee on blood pressure are controversial, since specific coffee components inhibit the hypotensive effect of chlorogenic acid (Suzuki et al., 2006). Bonita et al. (2007) surmise the role of coffee in the prevention of cardiovascular disease with regard to effect on the risk factors which are associated with heart disease such as lipids, blood pressure, inflammation, endothelial function, metabolic syndrome and potentially protective *in vivo* antioxidant activity. *In vivo*, chlorogenic acid inhibits chemically induced carcinogenesis of the large intestine, liver and tongue in rats and hamsters (Gonthier et al., 2003). Whereas the data on a potential procarcinogenic effect in some human organs remained inconclusive, epidemiology has clearly revealed coffee drinkers to be at a lower risk of developing cancers of the colon and the liver and possibly of several other organs (Huber and Parzefall, 2005). Associations between black tea and coffee consumption and risk of lung cancer show that chemoprotective effects of phytochemicals in coffee and tea may be overshadowed by the elevated risk associated with caffeine in these beverages (Baker et al., 2005). A recent report suggests that anticancer mechanism of caffeic acid or other plant polyphenols may involve mobilization of endogenous copper, possibly chromatin bound copper, and the consequent prooxidant action (Bhat et al., 2007).

In conclusion, the intake of coffee phenolics may be high, but their individual physiological effects may be limited due to their low bioavailability in the upper gastro-intestinal tract and due to interplay of the several different constituents of the coffee. On the other hand, several individual chemoprotectants out of the >1000 constituents of coffee were identified, which have scavenging abilities against some strongly metabolized individual carcinogens (Huber and Parzefall, 2005).

3. Cocoa phenolics

Cocoa pods from the cocoa tree (*Theobroma cacao*) provide the beans, which are fermented, dried and roasted to produce chocolate liquor, which is prepared by finely grinding the nib of the cocoa bean and is the basis for all chocolate products (Vinson et al., 1999; Wollgast and Anklam, 2000b). Cocoa powder is made by removing part of the cocoa butter from the liquor (Vinson et al., 1999). Unfermented Forastero cocoa

beans have been reported to contain 120–180 g/kg polyphenolic compounds (Misnawi et al., 2002). The total amount of soluble polyphenols in the dried fat-free mass of fresh cocoa beans is 15 to 20% (about 6% in air dried cocoa beans, containing 54% fat and 6% water), in fermented beans about 5%. Wollgast and Anklam (2000b) report on the change in composition and quantity during fermentation, drying, and the manufacture of chocolate. Three groups of polyphenols can be distinguished in cocoa: catechins or flavan-3-ols (about 37%), anthocyanins (about 4%; cyanidin glycosides) and proanthocyanidins (about 58%). The main catechin is (-)-epicatechin (Fig. 2) with up to 35% of polyphenol content (Wollgast and Anklam, 2000b). Proanthocyanidins (PA) are oligomers of flavan-3-ol monomer units (Fig. 2) formed from the association of several monomeric units: 2–10 units in (epi)catechin oligomers, over 10 units in (epi)catechin polymers. The PA differ in the position and configuration of their monomeric linkages, whereby C4→C8 and / or C4→C6 bonds are the predominant types. Cooper et al. (2007) showed that epicatechin concentrations can be used to predict the content of other polyphenols, especially B2 and C1, and total polyphenols content. Flavonol glycosides such as quercetin-3-O-arabinose, isoquercitrin, quercetin-3-O-glucuronide and quercetin have also been reported in cocoa samples (Sanchez-Rabaneda et al., 2003; Wollgast and Anklam, 2000b). LC/ESI-MS/MS has been shown to be an excellent tool for the screening of the flavonoid composition of cocoa samples, allowing the identification of hyperoside, luteolin-7-O-glucoside, isoorientin, orientin, vitexin, isovitexin, naringenin-7-O-glucoside, naringenin, apigenin and luteolin in cocoa samples for the first time (Sanchez-Rabaneda et al., 2003).

The lack of reliable values for PA content in food makes it impossible to accurately evaluate their dietary intake (Santos-Buelga and Scalbert, 2000). It has been estimated that the average intake of flavanols and PA is on the order of < 1 gram per day (Arts et al., 2000; Hammerstone et al., 2000). The average intake of PA in the US was very recently estimated to be 58 mg/day (monomers, dimers, trimers, and those above trimers contribute 7.1, 11.2, 7.8, and 73.9% of total PA). Therefore, PA account for a major fraction of the total flavonoids ingested in Western diets which underlines their nutritional importance (Prior and Gu, 2005).

