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A review of latest research findings on the health promotion properties of tea

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Abstract

Important progress has been made in the past five years concerning the effects of green and black tea on health. Experimentation with new accurate tools provide useful information about the metabolism of tea components in the body, their mode of action as antioxidants at the cellular level and their protective role in the development of cancer, cardiovascular disease and other pathologies. The use of tea components as nutraceuticals and functional foods are also discussed.

Keywords: Tea; Review; Anti-oxidant; Cancer; Cardiovascular; Health

1. Introduction

The consumption of tea is a very ancient habit and legends from China and India indicate that it was initiated about five thousand years ago. Archeological research reported by Jelinek in 1978 suggests that the infusion of leaves from different wild plants and also from the tea tree was probably already practiced more than 500 000 years ago [1]. Traditionally, tea was drunk to improve blood flow, eliminate toxins, and to improve resistance to diseases [2]. It was introduced progressively all around the world by traders and travellers. *Camellia sinensis* varieties arise from numerous selections and hybridizations that naturally occur between *Camellia* species because these taxa freely interbreed. Tea can be cultivated in many regions that have a high humidity, fair temperature, and acidic soils, from sea level to high mountains [1,3]. Freshly harvested tea leaves must be processed to inactive enzymatic oxidation for green tea production, or to control the oxidation by the leaf enzymes for the production of oolong and black teas [2].

Tea was associated with both lifestyle and nutritional habits as it was introduced into new countries. Rituals in China, Japan, and England give tea consumption a unique place between a mere beverage and a social function where food is closely associated with a state of mind. Tea time is usually set during afternoon between the major meals in a relaxed atmosphere. The modern life-style tends to alter this relation and to place tea among other beverages and fast foods. But scientific evidence about the action of diet on metabolism is changing the perception of food and data about the health benefits of tea could modify attitudes toward this very ancient beverage. Together with new health claim legislation, this could increase the consumption of tea.

The past five years have been rich in information coming from laboratories all around the world concerning the positive impact of food on human health. More and more emphasis is being placed on events at the cellular level. Much interest has centered on the role of oxidant/antioxidant activity in regards to the aging process and degenerative diseases like cancer, cardiovascular disease, and diabetes. Potentially active components from fruits, herbs, roots and leaves have been studied extensively. Special attention has been paid to the non-nutritive components of plant origin like teas, spices, and herbs. The results suggest that polyphenols especially the flavonoids possess a high antioxidant power which can protect cells against the adverse effects of reactive oxygen species. Tea contains a large amount of catechins, a group of very active flavonoids, and has been the topic of many studies. Data has been generated by research teams in the laboratory, with animals, and with humans in clinical or epidemiologic studies, each one producing useful but sometimes contradictory information. The

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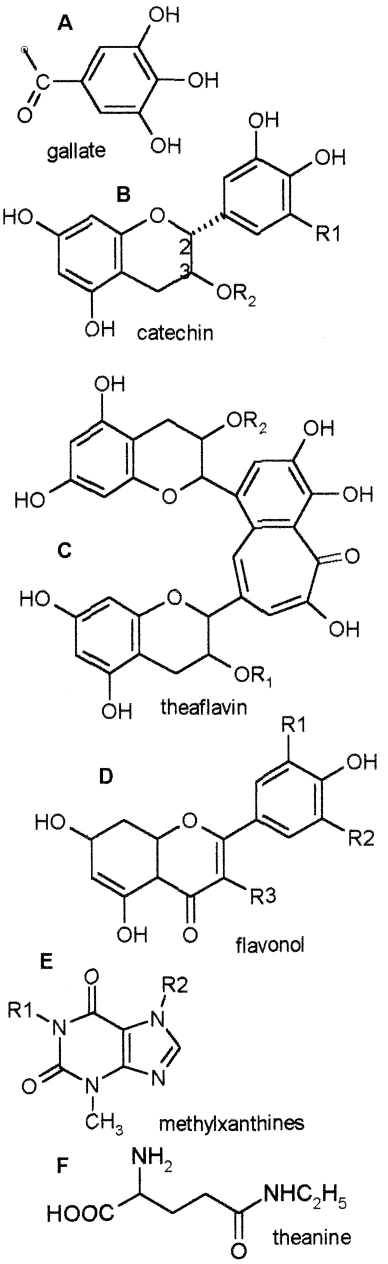
Table 1
Components of tea

	occurence (% dry weight)		
	green tea	black tea	structure
Catechins	**30-42**	**10-12**	
epigallocatechin gallate	11		**B** (-)2,3-cis R1=OH R2=**A**
epicatechin gallate	2		**B** (-)2,3-cis R1=H R2=**A**
gallocatechin gallate			**B** (+)2,3-trans R1=OH R2=**A**
epicatechin	2		**B** (-)2,3-cis R1=R2=H
epigallocatechin	10		**B** (-)2,3-cis R1=OH R2=H
gallocatechin			**B** (+)2,3-trans R1=OH R2=H
catechin			**B** (+)2,3-trans R1=R2=H
Teaflavin		**3-6**	
theaflavin-3-gallate			**C** R1=OH R2=OH
theaflavin-3'-gallate			**C** R1=**A** R2=OH
theaflavin-3,3'-digallate			**C** R1=OH R2=**A**
Thearubigens		**12-18**	**C** R1=**A** R2=**A**
Theogallin	**2-3**		
Proanthoocyanidin			
Flavonols	**5-10**	**6-8**	
quercetin			**D** R1=OH R2=H R3=OH
kaempferol			**D** R1=R2=H R3=OH
rutin			**D** R1=OH R2=H R3=O-rutinose
Methylxanthines	**7-9**	**8-11**	
caffeine	3-5		**E** R1=R2=CH_3
theobromine	0.1		**E** R1=H R_2=CH_3
theophylline	0.02		**E** R= CH_3 R2=H
Amino acids			
theanine	4-6		**F**
Organic acids			
caffeic acid			
quinic acid	2		
gallic acid			
Volatiles			
linalool			
delta-cardinene			
geraniol			
nerolidol			
alpha-terpineol			
cis-jasmone			
indole			
beta-ionone			
1-octanal			
indole-3-carbinol			
beta-caryophyllene			



purpose of this review is to bring together the most recent scientific information about the properties of tea and their effects on human health, using advances in our knowledge about how dietary components can affect defence mechanisms at the cellular level that the body uses to protect itself.

2. The chemical composition of tea

The composition of green tea has been thoroughly studied up to the nineteen eighties and is now well known [2,4,5,6,7]. The major constituents are listed in Table 1. Tea is the best dietary source of catechins. Epigallocatechin gallate (EGCG) is the major catechin in tea accounting for more than ten percent on a dry weight basis. However, catechin and epicatechin (EC) can also be found in chocolate, black grapes, red wine and apples [8,9,10]. Flavonols are more widely distributed. They are present in onion, endives, cruciferous vegetables, black grapes, red wine, grapefruits, apples, cherries and berries [8,9,11,12]. Quercetin, kaempferol and rutin are the most important flavonols in tea. Tea contains phenolic acids mainly caffeic, quinic

and gallic acids. Caffeic acid is also found in white grapes, berries, in most fruits, in some vegetables particularly in asparagus, olive and cabbage [8,12]. Tea is also a good source of methylxanthines primarily in the form of caffeine. It contains about one third the caffeine of coffee, the most well known source of caffeine. Theanine is an amino acid found only in tea leaves. Tea contains also many flavour compounds. Linalool, the most abundant, is also found in many food spices such as coriander, lavender, sage, and thyme [13].

Although the main constituents in tea have been elucidated previously, recent progress has been made in the identification of proanthocyanidins resulting from inter-flavonoid linkage [14,15] and in the identification of flavonol glycosides [16]. Flavonol glycosides, also found in white wine, need more investigation. Products resulting from the oxidation of catechins during black tea processing such as thearubigins and theaflavins are complex and more difficult to identify than single catechins [17]. More research is needed owing to the fact that these molecules seem to have important activity in the living organism. Important progress has been made on the analyses of these compounds, allowing for the quantification of flavonoids in human fluids and organ tissue [18,19,20]. Development of very sensitive and accurate analytical methods is a necessary step for the investigation of metabolic pathways.

