The Verde

Camellia sinensis

Nome botanico

Camellia sinensis Kuntze *(Theaceae)*

Parti usate

Foglia.

Componenti principali

Basi puriniche: caffeina, teofillina, teobromina, aminofillina. Composti polifenolici: catechine, flavonoli e loro glicosidi, acidi fenolici, tannini idrolizzabili.

Attività farmacologica

Attività antiossidante ed antiinfiammatoria. Azione termogenica e diuretica.

Impiego clinico

Condizioni di stress ossidativo. Prevenzione e terapia coadiuvante di patologie croniche conseguenti ad aumentata produzione di radicali liberi quali malattie cardiocircolatorie, dismetaboliche, neurodegenerative, ecc. Condizioni di sovrappeso e ritenzione idrosalina.

Controindicazioni

Non somministrare nei bambini al di sotto dei 12 anni.

Avvertenze e speciali precauzioni d'uso

Il The verde produce effetti di stimolazione centrale; si consiglia pertanto di assumere il prodotto al mattino e/o nel primo pomeriggio. Si sconsiglia l'uso prolungato e l'associazione con altri stimolanti. Non sono noti studi clinici controllati in donne in gravidanza e durante allattamento: in conformità con la prassi medica generale, il prodotto non deve essere impiegato senza prima avere sentito il parere del medico. Usare con cautela in pazienti con insufficienza epatica manifesta.

Interazioni

Nessuna nota.

Effetti indesiderati

Il The Verde può causare irritabilità, agitazione, insonnia e/o peggiorare questi sintomi se preesistenti. In soggetti sensibili sono stati riscontrati lievi disturbi gastrointestinali.

Note Bibliografiche

Composizione

I componenti di maggiore interesse farmacologico del The verde (*Camellia sinensis*) sono i polifenoli e le basi puriniche, soprattutto caffeina (teina). Tra i numerosi composti polifenolici (25-35%) prevalgono le catechine (flavanoli), contenute nella droga in ragione del 20-40% del peso secco. Esse si presentano sia in forma libera che legata all'acido gallico, con l'ossidrile dell'anello C in posizione 3[1]. Il più noto e studiato di questi composti è l'(-)-epigallocatechina-3-gallato (EGCG), uno dei uno dei più potenti antiossidanti naturali che si conosca; altri composti presenti corrispondono a epigallocatechina (EGC), catechina, epi-catechina (EC), epigallocatechina-3-O-gallato, gallocatechina-3-O-gallato, epigallo-3-O-metilgallato ed epicatechina-3-O-gallato (ECG)[2]. Sono inoltre presenti flavonoli e flavonglicosidi (kempferolo, quercetina, miricetina e loro glicosidi) in misura del 3-4%, e piccole quantità di acidi fenolici, tannini idrolizzabili, saponine.

Tutti i tipi di the derivano da un arbusto sempreverde della famiglia delle *Theaceae*, la *Camellia sinensis*. In Cina vengono prodotti più di 300 tipi di the, ma i più diffusi sono il The nero e il The verde. Il The nero rappresenta circa l'80% della produzione mondiale ed è consumato soprattutto in occidente. È ottenuto sottoponendo le foglie a fermentazione ed è la forma di uso comune nelle nostre case. Tale processo trasforma gran parte delle catechine in tearubigenine, le sostanze che conferiscono il noto aroma alla bevanda[3]. Il The verde è consumato in estremo oriente e in Giappone in particolare, dove

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1 *Jun X, Shuo Z, Bingbing L, Rui Z, Ye L, Deji S, Guofeng Z. Separation of major catechins from green tea by ultrahigh pressure extraction. Int J Pharm. 2010 Feb 15;386(1-2):229-31.*