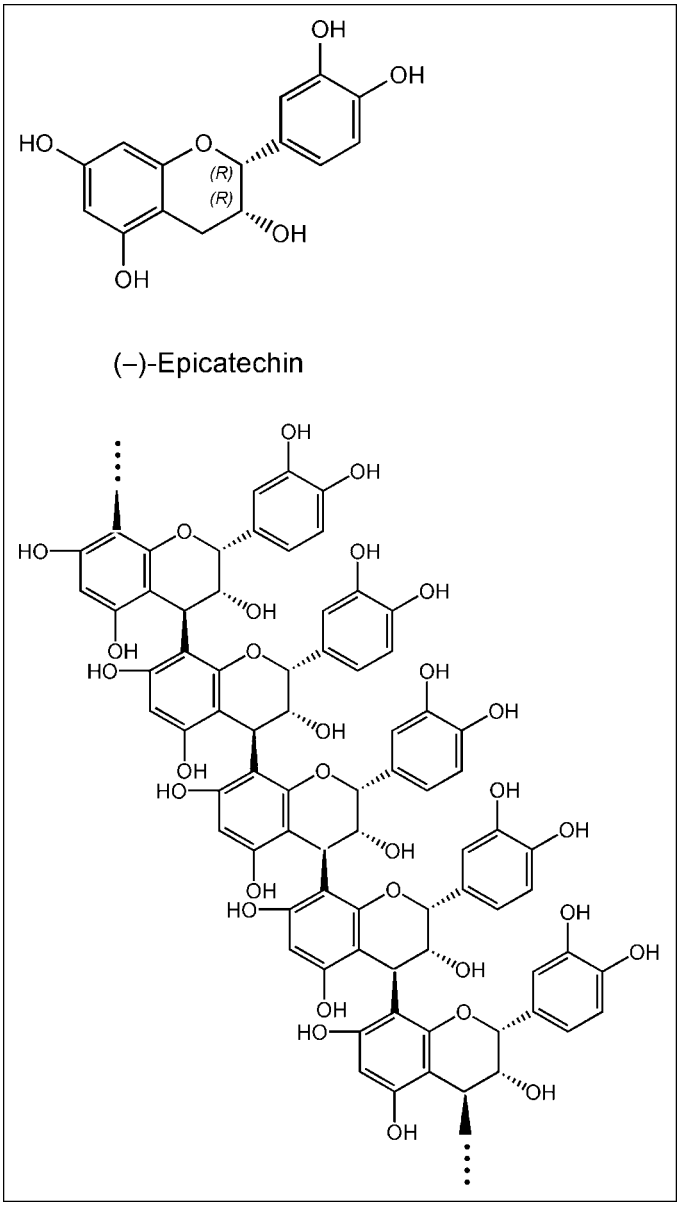


Fig. 2 Typical phenolic structures found in cocoa based products.

Estimates from human studies indicate that dietary flavanols, including those found in cocoa, display variable oral absorption, with reported values varying from less then 1 to greater than 50 percent of the ingested dose as cited by Rein et al. (2000), Richelle et al. (1999) and Schramm et al. (2003), but more realistic values of the observed average absorption should be around five percent (Richelle et al., 1999; Schramm et al., 2003; Wang et al., 2000b). The variable absorption of flavanols between subjects probably results from the complexity of the *in vivo* system, which involves limited absorption as well as extensive metabolism and degradation. Significant losses are also attributed to gastric pH-induced degradation (Zhu et al., 2002), enterocyte metabolism of flavanols, first pass metabolism, and the type and activity of intestinal microflora (Schramm et al., 2003). Plasma epicatechin level of 260 nmol/L can be achieved within 2 h after the consumption of 557 mg of PA containing 137 mg of epicatechin from a PA-rich chocolate (Rein et al., 2000). Similar values were noted 2–3 h after the ingestion of chocolate, epicatechin attained peak plasma concentrations of 380 nmol/L after an intake of 0.9 g of polyphenols (gallic acid equivalent) and 700 nmol/L after an intake of 1.7 g (Richelle et al., 1999). Orally administered epicatechin in mammals is thought to largely undergo glucuronidation at the level of the intestinal mucosa (Da Silva et al., 1998). Thus, the rise in epicatechin in plasma observed after the PA-rich chocolate intake may be due in part to epicatechin metabolites (in particular, unmethylated glucuronide, glucuronide-sulfate and unmethylated sulfate conjugates), as well as to free epicatechin (Rein et al., 2000). The knowledge on the bioavailability and metabolism of PA, which are the major determinants of the biological activity *in vivo* is very limited (Ma-