3. Metabolism and biodisponibility

Until recently, polyphenolic compounds were considered as antinutrients causing adverse effects by reducing the digestibility of proteins, and it was common thinking that polyphenols were poorly assimilated [21]. However, many researchers have concluded that polyphenols have important beneficial effects on human health and it is obvious that a better understanding of their metabolism is needed. Recently, the bioavailability of polyphenolic compounds and their distribution in the body have been investigated using sensitive and accurate methods to analyse metabolites in biological fluids and tissues [20,22].

Metabolism of tea constituents depends on their particular structure. Studies with radioactively labelled catechin in humans indicate that catechins are metabolized efficiently [22]. When green tea extract is consumed by healthy volunteers, EGCG, EGC, and EC are found in the plasma in a dose-dependant concentration varying between 0.2 and 2.0% of the ingested amount, with a maximal concentration 1.4 to 2.4 h after ingestion [18,19,23]. Catechin intake does not alter endogenous antioxidant levels [19]. The half-life for EGCG is about 5 h and for EGC and EC it varies between 2.5 and 3.4 h [23]. EGC and EC are partly recovered in urine but not EGCG. Catechin metabolites such as 4-hydroxybenzoic acid, 3,4-dihydroxybenzoic acid, 3-methoxy-4-hydroxy-hippuric acid and vanillic acid have also been detected in urine [18]. Catechin fed to rats has been found in kidney, liver, skin, lung, and heart blood [5]. Catechin glucuronidation, sulfation and *O*-methylation have been reported to occur in the liver of animals and humans [21,22]. *O*-methylated derivatives have been detected in the plasma and are excreted in bile and urine [21]. Conjugates can move from bile to the small intestine where they are deconjugated and cleaved by microorganisms to simple phenolic acids and lactones which are then absorbed via the intestinal mucosa [21]. Little is known about the bioavailability of black tea condensed tannins but it appears that they are absorbed as well [22].

The metabolism of quercetin and of its glycosides has also been studied [22]. Glucose conjugates are rapidly absorbed in the small gut [24,25]. Quercetin-3-rutinose or rutin is the main quercetin glycoside in tea. Bioavailability of rutin is 30% relative to onion which contains only quercetin-glucose conjugates [25]. Peak plasma levels in healthy subjects occur 9 h after the ingestion of rutin and the rate of elimination of quercetin is relatively low contributing to the antioxidant capacity of blood plasma [26]. Quercetin may be conjugated in the liver by phase II enzymes [22]. End products of quercetin metabolism in rats are simple phenols and CO_2 [21]. The fermentation rate by the intestinal microflora varies with its composition. *In vitro* fermentation of quercetin yields a high production of acetic acid and a low production of propionate and of butyrate. *In vitro* fermentation of catechin also produces acetic acid but only after a longer period, suggesting an inhibitory effect of gallic acid [21]. Lactase phlorizin hydrolase found in the brush border of the mammalian small intestine can deglucosylate flavonoids [27] and can interact with the sodium dependent glucose transport receptors in the mucosal epithelium [24]. Nothing is reported for other flavonoid glycosides. Proanthocyanidin is partly fermented by rumen microflora [21].

Polyphenols interfere with the absorption of other compounds in the diet. They have a strong affinity for proline-rich proteins such as casein, milk, gelatin, and saliva. The large, flexible, poorly water soluble polyphenols have the most effective binding capacity [22]. However, the consumption of milk and green or black tea does not affect the polyphenol concentration in blood, indicating that milk does not reduce tea polyphenol bioavailability [22,28]. The protein-binding capacity of polyphenols may reduce the digestibility of alimentary proteins and increase faecal nitrogen excretion in humans in a manner similar to that observed in herbivorous animals [22], even though the formation of protein-polyphenol complexes is limited to molecules accessible to soluble proteins [21]. In rats, the nitrogen excreted comes from endogenous proteins rather than from dietary protein intake [21]. Tannins can also bind digestive enzymes and reduce protein, starch and lipid digestibility, affect glycemic and insulinemic responses, increase fat excretion and reduce cholesterol absorption [21].

Tea polyphenols have a strong interaction with transition metal ions and form insoluble complexes with iron. This binding in the gastrointestinal tract strongly inhibits iron

absorption [21,22,29]. Black tea is more inhibiting than green tea. The inhibition has been observed, but to a lesser extent with other polyphenolic containing beverages such as cocoa, wine, and in herbal teas such as mint, vervain, lime flower and camomile [29]. The binding affects non-haem iron only and can be overcome by the presence of ascorbic acid [22]. When a long-term diet low in non-haem bioavailable iron content is consumed, partial adaptation occurs to maintain homeostatically body iron reserves, serum ferritin level and modulate faecal ferritin content [30]. No adverse effect has been observed in populations eating a varied diet, but in populations with a poor iron intake, anaemia is more prevalent [22]. Vegetarians might be advised to drink tea between meals because iron from plant sources is not as available and binding by tea could further reduce the amount of available iron in their diet. Inhibition in the absorption of zinc has been observed in rats but results with copper are not clear. Polyphenols can also interfer with the bioavailability of sodium and aluminium but not with manganese, calcium, or magnesium [21]. Knowledge about the digestion, absorption and metabolism of tea by humans is at its infancy and more research needs to be done.

4. Oxidation mechanisms

Information from recent research about cancer, cardiovascular, inflammatory diseases, and aging processes, indicates that all these events are closely related to a general process of oxidation regulation at the living cell level. More emphasis is being placed on the effects of some types of nutrients on antioxidant status. In order to better understand how tea and its components can affect the oxidative balance, it is necessary to describe the oxidation process in relation to cellular metabolism.

Oxygen is essential to maintain life, but it can have adverse effects if the number of highly reactive oxygen containing radicals exceed the needs of the cell or are not trapped adequately. Metabolic activities produce free radicals—unstable molecules able to react with electron donors to equilibrate its charge. This reaction is useful for the synthesis of nucleic acids, hormones, proteins, and, very often, a catalyst (iron, copper, manganese, molybdenum) is required. Free radicals are also naturally produced to intercept invaders like microbes and viruses. Different kinds of free radicals are generated that can injure the cell, but the cell circumvents their toxic activity by internal antioxidant mechanisms and by compartmentalization. Detoxification occurs through a multi-stage enzyme system where the molecules are activated by phase I enzymes (cytochrome P450, NADPH) and converted into electrophilic water soluble compounds, prior to their conjugation to detoxifying molecules (glutathione, UDP-glucuronosyl, amino acid) for inactivation, and excretion. Glutathione, vitamin E, vitamin C and superoxide dismutase are the cell's main internal defences. Phagocytic cells like neutrophils, monocytes and macrophages as well as T-lymphocytes and B-cells are especially active against invaders [31]. Knowledge of the molecular mechanisms supporting the action of free radicals in cells is increasing rapidly [32,33,34].

The oxidation/antioxidation balance is highly regulated. But oxidative stress induced by an overproduction of reactive oxygen species (ROS) leads to a disruption of cellular functions. Reactivity of oxygen species varies from high for hydroxyl radical (·OH), ferryl ion ($Fe^{2+}O$) or $Cu(OH)_2$, to lower reactivity for superoxide radical anion ($O_2^{\cdot-}$), peroxyl radical (ROO·), hydrogen peroxide (H_2O_2), singlet oxygen ($^1O_2$), hypochlorous acid (HOCl), nitric oxide (NO·), peroxynitrite ($ONOO^-$) and alkoxyl radicals (RO·) [35,36]. ROS can react together or with other molecules to form more or less reactive molecules. Free radicals are also generated by the external action of toxic substances, microbial attacks, ozone, UV radiation, cigarette smoke, or by intensive exercise [33,36,37,38,39]. Cells react by modifying activity over DNA expression and energy production. ROS alter membrane unsaturated fatty acids, decreasing their capacity to protect cell contents and exchanges with the environment. Protein oxidation by ROS has been identified as an important component of the aging process and damages resulting from radiation. The cell reacts to oxidation with an internal defence mechanism in which glutathione and other enzymes reconvert the oxidized molecules to their reduced form. When proteins bearing SH-groups are oxidized, it can result in severe injury owing to their metabolic importance notably as carriers, as enzymatic active groups, and in the respiratory process. The oxidation of nucleic bases in DNA induces mutations and heightens the risk of cancer occurrence. Lipid and protein oxidation are also correlated with increases in atherosclerosis and diabetic complications and a reduction of the immune function [40].