2 "…An aqueous acetone extract of proanthocyanidins prepared from healthy tea leaves was partially purified using Sephadex LH-20 chromatography. (…) **Seven fractions of high purity were isolated**. The identity of the compound present in each fraction isolated was established using electrospray ionization mass spectrometry (ESI-MS) and nuclear magnetic resonance (NMR) spectroscopy. **Five proanthocyanidins and two flavanol digallates, (-)-epigallocatechin digallate (EGCDG) and (-)-epicatechin digallate (ECDG) were isolated**. Comparison of spectral data of the proanthocyanidins isolated with those previously reported indicated that all five were known B-type proanthocyanidins with 2,3-cis stereochemistry in both the upper (u-unit) and the terminal (t-unit) units, and 4R configuration of the C-ring in the u-unit. **The proanthocyanidins were established to be dimers composed of (-)-epigallocatechin gallate (EGCG), (-)-epicatechin gallate (ECG) and (-)-epiafzelechin gallate (EAG) units with the following structures: EGCG-(4beta-->6)-EGCG, ECG-(4beta-->6)-EGCG, EGCG-(4beta-->6)-ECG, EAG-(4beta-->6)-EGCG, ECG-(4beta-->6)-ECG by analysis of spectral data**. Therefore HSCCC offers a powerful method for the separation of a group of closely related naturally occurring compounds." *(Savitri Kumar N, Maduwantha B Wijekoon WM, Kumar V, Nimal Punyasiri PA, Sarath B Abeysinghe I. Separation of proanthocyanidins isolated from tea leaves using high-speed counter-current chromatography. J Chromatogr A. 2009 May 8;1216(19):4295-302).*

3 "**Oolong tea manufactured via a semifermentation process possesses a taste and color somewhere between green and black teas. Alteration of constituents, particularly phenolic compounds, in the infusion of oolong tea resulting from its manufacture, was analyzed by high-performance liquid chromatography coupled to electrospray ionization tandem mass spectrometry**. The identified constituents contained 2 alkaloids, 11 flavan-3-ols, 8 organic acids and esters, 11 proanthocyanidin dimers, 3 theaflavins, and 22 flavonoid glycosides, including 6 novel acylated flavonol glycosides. The tentative structures of these 6 novel compounds were depicted according to their mass fragmentation patterns in MS(n) (n = 1-4). In comparison with caffeine as an internal standard, relative contents of the constituents in the infusions of fresh tea shoot and different oolong tea preparations were examined. A**pproximately, 30% catechins and 20% proanthocyanidins were**

rappresenta la bevanda ufficiale. Copre quasi il 20% della produzione mondiale ed è ottenuto da foglie leggermente torrefatte dopo la raccolta, quindi arrotolate a mano e seccate a fuoco dolce in modo da distruggere gli enzimi e quindi evitare ogni successiva fermentazione. Questo processo, che mantiene sia il colore verde sia il caratteristico sapore erbaceo della droga, lascia intatto il contenuto in polifenoli[4]. Esiste poi un terzo tipo di The, detto oolong, ottenuto con una semi-fermentazione. Ha una diffusionemolto inferiore, di circa il 2% ed è consumato in certe parti della Cina e a Taiwan.

Attività biologiche ed impieghi clinici descritti in letteratura

Le attività biologiche e gli impieghi clinici descritti per il fitocomplesso di *Camellia sinensis* sono:

Medicina popolare. Il consumo dell'infuso di foglie di The è secondo nel mondo solo a quello dell'acqua. Oltre ad essere una bevanda molto gradevole, il The è però anche una pianta medicinale di grande interesse, tradizionalmente utilizzata per millenni dalla medicina Cinese come tonico-stimolante, diuretico e astringente intestinale.

Azione sul metabolismo basale e sul peso corporeo. Il The verde viene frequentemente utilizzato nella dieta di soggetti che seguono programmi di riduzione del peso corporeo, con effetti evidenti seppure di entità modesta[5,6]. É noto che la somministrazione di metilxantine (4-8 mg/kg) in soggetti normali od obesi stimola il metabolismo basale, l'idrolisi dei trigliceridi (lipolisi) e, conseguentemente, la concentrazione degli acidi grassi liberi nel plasma e la loro β-ossidazione nei tessuti periferici[7]. Ma l'effetto del The verde sul metabolismo basale non dipende solo, come si potrebbe pensare, dalla caffeina contenuta nel fitocomplesso, bensì è dato anche dalle preziose catechine, tra cui

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oxidized during the manufacture of oolong tea from fresh tea shoots, and 20% of total flavonoids were decomposed in a follow-up drying process. Gallocatechin-3-O-gallate and theaflavins putatively produced in the semifermentation process of oolong tea were not detected in fresh tea shoots, and the majority of theaflavins were presumably transformed into thearubigins after drying." *(Dou J, Lee VS, Tzen JT, Lee MR. Identification and comparison of phenolic compounds in the preparation of oolong tea manufactured by semifermentation and drying processes. J Agric Food Chem. 2007 Sep 5;55(18):7462-8).*