nach et al., 2005; Santos-Buelga and Scalbert, 2000; Wollgast and Anklam, 2000a). The available studies indicate that the systemic bioavailability of polymerised PA is rather poor. Decomposition of cocoa procyanidins (trimer to hexamer) in the gastric milieu to mixtures of epicatechin monomer and dimer, thus enhancing the potential for their absorption in the small intestine has been reported (Spencer et al., 2000; Spencer et al., 2001). First reports indicate that at least monomers and dimers are absorbed, although the absorption of the dimers was negligible. The intestinal microflora seems to play an important role in the metabolism of PA. Oligomeric and polymeric PA have been shown to be degraded into various aromatic acids by the gut microbiota (Gonthier et al., 2003a; Ward et al., 2004). However, detailed information on the bioavailability and metabolism of PA in humans are lacking, because human intervention studies with purified PA have never been performed. Therefore, the quantitative importance of the degradation of PA into microbial metabolites is unclear and the exact structures of PA in plasma or urine structures (e.g. phase II metabolites) are not known.

Studies on health effects of polyphenols from cocoa or of chocolate and / or other cocoa products are reported to be scarce (Wollgast and Anklam, 2000a). Recent human studies have proven that chocolate has beneficial effects on some pathogenic mechanisms of heart disease such as endothelial function and blood pressure (Steinberg et al., 2003; Taubert et al., 2007; Vinson et al., 2006). Flavanol-rich foods can positively affect hemostasis, through mechanisms that either directly affect platelet function or increase certain endothelium-derived factors that maintain platelet acquiescence or increase fibrinolysis (Holt et al., 2006). In this context, a series of *in vivo* studies on the effects of flavanol-rich cocoa and chocolate on platelet activation and platelet-dependent hemostasis have also been reviewed (Holt et al., 2006). Epicatechin, the major polyphenol in chocolate and chocolate extracts, is a powerful inhibitor of plasma lipid oxidation due to polyphenols' ability to bind to lower density lipoproteins (Vinson et al., 2006). Polyphenolic substances derived from cocoa powder may contribute to a reduction in LDL cholesterol, an elevation in HDL cholesterol, and the suppression of oxidized LDL (Baba et al., 2007a and 2007b). Extensive studies on cocoa extracts, consisting of monomeric catechins and oligomeric procyanidins with 2–18 monomeric units have been conducted. However, so far their results have been only published in a US patent application, suggesting anti-atherogenic, anti-carcinogenic, anti-inflammatory, immune-modulating, and antimicrobial activity properties of cocoa extracts (Wollgast and Anklam, 2000a).

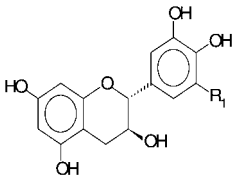
In vitro, extracts of PA-rich foods as well as isolated PA fractions exhibit remarkable antioxidant and radical-scavening activities, they show anti-inflammatory properties, and they inhibit LDL oxidation, platelet aggregation and the growth of several cancer cell lines (Dixon et al., 2005; Steinberg et al., 2003). *In vivo* studies performed in animals mainly focus on the potential chemopreventive effect of PA on colorectal cancer as well as on preventive effects against coronary heart diseases (Gosse et al., 2005; Nomoto et al., 2004; Rasmussen et al., 2005). Most of these studies show promising results, but the relevance for humans as well as the contribution of PA *per se* remains unclear, because in the majority of the studies PA-rich extracts or foods have been used which contain poorly defined polyphenol mixtures.

In conclusion, the citation: "It is yet to early to give an answer to the question, whether chocolate and / or other sources rich in catechins and procyanidins are beneficial to human health and thereby becoming functional in their nature" (Wollgast and Anklam, 2000a) still explains the current status. Especially, since factors like food matrix (e.g. consumption of milk at the same time as dark chocolate reduce the bioavailability of polyphenols) still need to be considered (Dixon et al., 2005; Serafini et al., 2003).