Although cells possess enzymatic and non-enzymatic protection against ROS, antioxidants from nutrients contribute to the overall protection of the cell integrity and the immune function [31,32,36,41,42,43,44]. It is not easy to evaluate the impact of complex combinations of different food components and their action on cell metabolism. But it has been concluded that ascorbic acid and tocopherols are the best protectors against a wide range of oxidizing molecules. Their relation to the endogenous mechanism of protection, mainly GSH, has been well studied [36,43]. Adequate mineral nutrition including selenium, copper and zinc is important for the optimal activity of the enzymatic system against oxidation [32,36]. Carotenoids including lycopenes also act as antioxidants mainly for the protection of cell membranes and DNA integrity [45].

Another group of widely distributed compounds that are important in the defence against oxidation is the polyphenolic compounds—mainly the flavonoids—which are present only in plants. Fruits, vegetables, and herbs in diets are believed to protect against cancers and many diseases and this is related, for a part, to their antioxidant properties. Although they are also good sources of vitamins A, C, and

E, and mineral enzyme co-factors, they possess specific molecules exhibiting high antioxidant properties. Tea contains up to one-third of dry-weight of catechins and other polyphenols like quercetin, myricetin, and kaempferol, which exhibit powerful antioxidant activities.

In vitro models for measuring the antioxidant properties of plant polyphenols are well established. In the lipoprotein oxidation model that simulates the oxidation of low-density lipoproteins responsible for atherosclerosis, flavanols found in tea exhibit the most powerful antioxidant activity; 20 times more potent than vitamin C [46,47]. Quercetin and caffeic acid are also very good antioxidants. Caffeic acid exhibits an antioxidant activity as high as kaempferol and is an efficient scavenger of peroxyl radicals [8]. Different methods of evaluation of the antioxidant activity of polyphenols suggest that they can prevent lipid hydroperoxide formation [20,48,49], photo-enhance lipid peroxidation [50] and DNA damage [51]. They exibit scavenging activity against superoxide radicals [51,52], free radicals [8,52], peroxynitrite [35,53,54], alter the catalytic activities of many enzymes notably oxidative ones [35], modify the protein phosphorylation process [55], and chelate iron and copper preventing metal-catalysed free-radical formation [8]. Polyphenols inhibit the formation of harmful N-nitroso compounds when nitrogen-containing compounds are exposed to endogenous or exogenous nitrosating agents [44]. Flavonoids can spare urate, β-carotene, vitamins C and E, contributing to the overall antioxidant protection mechanism of the cell [56]. Flavonoids in high concentration or in the presence of Cu^{2+} act also as pro-oxidants and can inhibit P-450-catalysed activity [35] in a manner similar to that reported for ascorbic acid and α-tocopherol [57,58,59].

The scavenging activity of different catechin molecules is related to the number of *o*-dihydroxy and *o*-hydroxyketo groups, C_2-C_3 double bonds, concentration, solubility, the accessibility of the active group to the oxidant, and the stability of the reaction product [58,60]. EGCG is the most potent tea antioxidant with four dihydoxy groups. The addition of glycosidic functions to the flavonoid molecule reduces the antioxidant activity as is observed with rutin, the glycoside of quercetin [46]. Flavonoid glycosides reactivity against ROS and the recycling potential of the cell is relevant in determining intracellular oxidant/antioxidant status [61]. Deleterious effects of ROS on cellular membranes and internal structures can alter metabolism and may contribute to the onset of cancer, cardiovascular disease and impairment of the immune function.

5. Protective effect of tea against cancer

Initiation, promotion and progression in cancer development are modulated by many factors related to metabolism, diet, and external environment. Accumulation of reactive oxygen species in cells and resulting modifications in DNA structure, enzymatic activity, and defence mechanisms all influence the development of the cancer pathogenesis [34]. Consequently, antioxidants such as those found in tea can play an important role in prevention and control of cancer development.

Many studies have been conducted with malignant cell line cultures *in vitro*, with animals, and more recently with humans. More and more emphasis is being placed on the molecular mechanisms involved to better understand the causes of various cancers and the possible functions of dietary components that could prevent the onset of cancer.

5.1. Mechanistic studies

In cancer research, *in vitro* studies are very accurate tools to investigate events and outcomes at the cellular level. Although they do not take into account the overall regulation mechanism of the whole organism, the biodisponibility of the target compounds, or the interactions with multi-external factors, they have generated much useful information. *In vitro* studies have shown that tea catechins act as potent inhibitors of carcinogenesis at the three stages of cancer development.

5.2. Cancer initiation

Procarcinogens that are activated by phase I enzymes such as cytochrome P450 enzymes are able to modify genomic DNA and induce tumor formation. Tea flavonoids can directly neutralise the procarcinogens by their strong oxygen scavenging activity, before cell injury occurs. Phenolics from green tea can prevent the *in vitro* formation of nitrosamines, a group of carcinogens also found in tobacco [44,62,63]. Tea polyphenols can inhibit the formation of heterocyclic amines from cooked fish and meat which are genotoxic carcinogens associated with cancer of the breast, colon and pancreas [50]. In Ames tests, DNA damage assays, and scavenging superoxides tests, EGCG exhibits the highest protection against mutations, DNA scissions, and in non-enzymatic interception of superoxide anions, while ECG is the best enzymatic scavenger [51,64]. Black, green and oolong teas significantly decrease the reverse mutation induced by different mutagens in cell culture assays indicating that tea can prevent the development of cancer by an antimutagenic protection correlated to its antioxidant properties [65,66,67,68,69,70,71]. Synergistic activity between catechins can also occur. EC, by itself is inactive, but when it is administrated with EGCG to a lung cancer cell line, it enhances apoptosis induced by EGCG [72,73]. Antioxidant supplementation can also increase lymphocyte resistance to oxidative damage [44]. Some studies indicate that tea polyphenols interact with the enzymatic defence mechanism in cells. EGCG inhibits the action of phase I enzymes preventing the activation of procarcinogens, and induces phase II enzymes which conjugate active carcinogens, and results in inactivation, and excretion [63,74]. These polyphenols thus

contribute to cancer prevention at the initiation stage of the carcinogenesis process.

5.3. Cancer promotion

When mutations affect DNA, it can result in the formation of neoplastic cells [44]. The signal transduction cascade including the factors $NF_{\kappa}B$ (nuclear factor kappa B) and AP-1 (activator protein 1) is redox-regulated and is therefore sensitive to the oxidant/antioxidant status of the cell [34]. It has been reported that EGCG and theaflavin-3-3′-digallate block AP-1, a signal transducer initiating the development of skin carcinogenesis [75,76,77,78] and can inhibit the mitotic signal tranducers responsible for cell proliferation [74]. Studies with liposomes have shed light on the mode of action of EGCG on the protein kinase activator, an enzyme related to the cell activation process in the promotion of tumors. EGCG inhibits the interactions between proteins and ligands by a sealing effect and prevents their binding [79]. EGCG and ECG stimulate gap junctional intercellular communication and prevent inhibition by the tumor promoters, a mechanism which plays an important role in the promotion of cancer [50]. Telomerase is an enzyme essential for unlocking the proliferative capacity of cancer cells and is lacking in normal somatic cells. It is reported that EGCG strongly inhibits telomerase activity, and thus induces senescence, limiting the life span of cancer cells, in both leukemias and solid tumors [80]. Caffeine exhibits an inhibitory effect on the potentially lethal damage repair mechanism in radiosensitive cells. This mechanism has been identified in malignant human tumors and its reduction improves radio-sensitivity and radiotherapy [81].