4 *Lin YS, Tsai YJ, Tsay JS, Lin JK. Factors affecting the levels of tea polyphenols and caffeine in tea leaves. J Agric Food Chem. 2003 Mar 26;51(7):1864-73.*

5 "…The purpose of this study was to examine the effects of a three-week supplementation with GTE on human energy metabolism during submaximal cycling exercise. (…) In conclusion, **these results suggest only slight effects on whole-body metabolism after supplementation with green tea estract**." *(Eichenberger P, Colombani PC, Mettler S. Effects of 3-week consumption of green tea extracts on whole-body metabolism during cycling exercise in endurance-trained men. Int J Vitam Nutr Res. 2009 Jan;79(1):24-33).*

6 "…**the study found little benefit in consuming green-tea extract on fat oxidation or cycling performance, unlike caffeine, which did benefit cycling performance**." *(Dean S, Braakhuis A, Paton C. The effects of EGCG on fat oxidation and endurance performance in male cyclists. Int J Sport Nutr Exerc Metab. 2009 Dec;19(6):624-44).*

7 "**High caffeine intake was associated with weight loss through thermogenesis and fat oxidation and with suppressed leptin in women.** In habitual low caffeine consumers, the green tea-caffeine mixture improved weight maintenance, partly through thermogenesis and fat oxidation." *(Westerterp-Plantenga MS, Lejeune MP, Kovacs EM. Body weight loss and weight maintenance in relation to habitual caffeine intake and green tea supplementation. Obes Res. 2005 Jul;13(7):1195-204).*

l'(-)-epigallocatechina-3-gallato, che hanno numerosi effetti tra cui quello di produrre un aumento della termogenesi[8]. L'attività di riduzione del peso corporeo di estratti di The verde decaffeinati supporta tale ipotesi, suggerendo anche la possibilità di poter impiegare preparati privi effetti stimolanti centrali[9]. Catechine del the e caffeina sembrano tuttavia avere effetti sinergici ai fini di propgrammi di riduzione del peso[10]. Uno studio nel ratto mostra un potente effetto soppressivo del The verde sulla biosintesi dei grassi in ratti nutriti con una dieta iperlipidica, soprattutto grazie alla sua capacità di attivare il recettore beta adrenergico e quindi la termogenesi nel tessuto adiposo bruno[11]. Sempre su ratti tenuti a dieta iperlipidica, l'(-)-epigallocatechina-3-gallato ha mostrato di

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[8] "**Tea catechins, especially (-)-epigallocatechin gallate (EGCG), appear to have antiobesity and antidiabetic effects**... **The mechanisms of its actions may be related to certain pathways, such as through the modulations of energy balance, endocrine systems, food intake, lipid and carbohydrate metabolism, the redox status, and activities of different types of cells (i. e., fat, liver, muscle, and beta-pancreatic cells)**. Because the EGCG receptor, the so-called 67-kDa laminin receptor (LR), has been discovered with colocalization of other types of LR and cytoskeleton in both cancer cells and normal cells, this may explain that EGCG possesses numerous actions." *(Kao YH, Chang HH, Lee MJ, Chen CL. Tea, obesity, and diabetes.. Mol Nutr Food Res. 2006 Feb;50(2):188-210).*

[9] "**We investigated whether regular decaffeinated green tea intake could modulate body weight in an experimental model of obesity**. Male leptin-deficient (ob/ob) mice and their C57BL/6J lean littermates (4 weeks of age; n 20/genotype) were assigned randomly to receive either decaffeinated green tea or vehicle, for 6 weeks. Body weights were recorded weekly and fluid intake was measured at each replacement. Blood was collected from the heart into collection tubes, with Li(+)-heparin as the anticoagulant. **Administration of decaffeinated green tea to ob/ob mice significantly slowed their rate of weight gain, as compared with animals that were fed buffer alone. This effect is apparent after only 1 week of supplementation**. No significant difference was recorded between C57BL/6J lean mice administrated decaffeinated green tea and those given buffer alone. **Decaffeinated green tea consumption by ob/ob mice was also associated with significantly lower cholesterolemia, triglyceridemia, and adiponectin concentration**. Fecal lipids did not change significantly throughout the experiment. **In conclusion, administration of decaffeinated green tea might contribute to weight control and provides an opportunity for through-the-day consumption, without the excitatory effects of caffeine**." *(Richard D, Kefi K, Barbe U, Poli A, Bausero P, Visioli F. Weight and plasma lipid control by decaffeinated green tea. Pharmacol Res. 2009 May;59(5):351-4).*