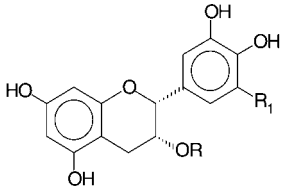
4. Tea phenolics

Tea is one of the most widely consumed beverages, second only to water. Based on the manufacturing technique, teas can be classified as green tea (unfermented), oolong (semi-fermented) and black tea (fully fermented). Phenolic compounds in tea belong structurally mainly to flavan-3-ols (Fig. 3), and these form 20–30% of the dry weight of green tea (Wang et al., 2000a). The major catechins in fresh tea leaves and green tea are (-)-epigallocatechin gallate (EGCG; 9170–14900 μmol/100 g leaf), (-)-epi-gallocatechin (EGC; 8060–17900 μmol/100 g leaf), (-)-epicatechin gallate (ECG; 1400–2350 μmol/100 g leaf) and (-)-epicatechin (EC; 2360–5800 μmol/100 g leaf) (Sakakibara et al., 2003) depending on art and cultivation conditions. The main flavonols in tea leaves are quercetin, kaempferol and myricetin. They make up 2–3% of the water-soluble extractive in green tea (Wang et al., 2000a). Black tea infusions also contained relative high levels of the afore mentioned catechins in the range 102–418 mg of total catechins/L (Arts et al., 2000). During tea fermentation, the four major tea catechins are enzymatically oxidized and converted to various oxidation products comprising black tea polyphenols. Of these oxidation products, characteristic pigments are usually classified into two major groups, theaflavins and thearubigins (Tanaka et al., 2005; Wang et al., 2000a). The theaflavin content of black tea leaves is usually 0.8–2.8% depending on the conditions of fermentation. On the other hand, thearubigins constitute up to 60% of the solids in black tea infusions (Tanaka et al., 2005). There are four main theaflavins, theaflavin, theaflavin 3-gallate, theaflavin 3′-gallate, and theaflavin 3,3′-digallate, in black tea, formed through the reaction between quinones derived from a simple catechin and a gallocatechin (Wang et al., 2000a). The thearubigins remain ambiguous with relative molecular masses in the range 700–40,000 Da and little is known about their chemical structures (Tanaka et al., 2005; Wang et al., 2000a). Besides these many unidentified colorless oxidation products are also produced during tea fermentation.

The daily intake of catechin and proanthocyanidin dimers and trimers has been estimated to be 18–50 mg/d (Manach et al., 2005). The bioavailability of green tea catechins, including epigallocatechin gallate (EGCG), epigallocatechin (EGC), epicatechin gallate (ECG) and epicatechin (EC) is low in both



Flavan-3-ol	R	A
(+) Catechin	H	H
(+) Gallocatechin	H	OH



Flavan-3-ol	R	R_1
(-) Epicatechin	H	H
(-) Epicatechin-3-gallate	3,4,5 Trihydroxybenzoyl	H
(-) Epigallocatechin	H	OH
(-) Epigallocatechin-3-gallate	3,4,5 Trihydroxybenzoyl	OH

Fig. 3 Representatives of major tea phenolic compounds.

animals and humans (Chan et al., 2007; Feng, 2006; Williamson and Manach, 2005). The extent of efflux transport in Caco-2 cells was, in descending order, EC > EGC > ECG = EGCG (Chan et al., 2007). It has been also found that efflux transporters Pgp, MRP1 and MRP2 play roles in the absorption and excretion of green tea catechins (Feng, 2006). Several processes including intestinal metabolism, microbial metabolism, hepatic metabolism and chemical degradation have been suggested to be involved in the fate of green tea, and to be responsible for its low availability in humans (Feng, 2006). The pharmacokinetic data indicate that the oral bioavailability of EGCG in a conscious and freely moving rat was about 4.95%. The elimination half-life of EGCG was 62 +/– 11 and 48 +/– 13 min for intravenous (10 mg/kg) and oral (100 mg/kg) administration, respectively (Lin et al., 2007).