5.4. Cancer progression

Many studies indicate that tea polyphenols can inhibit the growth of malignant cells and induce apoptosis even in malignant cell lines resistant to CD95-mediated apoptosis [51,82,83]. Some results suggest that EGCG and EGC induce apoptosis due to their pro-oxidative activity [23,59]. In a study where EGCG and curcumin have been tested on oral cancer cell lines, EGCG blocked cell division in G_1, whereas curcumin blocked cell division in S/G_2M. When used in combination, EGCG and curcuma exhibit a synergistic effect [84]. Theaflavin-3,3′-digallate and EGCG have antiproliferative activities on tumor cells through the blockage of growth factor binding to the receptor and the suppression of mitogenic signal transduction [85,86]. Volatiles in tea have been found to be moderately cytotoxic against human carcinoma cells, with beta-ionone and nerolidol exhibiting the strongest activity [13]. EGCG inhibits urokinase, an enzyme with a proteolytic activity which is essential for cancer growth and metastasises formation, by interfering with the enzyme's ability to recognize its substrates [87]. EGCG can also kill specifically transformed cells by adenovirus [50]. Tea polyphenols can specifically inhibit DNA synthesis of rat hepatoma cells, leukemia cells and lung carcinoma cells [50,59,88,89]. The adhesion of mouse lung carcinoma cells to fibronectin, a plasma protein, can be inhibited by EGCG, hindering cancer progression [90]. Cell invasion and formation of metastasises could be facilitated by the secretion of a matrix degrading-zinc-enzyme. The invasion by highly metastatic lung carcinoma cells is prevented by theaflavin and theaflavin digallate, by the inhibition of the collagenase activity of their matrix metalloproteinases [91].

Immune cells play an important role in host defence against tumor development and progression [44]. Their plasma membranes are rich in polyunsaturated fatty acids, and are thus susceptible to oxidation by ROS [92]. Besides their antioxidant activity, flavonoids exhibit a modulating effect on cells responding to a stimulus or antigen-activated cells, like mast cells, lymphocytes, macrophages, platelets, hepatocytes, and smooth muscle [55]. The tumor necrosis factor alpha (TNF-α) is a cytokine induced by tumor promoters that stimulates the production of cell adhesion molecules and the inflammatory process response [55,79]. ECG, EGCG, and EGC inhibit TNF-α release and reduce cancer promotion [79]. Inhibition of $NF_{\kappa}B$ by EGCG may also inhibit TNF-α expression [23]. Quercetin can also block this reaction [55]. Theaflavin-3-3′-digallate may suppress the activation of $NF_{\kappa}B$ through inhibition of the KappaB kinase activity as demonstrated in macrophages [93]. The activation of immune B cells involved in antibody production induces the phosphorylation of tyrosine residues of proteins implicated in cancer cell proliferation. EGCG selectively inhibits the tyrosine phosphorylation in the intracellular transduction pathway and the spheroid and colony formation in vascular smooth muscle cells [94]. Flavonoids appear to inhibit the expression of the multi-drug resistance gene and modulate topoisomerase activity associated with tumor growth [55].

It is evident that tea polyphenols exhibit many protective activities and different metabolic pathways are involved. They act as antioxidants, they selectively inhibit specific enzyme activities, they target and repair DNA aberrations. Many components in tea are active and although each one has its own role, it now appears that some components exhibit synergistic activity. The positive effects of tea and tea components on various stages of cancer development (*in vitro*) are summarized in Fig. 1. Further research is needed for a better understanding at the cellular level of the complex process of cancer development and inhibition. Then it will be possible to explain how the components of tea promote cancer prevention and inhibition.

5.5. In vivo cancer studies

Many studies have been conducted with animals, mostly with rodents, to get a better understanding of the effect of tea components on cancers in the living organism. These

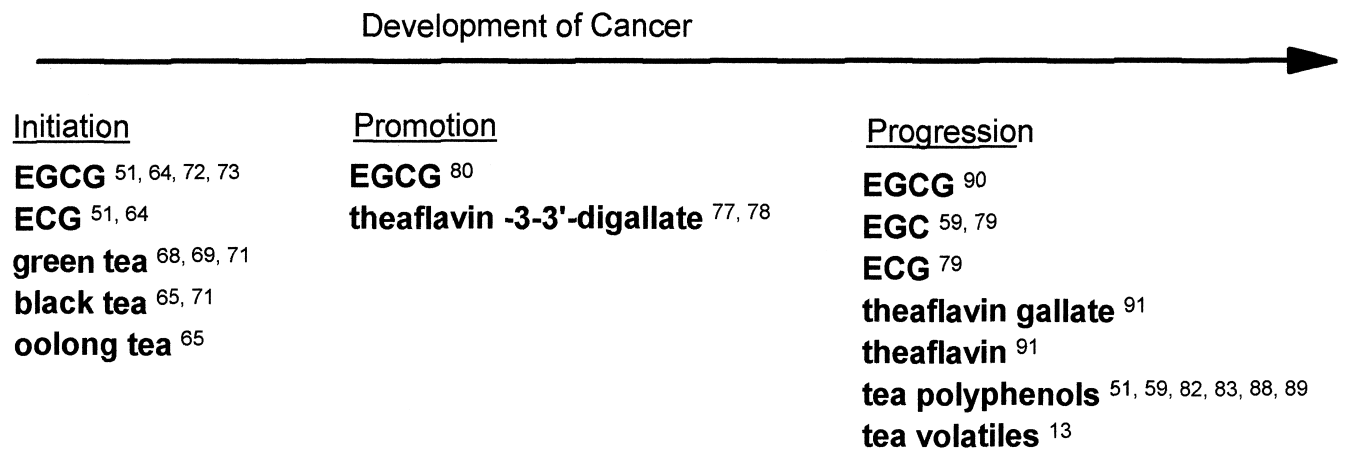


Fig. 1. Summary of tea and tea components inhibiting effects in initiation, promotion, and progression of cancer (refer to text for details).

studies show that tea protects against many types of cancer and at most stages of carcinogenesis [95].

5.6. Skin cancers

The activity of tea and tea polyphenols on the inhibition of skin tumorigenesis has been well studied. Early studies have demonstrated that topical application or ingestion of green tea polyphenols or EGCG inhibit tumor initiation and promotion by chemical carcinogens and UV light in mice [96,97,98,99]. Black tea has similar effects [99,100,101, 102]. More recent studies indicate that caffeine may be an important constituent of tea in regards to the chemoprevention of UVB light-induced carcinogenesis [101,103]. It has been reported in some studies that decaffeinated black tea enhanced the tumorigenesis induced by UVB light or a chemical promoter [102,103], while in other studies it reduced tumorigenesis to a lesser extent than whole tea extract [101,102]. Some decaffeination processes may be suspect because of the possible production of toxic residues or decomposition by-products. Bioactivation and metabolism of mutagens and promutagens administred orally to rats are modulated by green and black teas, and caffeine appears to be the active ingredient [104]. Topical application of a green tea polyphenolic fraction on mice skin papillomas can decrease significantly the conversion of benign tumors to malignant tumors [105]. Oral administration of green tea, black tea or EGCG inhibits the growth of well-established skin tumors and, in some cases, tumor regression can be observed. Complete regression was observed in 4% papilloma-bearing mice ($n = 346$) [99]. The growth of nonmalignant tumors, squamous cell carcinomas and tumor volume decreased significantly when tumor-bearing mice were fed with black tea. Inhibition of DNA synthesis and enhancement of apoptosis have been observed [99,102]. The application of a chemical tumor promoter to mouse skin induces an inflammatory response as an early step to tumor development. Topical application of black tea polyphenols significantly inhibits markers of inflammatory responses like epidermal edema, hyperplasia, leukocytes infiltration, induction of epidermal ornithine decarboxylase, pro-inflammatory cytokine IL-1α mRNA expression, and cyclooxygenase activity [100]. The molecular study of mouse skin tumors induced by UVB radiation indicates differences in the position of mutations in the p53 gene when mice are treated with green tea [106].