[10] "**Green tea catechins (GTCs) with or without caffeine have been studied in randomized controlled trials (RCTs) for their effect on anthropometric measures and have yielded conflicting results. The objective was to perform a systematic review and meta-analysis of RCTs of GTCs on anthropometric variables, including body mass index (BMI), body weight, waist circumference (WC), and waist-to-hip ratio (WHR).** Design: A systematic literature search of MEDLINE, EMBASE, CENTRAL, and the Natural Medicines Comprehensive Database was conducted through April 2009. RCTs that evaluated GTCs with or without caffeine and that reported BMI, body weight, WC, or WHR were included. The weighted mean difference of change from baseline (with 95% CIs) was calculated by using a random-effects model. Results: Fifteen **studies (n = 1243 patients) met the inclusion criteria.** On meta-analysis, GTCs with caffeine decreased BMI (-0.55; 95% CI: -0.65, -0.40), body weight (-1.38 kg; 95% CI: -1.70, -1.06), and WC (-1.93 cm; 95% CI: -2.82, -1.04) but not WHR compared with caffeine alone. GTC ingestion with caffeine also significantly decreased body weight (-0.44 kg; 95% CI: -0.72, -0.15) when compared with a caffeine-free control. Studies that evaluated GTCs without concomitant caffeine administration did not show benefits on any of the assessed anthropometric endpoints. Conclusions: **The administration of GTCs with caffeine is associated with statistically significant reductions in BMI, body weight, and WC; however, the clinical significance of these reductions is modest at best**. **Current data do not suggest that GTCs alone positively alter anthropometric measurements**." *(Phung OJ, Baker WL, Matthews LJ, Lanosa M, Thorne A, Coleman CI. Effect of green tea catechins with or without caffeine on anthropometric measures: a systematic review and meta-analysis. Am J Clin Nutr. 2010 Jan;91(1):73-81).*

[11] "…Feeding a high-fat diet containing water extract of green tea at the concentration of 20g/kg diet prevented the increase in body fat gain caused by high-fat diet without affecting energy intake. Energy expenditure was increased by green tea extract which was associated with an increase in protein content of interscapular brown adipose tissue. The simultaneous administration of the beta-adrenoceptor antagonist propranolol(500 mg/kg diet) inhibited the body fat-suppressive effect of green tea extract. Propranolol also prevented the increase in protein content of interscapular brown adipose tissue caused by green tea extract.

ridurre sensibilmente la massa grassa e di migliorare significativamente il profilo lipidico con un effetto che sembra parzialmente mediato dalla modulazione di una serie di geni coinvolti in vari processi biologici quali l'adipogenesi, la lipolisi, la beta-ossidazione e la termogenesi[12]. Un altro studio sembra confermare, alla base del meccanismo di riduzione del peso degli estratti di The verde e delle catechine in particolare, un effetto di down regulation dell'espressione genica del complesso dell'acido grasso sintasi - che tra l'altro risulta sovraespressa in alcuni tipi di tumore alla mammella[13] - accanto ad una induzione dell'aumento del dispendio energetico nei mitocondri[14]. Uno

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Digestibility was slightly reduced by green tea extract and this effect was not affected by propranolol. Therefore it appeared that **green tea exerts potent body fat-suppressive effects in rats fed on a high-fat diet and the effect was resulted in part from reduction in digestibility and to much greater extent from increase in brown adipose tissue thermogenesis through beta-adrenoceptor activation.**" *(Choo JJ. Green tea reduces body fat accretion caused by high-fat diet in rats through beta-adrenoceptor activation of thermogenesis in brown adipose tissue. J Nutr Biochem. 2003 Nov;14(11):671-6).*