Recent studies have demonstrated that green tea catechins undergo methylation, glucuronidation and sulfation in *in vitro* systems, in animals, and in humans (Feng, 2006; Manach et al., 2005; Williamson and Manach, 2005). EGCG is the only known polyphenol present in plasma in large proportion (77–90%) in a free form (Manach et al., 2005). The other catechins are highly conjugated with glucuronic acid and / or sulfate groups. The exact nature of the major circulating metabolites of epicatechin has been elucidated (Natsume et al., 2003). Microbial metabolites, mostly in conjugated forms, were also found in plasma and urine after green tea intake (Lee et al., 2006; Manach et al., 2005). These metabolites accounted for 6–39% of the ingested epigallocatechin and epicatechin, 8–25 times the levels measured for the unchanged compounds (Manach et al., 2005). A recent review covers the different aspects of pharmacokinetics, absorption, distribution, drug metabolism and excretion properties of green tea in *in vitro* systems, in animals, and in humans as well as the factors affecting their biotransformation and bioavailability: drug-drug inhibitory and inductive interactions of phase I and phase II enzymes, inhibition of non-drug-metabolizing enzymes, transporters, chemical instability, epimerization and interindividual variability (Feng, 2006). With regard to theaflavins and thearubigins, not much is known about their bioavailability. A study conducted to determine the bioavailability and bioactivity of tea polyphenols and theaflavins in human serum and human and mouse tissues showed that these were found in the small and large intestine, liver, and prostate in conjugated and free forms, but were not detectable in serum (Henning et al., 2006).

There is a long series of articles describing beneficial effects of tea phenolic compounds in biological systems *in vitro*, in animals, and in humans leading recently to many critical reviews on this subject (Cabrera et al., 2006; Dryden et al., 2006; Fujiki, 2005; Gardner et al., 2007; Higdon and Frei, 2003; Williamson and Manach, 2005; Zaveri, 2006). In human intervention studies, tea phenolics increased plasma antioxidant activity, as assessed with a variety of decreased plasma lipid peroxide and malondialdehyde concentrations, increased plasma ascorbate concentrations, decreased nonheme iron absorption, and increased the resistance of LDL to oxidation (Manach et al., 2005). A review of health benefits of black tea suggests sufficient evidence for an improved antioxidant status at intakes of one to six cups per day. A maximum intake of eight cups per day would minimise any risk relating to excess caffeine consumption (Gardner et al., 2007). Several epidemiological studies have shown beneficial effects of green tea in cancer, cardiovascular, and neurological diseases (Zaveri, 2006). The health benefits associated with green tea consumption have also been corroborated in animal studies of cancer chemoprevention, hypercholesterolemia, artherosclerosis, Parkinson's disease, Alzheimer's disease, and other aging-related disorders (Zaveri, 2006). Recent work shows that green and black tea have shown promise in the chemoprevention of prostate cancer (Henning et al., 2006; Siddiqui et al., 2006). Most animal studies indicate that tea has strong chemopreventive effects against lung tumorigenesis, although epidemiological studies on the cancer-preventive effects of tea produce inconsistent results (Clark and You, 2006). In view of the increasing interest in the association between dietary flavonoids and cancer initiation and progression, this important field is likely to witness expanded effort and to attract and stimulate further vigorous investigations (Kandaswami et al., 2005). Substantial *in vitro* and animal studies support the beneficial effects of polyphenols in many gastrointestinal diseases (Dry-

den et al., 2006). Recent human studies suggest that green tea may also contribute to the promotion of oral health and other physiological functions such as anti-hypertensive effect, body weight control, anti-inflammatory, anti-antibacterial and antivirasic activity, solar ultraviolet protection, bone mineral density increase, anti-fibrotic properties, and neuroprotective power (Cabrera et al., 2006; Gardner et al., 2007; Sutherland et al., 2006).

5. Conclusion

In conclusion a review of 93 intervention studies on bioavailability and bioefficacy of polyphenols in humans summarises the actual situation perfectly: Compared with the effects of polyphenols *in vitro*, the effects *in vivo*, although significant, are more limited (Williamson and Manach, 2005). Therefore, more epidemiological, human intervention studies and clinical studies, especially those reflecting long-term dietary consumption of polyphenols need to be undertaken for their efficacy to be fully elucidated (Scalbert et al., 2005; Sutherland et al., 2006; Williamson and Manach, 2005).

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