5.7. Lung cancer

Studies of the effects of green and black teas on the development of lung cancer in mice have promising implications for humans. Reduction in lung tumor number is observed when mice are treated with green or black tea, EGCG, or decaffeinated teas prior to chemical induction of lung tumorigenesis [96,107]. Similar results are obtained when a tobacco-specific nitrosamine (NNK) is administrated [23,108] or when lung tumors are allowed to develop spontaneously [109]. EGCG, EGC, and theaflavin-3-3′-digallate are the most potent components [23]. Green tea suppresses the increase in 8-hydroxydeoxyguanosine formation in mouse lung DNA but not O6-methylguanine. Both purine derived bases are essential in lung tumorigenesis in mice [108].

5.8. Digestive tract and other cancers

The relationship between tea consumption and digestive tract cancers has been also studied in animal models. High doses of theaflavin, black tea or green polyphenols, or EGCG reduce tumor multiplicity but not esophageal tumor incidence, when administrated to rats [96,110]. In another study, it was reported that rats bearing esophageal tumors and receiving low doses of decaffeinated black tea or decaffeinated green tea, had reductions in tumor incidence, multiplicity, and size [95]. Green tea infusion also inhibits forestomach chemically induced cancer in mice [96]. In two

different studies about the effects of tea on azomethane-induced colon cancer in rats, one reported that tea failed to reduce the incidence or the multiplicity of colon cancer while in the other, black tea extract and a high-dose of EGCG reduced premalignant lesions [110,111]. A small suppression of azomethane-induced aberrant crypt foci in rat colon has been observed in animals fed with green tea [112,113]. However, a green tea polyphenol fraction delivered in low concentration during the initiation and the post initiation period to rats treated with azomethane, reduced significantly the tumor incidence in the large bowel [95]. Cooked meat contains heterocyclic amines responsible for colon cancer in rodents and in humans. Heterocyclic amine-induced aberrant crypt formation in rat colon can be inhibited by green tea, EGCG, or a black tea polyphenol fraction [95,114]. A positive synergistic effect has been observed when green tea and phytic acid are combined [112]. Tea does not affect the cytochrome P450 specific activity for azomethane-metabolic activation but could work by other mechanisms such as the inhibition of some activating enzymes or the scavenging of reactive intermediates [110,111, 113]. In heterocyclic amine-induced colon tumors, tea stimulates phase I and phase II detoxifying enzymes for the rapid excretion of mutagens [114]. Suppression of DNA lesions caused by oxidative damage related to colon cancer in rats has been reported [95]. Positive effects in inhibition has been reported for rats consuming green tea during the initiation and the postinitiation of carcinogens [95]. Beneficial effects of tea have also been observed in rat, mice or hamster in the inhibition of liver cancer [95,96,107,113]. More recently, the effects of tea on the development of mammary gland and prostate cancer have been studied. No significant effect of tea on mammary gland tumorigenesis can be observed in rats fed a normal diet [96,115,116]. However, a partial inhibition is observed when tumorigenesis is enhanced by a high fat diet [115]. Spontaneous mammary tumor formation is markedly inhibited in mice fed green tea polyphenols and aluminium hydroxide [96]. Intraperitoneal injection of EGCG, but not other catechins, inhibits the growth and reduces the size of tumors initiated by human prostate and breast cancer cell lines inoculated into mice and rats [117,118]. Tea can also be helpful in chemotherapy. Oral administration of green tea to mice bearing implanted Ehrlich ascites carcinomas with doxorubicin increases the efficacy of the chemotherapy [119]. Development of mammary tumors in mice is also completely inhibited by a combination of tamoxifen and green tea. Tamoxifen alone inhibits 50% and tea alone has no significant effect [120]. Theanine enhances the anti-tumor activity of doxorubicin and inhibits hepatic metastasis in mice with ovarian carcinoma [121]. Tea is bioactive against carcinogenesis in animals for skin, lung, gastrointestinal tract and hormonal-dependant cancers and could be a good support in cancer chemotherapy. Results from studies about the effects of tea and tea components on the various stages of cancer in animal models are summarized in Fig. 2.

5.9. Human cancer studies

Studies *in vitro* with cell lines and *in vivo* with animals provide information useful for the understanding of human carcinogenesis and chemoprevention. Studies with humans are far more complex to cary out. Diversity in food habits, lifestyle, heredity, age, gender, and environment make unambiguous interpretation of the data difficult. In epidemiologic studies about the effects of tea consumption on health, the confonding factors are generally more variable than the effect tested and the results are not conclusive. This problem has been reviewed [96,122,123,124]. Cohort studies suggest a protective effect of green tea for colon [109], urinary bladder, stomach, pancreatic, and esophageal cancers [124]. In a Japanese population survey, an overall protection together with a slowdown in increase of cancer incidence with age was reported [125]. The effects are more pronounced when the consumption rises over 10 cups of tea per day.

Tea polyphenols act in the gastrointestinal tract modulating the composition of the gut micro-flora. A high content in clostridia and a low percent of bifidobacteria have been observed in the intestinal microflora of patients with colon cancer. Tea polyphenols selectively inhibit the growth of clostridia and promote bifidobacteria colonisation contributing to a decrease in the pH value of feces [5]. Viruses, bacteria, and worms have been implicated in the development of cancers; hepatitis viruses, herpes viruses, *Helicobacter pylori*, and parasitic worms are some well-known causes of cancer [51]. Tea can play another role in the prevention of cancer through its antimicrobial activity [126]. It has been demonstrated that tea can inhibit the growth of *Helicobacter pylori* associated with gastric cancer [127,128]. The cellular process involved could be the generation of powerful oxidants to destroy the invaders and protect the cells. Bacteria can also synthesize nitrosating agents endogenously and activate macrophages [44]. Nitrosating agents that are potentially carcinogenic, can be destroyed by polyphenols.

5.10. Cancer biomarkers

Case-control studies are more informative than food consumption surveys although they show mixed results. The identification of biomarkers for different stages of cancer development brings new tools for studies with human subjects. Biomarkers are measurable biological parameters applicable to easily available materials (blood, urine, etc) that are associated with individual susceptibility or early indicators of disease [129]. The most commonly used biomarkers related to cancer are: measurements of DNA damage in lymphocytes, variation in the ROS status, specific enzymatic activity of target enzymes like xanthine oxidase, ornithine decarboxylase or protein kinase, activation of the signal transduction cascade, and overexpression of oncogene-associated genes like c-*Jun* or c-*Fos* genes [74].