[12] "**The aim of this study was to investigate the antiobesity effect of (-)-epigallocatechin-3-gallate (EGCG) in diet-induced obese mice.** Male C57BL/6J mice were fed on a high-fat diet for 8 weeks to induce obesity. Subsequently they were divided into 3 groups and were maintained on a high-fat control diet or high-fat diets supplemented with 0.2 or 0.5% EGCG (w/w) for a further 8 weeks. Changes in the expression of genes related to lipid metabolism and fatty acid oxidation were analyzed in white adipose tissue, together with biometric and blood parameters. Results: **Experimental diets supplemented with EGCG resulted in reduction of body weight and mass of various adipose tissues in a dose-dependent manner**. **EGCG diet also considerably lowered the levels of plasma triglyceride and liver lipid**. In the epididymal white adipose tissue of EGCG diet-fed mice, the mRNA levels of adipogenic genes such as peroxisome proliferator-activated receptor-gamma (PPAR-gamma), CCAAT enhancer-binding protein-alpha (C/EBP-alpha), regulatory element-binding protein-1c (SREBP-1c), adipocyte fatty acid-binding protein (aP2), lipoprotein lipase (LPL) and fatty acid synthase (FAS) were significantly decreased. However, the mRNA levels of carnitine palmitoyl transferase-1 (CPT-1) and uncoupling protein 2 (UCP2), as well as lipolytic genes such as hormone sensitive lipase (HSL) and adipose triglyceride lipase (ATGL), were significantly increased. Conclusion: These **results suggest that green tea EGCG effectively reduces adipose tissue mass and ameliorates plasma lipid profiles in high-fat diet-induced obese mice. These effects might be at least partially mediated via regulation of the expression of multiple genes involved in adipogenesis, lipolysis, beta-oxidation and thermogenesis in white adipose tissue.**" *(Lee MS, Kim CT, Kim Y. Green tea (-)-epigallocatechin-3-gallate reduces body weight with regulation of multiple genes expression in adipose tissue of diet-induced obese mice. Ann Nutr Metab. 2009;54(2):151-157).*

[13] "Fatty **acid synthase (FAS) is a key enzyme in lipogenesis. FAS is overexpressed in the malignant human breast carcinoma MCF-7 cells and its expression is further enhanced by the epidermal growth factor (EGF). The EGF-induced expression of FAS was inhibited by green and black tea extracts. The expression of FAS was also suppressed by the tea polyphenol (-)-epigallocatechin 3-gallate (EGCG), theaflavin (TF-1), TF-2 and theaflavin 3,3′-digallate(TF-3) at both protein and mRNA levels that may lead to the inhibition of cell lipogenesis and proliferation**. Both EGCG and TF-3 inhibit the activation of Akt and block the binding of Sp-1 to its target site. **Furthermore, the EGF-induced biosyntheses of lipids and cell proliferation were significantly suppressed by EGCG and TF-3. These findings suggest that tea polyphenols suppress FAS expression by downregulating EGF receptor/PI3K/Akt/Sp-1 signal transduction pathway**, and tea and tea polyphenols might induce hypolipidemic and antiproliferative effects by suppressing FAS**.**" *(Yeh CW, Chen WJ, Chiang CT, Lin-Shiau SY, Lin JK. Suppression of fatty acid synthase in MCF-7 breast cancer cells by tea and tea polyphenols: a possible mechanism for their hypolipidemic effects. Pharmacogenomics J. 2003;3(5):267-76).*

[14] "Among the health-promoting effects of tea and tea polyphenols, the cancer-chemopreventive effects in various animal model systems have been intensively investigated; meanwhile, the hypolipidemic and antiobesity effects in animals and humans have also become a hot issue for molecular nutrition and food research. **It has been demonstrated that the body weights of rats and their plasma triglyceride, cholesterol, and LDL-cholesterol have been significantly reduced by feedings of oolong, black, pu-erh, and green tea leaves to the animals. It has been suggested that the inhibition of growth and suppression of lipogenesis in MCF-7 breast cancer cells may be through down-regulation of fatty acid synthase gene expression in the nucleus and stimulation of cell energy expenditure in the mitochondria**. The experimental data indicated that the molecular mechanisms of fatty acid synthase gene suppression by tea polyphenols (EGCG, theaflavins) may invite down-regulation of EGFR/PI3K/Akt/Sp-1 signal transduction pathways**.**" *(Lin JK, Lin-Shiau SY. Mechanisms of hypolipidemic*

studio clinico pilota indica una sensibile riduzione del peso corporeo in sei pazienti in sovrappeso trattati con (-)-epigallocatechina-3-gallato (300 mg per due volte al giorno), presumibilmente dovuta ad un incremento della lipolisi indotto dall' EGCG[15].