Biomarkers first used in animals studies are promising

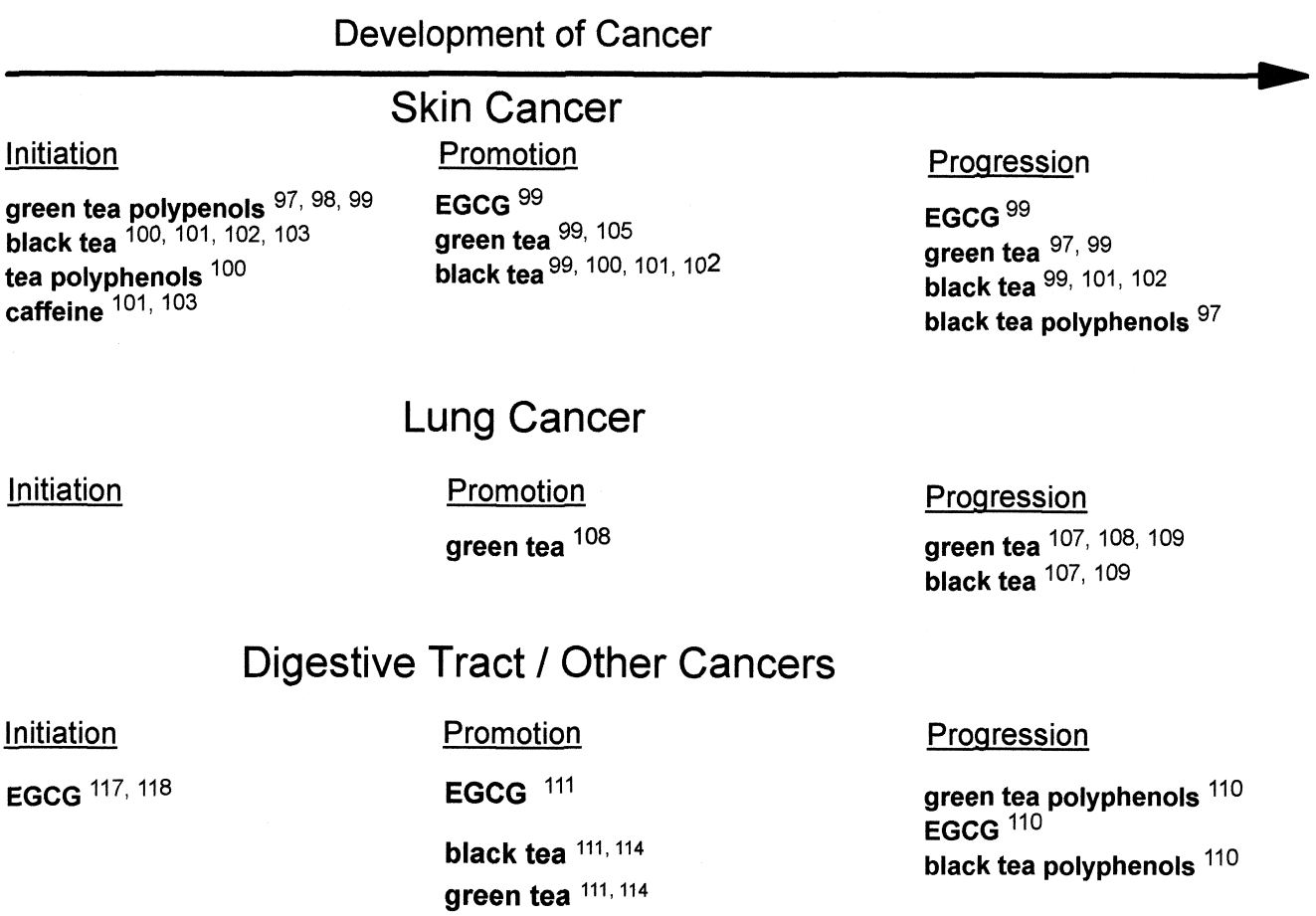


Fig. 2. Summary of the effects of tea and tea components on the various stages of cancer in animal models (refer to text for details).

tools for human studies although they are sensitive to phenotypic and genotypic polymorphism and must be accurately validated [129]. In a study with oral leukoplakias diagnosed patients at Beijing Dental Hospital, the effects of tea administrated orally or topically were monitored. Micronuclei from exfoliated cells of buccal mucosa and from lymphocytes and chromosome aberration in lymphocytes were used as biomarkers. Results indicate a reduction in the number of micronuclei and DNA aberrations in the treated group, compared to the control group. Reduction in the number of micronuclei indicates that the cell proliferation rate has decreased. The number and the volume of lesions were also reduced. These results provide good evidence of the protective effects of tea on oral cancer [130].

In two case-control studies conducted in Japan, increased tea consumption was associated with decreased numbers of axillary lymph node metastasis in premenopausal patients, increased expression of progesterone and estrogen receptors in postmenopausal ones, and a lower recurrence rate of breast cancer among stage I and II patients, along with a longer disease-free survival period [73,131]. Oxidative stress parameters have been used to measure the effect of green tea in smoker and nonsmoker volunteers. Drinking green tea significantly reduces oxidative DNA damage, lipid peroxidation and free radical generation in smokers. Decreases in oxidative stress in nonsmokers has also been observed. Inter-individual variations in the antioxidant effects has been reported and can be related to variations in tea metabolism, oxidative stress status, and genotypes [132].

The development of new biomarkers, sensitive separation and dosage methods, and new molecular data about the process of cancer development, provide important tools that can be used for cancer human studies [133].

6. Protective effect of tea in cardiovascular disease

The onset of cardiovascular disease (CVD) depends on numerous factors that can be modulated by components in the diet. In a large cohort study conducted in seven countries over 25 years, the average flavonol and flavone intake appears to be inversely correlated with mortality rates from coronary heart disease [11].

In coronary heart disease, atherosclerotic plaques protude from the inner surface of the arteries, narrow the

lumen, and reduce blood flow [134]. At the first stage, low-density lipoprotein (LDL) deposits at lesion sites of the arterial wall and is subjected to oxidation when protectors such as tocopherols are depleted. Later, oxidation of LDL induces modification in lipoproteins, stimulates inflammatory reactions, causes monocytes and monocyte-derived macrophages to accumulate in large amounts of oxidized LDL, and forms lipid-laden foam cells and atherosclerotic plaques. The intake of saturated fat and smoking habits accelerate these events. Recent studies conducted *in vitro*, with animal models, and with humans suggest that tea and its components can play a protective role in the development of CVD.

6.1. Lipoprotein oxidation

Oxidation of LDL is recognized as an important step leading to atherosclerosis and there are several reports indicating that tea inhibits the oxidation of LDL *in vitro* [6]. Studies testing the antioxidant effect of tea polyphenols on LDL and VLDL (very low-density lipoproteins) oxidation indicate that EGCG is very effective and has a lipoprotein-bound antioxidant activity greater than tocopherol [135]. Black tea extract also increases the resistance of LDL to oxidation in a concentration dependent manner [136], but at low concentrations, tocopherol is more effective [137]. Theaflavin digallate pretreatment of macrophages or of endothelial cells from mice inhibits, in a concentration- and time-dependant manner, the cell-mediated oxidation of LDL [138]. Green tea catechins suppress or inhibit the proliferation of smooth muscle cells of bovine aorta which produce connective tissue leading to luminal narrowing and sclerosis of the arteries [139]. Caffeine and theanine do not affect this process. In human aortic endothelial cells, tea extracts, catechin and epicatechin exhibit a dose dependant inhibition on the formation of early lipid peroxidation products and late lipid peroxide decomposition products [140]. Tea polyphenols probably reduce superoxide production in cells and chelate iron ions but the mechanism of action has not been elucidated yet [138]. Flavonoids like quercetin, myricetin and kaempferol can also protect LDL from oxidation by regenerating tocopherol, an important endogenous antioxidant in humans [141].

6.2. Animal cholesterol metabolism studies

The effects of tea on the cardiovascular system have also been reported in experimental studies with animals. Green tea reduces significantly serum and liver cholesterol, atherogenic index, and liver weight by lowering lipid deposition in hypercholesterolemic diet-induced rats [142]. HDL-cholesterol and triglyceride levels remain unchanged. In another study, rats supplemented with black tea had a reduction of their atherogenic index, an inhibition of smooth muscle cell proliferation and a suppression of the production of oxidized LDL [143]. Rats fed with 2.5% green tea leaves in the diet for a long time had a reduction in blood triglycerides and total cholesterol contents, enhancement in the superoxide dismutase and phase II enzyme activities in the liver without any liver or kidney damage [144]. Green or black tea at a lower level, also improved plasma lipid profiles and reduced LDL and VLDL oxidation in hamsters fed a normal or a high cholesterol diet [145]. Reduction in the cholesterol level could be due to precipitation of cholesterol and feacal elimination [134,146] or to inhibition of squalene epoxidase, a rate-limiting enzyme in cholesterol biogenesis, as demonstrated in rats [147].

6.3. Human cholesterol metabolism studies

Results in human studies are not as clear as studies using animals. Although some epidemiological studies seem to indicate that tea can reduce LDL oxidation, most studies show no significant association [11,134,148,149]. A protective effect against ischemic heart disease has been reported in the Rotterdam Study [150]. Results are also inconclusive in clinical and case-control studies. Serum lipid concentration, resistance of LDL to oxidation, and oxidative damage to lipids remain unchanged although total antioxdant activity in the plasma is slightly increased in volunteers consuming 600 or 900 ml tea per day [136,148]. This consumption is low compared to concentrations used *in vitro* and in animal tests and it could mean that animal model results cannot be extrapolated to humans. However, one study emphasizes the importance of the genetic heterogenity of lipid metabolism in the human population [151]. There are three isoforms (APOE2, APOE3, and APOE4) of the Apolipoprotein E corresponding to differences in the gene sequence in chromosome 19. Individuals bearing at least one E4 allele have higher levels of serum total cholesterol, LDL cholesterol and triacylglycerols. The effects of tea consumption varies with genotype. Beneficial effects on some risk-associated factors are higher in individuals bearing the E2 allele than those without the E2 allele. Main benefits are related to the coagulation/fibrinolysis system rather than to the lowering of blood cholesterol levels. In E4 allele bearing subjects, no statistically significant results have been observed [151]. Decreases in cholesterol, triglycerides and LDL-cholesterol along with an inhibition of digestive lipase by tea can decrease fat absorption and reduce body weight [144,152]. It is reported that green tea and caffeine have thermogenic properties, promote fat oxidation and play a role in the control of body composition probably via sympathetic activation of thermogenesis that can reduce obesity [153]. Caffeine and oolong tea can also enhance noradrenaline-induced lipolysis in fat cells, preventing obesity and fatty liver, and inhibit pancreatic lipase activity in obese mice induced by a high-fat diet [154]. The effect may have broader implications because obesity increases the risks for cancer and CVD.

6.4. Inflammation processes in CVD

Atherosclerosis is a disease with a strong inflammatory component [134]. Rutin and catechins from tea exhibit anti-inflammatory actions in animals and capillary strengthening properties. They inhibit arachidonic acid and histamine metabolism along with the migration of murine neutrophils. Catechins and quercetin in *in vitro* studies, inhibit the release of lysosomal enzymes, the chemiluminescence response and the production of free radicals associated with neutrophil function. EGCG stimulates *in vitro* the release of interleukin-1 from monocytes [134] and inhibits the leucocytes transmigration through endothelial cell monolayers associated with the inflammation process [155].

6.5. CVD and hypertension

The pathogenesis of hypertension represents an important risk factor for cardiovascular complications [156] and possesses a strong genetic component [157]. The balance in the endothelium between vasoconstrictors such as thromboxane and isoprostanes and vasodilators such as nitric oxide and ROS contribute to vascular resistance and to endothelium-dependent contraction [156]. Antioxidants can be very useful in the protection and restoration of endothelial function. *In vitro* studies have shown that flavonoids, mainly quercetin, produce a relaxant effect on contraction of rat aortic strips [134]. The effects of green tea catechins on phospholipase A2 activity and the antithrombotic reaction of platelets have been investigated in diabetic rats. Catechin supplementation maintains a normal level of platelet thromboxane A2 formation and improves platelet aggregation [158]. In an epidemiological study, black tea consumption has been inversely associated to the systolic blood pressure [134]. But in a case study, drinking black or green tea in moderate quantities did not improve blood pressure in humans [159]. It has been reported that theanine, at high doses, decreases significantly the blood pressure in spontaneously hypertensive rats but does not alter blood pressure in normal rats, although it decreases the brain 5-hydroxyindole level in both types of animals [160]. This subject has not been fully investigated [134].

Research on both overall cholesterol status and the mechanisms which regulate cholesterol metabolism indicate that tea itself and various tea ingredients such as EGCG, polyphenols and catechins can prevent or reduce cholesterol related events that could lead to CVD. The use of tea to control hypertension and obesity may also impact on the incidence of CVD. However, to date, few studies have been published that confirm these results in humans. As more is learned about the genetic diversity of the human population, it will be easier to explain the variability in results that occur in human studies concerning nutrition, metabolism and CVD. In the near future, it will be possible to identify sub-populations at risk for CVD that will benefit most from the addition of tea to the diet.

7. Protective effects of tea in other diseases

Tea can act on many cellular functions and impact positively on cancer and CVD, and it is likely that tea can also be helpful in other pathologies. Many reports support this statement. It is reported that tea can improve gastrointestinal function [5], ethanol metabolism, kidneys, liver, pancreas, stomach injuries, protect skin and eyes, alleviate arthritis, allergies, diabetes, prevent infections, dental caries, and can improve other diseases that have an inflammation component. The beneficial effects of tea on neurological and psychological health have also been reported.

7.1. Renal effects

Renal hypertension is one form of hypertension associated with constriction of the renal artery or kidney injury. In reducing blood pressure, green tea catechins improve kidney function in rats. Catechins increase the excretion of sodium and prostaglandin E_2 and improve the renal circulatory state [161]. Green tea catechins suppress the progression of renal failure and relieve mesangial proliferation and glomerular sclerotic lesions in nephrectomized rats [162]. The distal uriniferous tubule is suggested as the probable site of action of green tea catechins [161]. A cultured epithelial cell line with similar characteristics to the proximal uriniferous tubule known to be injured in ischemic renal failure, has been used to study the effect of tea on oxidative stress-induced apoptosis. Results indicate a protective effect of green tea, tea catechins and of theanine against oxidative stress, and LDH leakage after assessment of ischemic-reperfusion injury [82,163]. Rats receiving green tea prior to induced nephropathy, have decreased blood levels of urea nitrogen and creatine, and lower urinary levels of protein and glucose indicating a reduction in the effects of the damaged kidney [164]. By its direct action at the kidney level, tea can improve overall renal function.

7.2. Diabetes

Green tea can reduce blood glucose levels in aged rats, an indicator of diabetes frequently observed in the aging population [165]. Tea suppresses the activity of glucose transporters in the intestinal epithelium and is believed to reduce dietary glucose intake [166]. A reduction in oxidative damage to lymphocyte DNA has been observed in diabetic patients receiving quercetin and tea [167].

7.3. Skin and eye protection

Skin tissue is highly metabolically active and is very susceptible to oxidative stress from environment and endogenous sources. Black tea polyphenols protect against UVB-induced erythema, tyrosine phosphorylation and inflammation response in mouse and human skin and pretreatment can reverse the UVB-induced expression of early response

genes [168,169]. EGCG and ECG inhibit 5α-reductase present in the skin and associated with androgen-dependent dermatologic disorders such as acne [170]. EGCG can protect against UVB-induced immunosuppression which reduces the immunomodulatory cytokine interleukin-10 in skin and markedly increases interleukin-12 in the draining lymph node, a mediator and adjuvant for induction of contact sensitivity as demonstrated in mice [171]. The eye is highly susceptible to damage due to sunlight, oxygen, chemicals, pollutants and to aging. Green tea polyphenols such as EGCG can protect the rabbit eye lens against photooxidative stress induced by UVA. EGCG enters the eye, reaches the lens and inactives catalase induced by UVA exposure [172].

7.4. Antihistaminic and anti-arthritis effects

The release of histamine from mast cells is associated with inflammation, dermatis, urticaria, mastocytosis and asthma in allergic responses triggered by environment antigens. Beside its anti-inflammatory properties, tea extract exhibits an antihistaminic effect on rat peritoneal mast cells and inhibits hyaluronidase activity [173]. EGCG can inhibit histamine release up to 90% in rat cell culture [170]. The inhibitory effect of the histamine release is likely related to the triphenol moiety of the molecule. Quercetin produces an anti-inflammatory activity in cells activated by an antigen and causes a concentration-dependant inhibition of histamine release [174]. Quercetin also inhibits protein kinase C, an enzyme important in the activation of the secretory process, by blocking the ATP binding site in the catalytic portion of the enzyme [174]. Green tea polyphenols produce a significant reduction in arthritis incidence with a marked reduction of inflammatory mediators, of neutral endopeptidase activity, of IgG and type II collagen-specific IgG levels in arthritic joints in mice [175].

7.5. Antibacterial effects

Black tea extract affects the gastrointestinal motility in mice resulting in an accelerated transit time [176]. A study on faecal conditions of elderly residents in a long-term care facility indicated that tea catechins can significantly improve bowel activity [177]. The modulation activity of tea on the intestinal microflora has been demonstrated [127]. Tea extracts exhibit inhibitory effects against *Vibrio cholerae*, *Salmonella typhi*, *Campilobacter jejuni*, *Campilobacter coli*, *Helicobacter pylori*, *Shigella*, *Salmonella*, *Clostridium*, *Pseudomonas*, *Candida*, *Mycoplasma* and *Cryptococcus* [5,127,170,178,179,180]. The later is responsible for gastric and duodenal ulcers that can induce cancer. Broadly, Gram-positive bacteria are more sensitive to tea extracts than Gram-negative bacteria [181]. Tea can modify overall metabolism by modulating the intestinal bacteria growth. Drinking tea leads to a reduction of enterobacteria which produce ammonia, skatole and other harmful amines and a beneficial increase in the level of lactobacilli and bifidobacteria which produce organic acids and lower the intestinal pH [5,126]. Tea can inhibit the growth of *Staphylococcus aureus* and of *Vibrio parahaemolyticus* responsible for cholera and diarrhoeal diseases, and it can reverse the methicillin-resistance in staphylococci [181,182]. Aqueous tea extract contains factors which can reverse the aflatoxin toxicity of *Bacillus megaterium* and inhibit extracellular release of Vero toxin from enterohemorrhagic *Esherichia coli* [183,184].

7.6. Effects of tea on dental carries

Green tea, EGCG and ECG exhibit inhibitory effects on the growth of cariogenic bacteria by inhibiting the adherence and the growth of bacteria at the tooth surface and the glucan synthesis by streptococci [185,186]. Flavour compounds, indole and delta-cadinene in tea have a synergistic effect in the inhibition of the growth of *Streptococcus mutans* [13]. EGCG also inhibits the growth and the adherence of *Porphyromonas gingivalis*, a bacteria responsible for periodontal disease [187,188].

7.7. Antiviral effects

Tea can have a beneficial effect against viral infection [5,51]. Tea polyphenols strongly inhibit rotavirus propagation in monkey cell culture and influenza A virus in animal cell culture [5]. It is reported that several flavonoids including EGCG and ECG inhibit retrovirus human immunodeficiency virus (HIV) propagation by inhibiting reverse transcriptase, an enzyme allowing the establishment of the virus in host cells [5]. The antimicrobial activity of tea in humans is not well documented and should be studied in a multidimensional way because several mechanisms are implicated: the immune system, heredity, cell biology, environment, microbial ecology, etc.

7.8. Other metabolic effects

Benefits of tea on many other functions have been reported. Pretreatment with black tea can protect against cytotoxicity of chromium and arsenic salts in marrow cells of mice, by reducing chromosomal aberration induced by these heavy metal salts [189]. EGCG and ECG exhibit a cytoprotective effect against quinone induced hepatotoxicity by reducing lactate dehydrogenase leakage, improving cell viability and maintaining protein thiol levels [190]. Glycosidic flavonoids of green tea suppress the D-galactosamine-induced increase of plasma alanine and aspartate aminotransferases and so prevent liver injury in rats [191]. Soluble tea fiber fraction, but not the caffeine-containing fraction can significantly suppress liver injury as reported in rats [192]. An increase in the number of hepatic peroxisomes and a rise in the microsomal lauric acid hydroxylation have been observed in rats treated with green or black tea [193]. Green tea, EGCG and caffeine administered to mice before receiving ethanol improve metabolism by lower-

ing the ethanol and acetaldehyde concentration in blood and liver [194]. EGCG injected in rats reduces food intake, body weight, blood level of testosterone, estradiol, leptin, insulin, insulin-like growth factor I, glucose, cholesterol, triglycerides and the growth of the prostate, uterus and ovary [118]. Tea may affect the reproductive function; drinking one-half cup of tea or more daily has doubled the odds of conception per cycle in a prospective study in 210 women [195].

7.9. Neurological and psychological effects

Some studies indicate that tea can improve neurologic and psychologic functions. Tea ingestion by volunteers induces a rapid increase in alertness and information processing capacity and, when taken through the day, prevents the diurnal pattern of performance reduction [196]. These effects are not entirely due to caffeine. Theanine acts as a neurotransmitter in the brain and decreases blood pressure significantly in hypertensive rats [197]. Alpha-waves are a relaxation index indicating relaxation without drowsiness. In volunteers, alpha-waves are generated in the occipital and parietal regions of the brain surface within 40 minutes after administration of theanine in a dose-dependent manner. Theanine is absorbed, modulates brain serotonin and dopamine levels, improving memory, learning ability, and affects emotions [197,198]. In other studies, a tea break at work is associated with a high social support, time to express feelings, increased resilience, and relaxation for women [199,200]. Diets rich in antioxidants including phenolic compounds are effective in preventing oxidative stress-induced reductions in neuronal functions and in reducing or retarding the functional central nervous system deficits associated with aging [201]. Some antioxidants are reported to protect neurons against A beta toxicity, a possible cause of Alzheimer's disease and could be of interest in other pathologies associated with oxidative damage such as Parkinson's disease [51,202]. However, tea has not been evaluated in the treatment of these pathologies. Investigations were carried out in mice with experimentally induced convulsions to evaluate the effect of acute and chronic administration of green or black tea. Tea appears to accelerate the onset of convulsion, to increase duration and mortality. Tea may be acting on Ca(2+) channels and not through GABA in brain [203].

In the aging process, it appears that the balance between oxidant and antioxidant is lost and oxidative stress increases. Antioxidant supplementation can be helpful and long-term studies indicate that dietary antioxidants can improve the effects of oxidative stress and age-associated diseases [31].

Future progress in the evaluation of the effects of tea on humans depends on the development of new experimental systems. Exploration at the cellular level allows a better understanding of the underlying mechanisms regulating functions in normal and pathologic states. Development of more specific and sensitive methods with more representative models along with the development of good predictive biomarkers will give a better understanding of how tea interacts with endogenous systems and other exogenous factors.

8. Tea uses as a food additive

The antioxidant properties of tea polyphenols has raised interest in this possible additive by the food industry looking for an "healthy" image. Green tea polyphenols are used in food with a high water content or in cooked products as a natural antioxidant replacing controversial synthetic ones, owing to their water solubility and resistance to heat degradation. Green tea extracts provide a highly effective protection against oxidation for oil-in-water emulsions at pH 5.5 during long storage periods in the absence of ferric ions [204]. It is reported that green tea polyphenols exhibit an antidiscoloring effect on β-carotene stronger than L-ascorbate [205]. Incorporated into juices or other foods they can improve product quality and justify functionnal food designation [206]. Tea extracts are added to chewing gum and candies to reduce caries and deodorize breath from garlic, fish (trimethylamine), methyl mercaptan, ammonia, and tobacco smoke odors [5]. Their uses in medicine and in paliative care are now emerging. L-theanine can be added to beverages, cookies, candies or ice cream to produced a relaxing effect and to mask the bitter taste in some foods [197]. The setting of appropriate regulations will assist the industry in establishing supplementation levels that will be beneficial and safe for consumers.

9. Tea in perspective

Although tea cannot be granted official health claims now, it can be recognize as an important part of a sound diet. Moving from a traditional beverage associated with rituals, tea is now viewed as a healthy drink, a source of pharmacologically active molecules, an important member of the antioxidant food group, and a functionnal food endowed with beneficial health properties. New products and uses are emerging and tea is consumed in different manners. Iced tea is now a convenient alternative to soft drinks and is found in groceries and fast food facilities. Recently, encapsulated green tea extracts appeared on the health store shelves for those who do not like to drink tea, but who seek its benefits.

The amount of experimental evidence documenting the properties of tea and its constituents continues to increase. At the same time the factors both endogenous and exogenous that influence the incidence and progression of many chronic diseases are becoming better defined and understood. It is apparent that the tea is a source of a wide range of phytochemicals that are digested, absorbed and metabolized by the body, and that tea constituents exert their effects at the cellular level. Tea's status as a functional food lends credibility to what has been believed by tea drinkers for centuries.

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