L'estratto di The verde sembra favorire il dimagrimento anche grazie alla sua capacità di inibire l'attività dell'enzima catecol-O-metiltransferasi, che degrada le catecolamine, grazie a un effetto positivo sulla stimolazione simpatica della termogenesi[16,17]. A tale proposito, i principali componenti del fitocomplesso della droga mostrano effetti complementari: le catechine inibiscono la catecol-O-metil transferasi e la caffeina inibisce le fosfodiesterasi, aumentando gli effetti adrenergici. Infine, le metilxantine, e in particolare la caffeina, stimolano la muscolatura striata, aumentandone la forza di contrazione e diminuendo il senso di fatica muscolare, con un effetto glicogenolitico e lipolitico che favorisce la disponibilità muscolare di glucosio ed acidi grassi. Inoltre, alcune catechine avrebbero la capacità di inibire le α-amilasi e potrebbero con questo meccanismo contribuire ad una sensibile riduzione dell'assorbimento intestinale dei carboidrati e, quindi, del peso corporeo[18].

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and anti-obesity effects of tea and tea polyphenols. Mol Nutr Food Res. 2006 Feb;50(2):211-7).

[15] "…Recent data from human studies indicate that the consumption of green tea and green tea extracts may help reduce body weight, mainly body fat, by increasing postprandial thermogenesis and fat oxidation. However, human studies investigating the metabolic effects of the most predominant tea catechin, EGCG, alone are absent. Methods: **In a randomized double blind, placebo-controlled, cross-over pilot study, six overweight men were given 300 mg EGCG/d for 2d. Fasting and postprandial changes in energy expenditure (EE) and substrate oxidation were assessed**. Results: Resting EE did not differ significantly between EGCG and placebo treatments, although during the first postprandial monitoring phase, respiratory quotient (RQ) values were significantly lower with EGCG compared to the placebo. **These findings suggest that EGCG alone has the potential to increase fat oxidation in men and may thereby contribute to the anti-obesity effects of green tea**. However, more studies with a greater sample size and a broader range of age and BMI are needed to define the optimum dose." *(Boschmann M, Thielecke F.University Medicine Berlin, Charité Campus Buch, Franz-Volhard-Center for Clinical Research, Germany. The effects of epigallocatechin-3-gallate on thermogenesis and fat oxidation in obese men: a pilot study. J Am Coll Nutr. 2007 Aug;26(4):389S-395S).*

[16] "Epidemiological studies have shown that intake of tea catechins is associated with a lower risk of cardiovascular disease. The antioxidative activity of tea-derived catechins has been extensively studied. **Reports have shown that green tea extract intake is associated with increased weight loss due to diet-induced thermogenesis, which is generally attributed to the catechin epigallocatechin gallate. That catechin-polyphenols are known to be capable of inhibiting catechol-O-methyltransferase (the enzyme that degrades norepinephrine) is a possible explanation for why the green tea extract is effective in stimulating thermogenesis by epigallocatechin gallate to augment and prolong sympathetic stimulation of thermogenesis**. Knowledge about thermogenesis-induced weight loss produced by green tea's epigallocatechin gallate and its ability to inhibit catechol-O-methyltransferase is important for health benefits and for prolonging the action of norepinephrine in the synaptic cleft**.**" *(Shixian Q, VanCrey B, Shi J, Kakuda Y, Jiang Y. Green tea extract thermogenesis-induced weight loss by epigallocatechin gallate inhibition of catechol-O-methyltransferase. J Med Food. 2006 Winter;9(4):451-8).*

[17] "Positive effects on body-weight management have been shown using green tea mixtures. **Green tea, by containing both tea catechins and caffeine, may act through inhibition of catechol O-methyl-transferase, and inhibition of phosphodiesterase. Here the mechanisms may also operate synergistically. A green tea-caffeine mixture improves weight maintenance, through thermogenesis, fat oxidation, and sparing fat free mass**. The sympathetic nervous system is involved in the regulation of lipolysis, and the sympathetic innervation of white adipose tissue may play an important role in the regulation of total body fat in general. **Taken together, these functional ingredients have the potential to produce significant effects on metabolic targets such as thermogenesis, and fat oxidation**. An ethnic or genetic effect, and habitual caffeine or green tea catechin intake may act as confounders; this remains to be revealed." *(Westerterp-Plantenga MS. Green tea catechins, caffeine and body-weight regulation. Physiol Behav. 2010 Feb 13. [Epub ahead of print]).*

[18] "Tea catechins undergo various metabolic changes after they are taken orally, though a large percentage are excreted intact

Un altro studio nel ratto indica che l'estratto di The verde migliora la performance fisica di durata nel ratto, grazie soprattutto a un'aumentata capacità metabolica e ad una migliore utilizzazione degli acidi grassi come fonte energetica muscolare[19].

Attività tonica e stimolante. L'attività stimolante del The verde sul sistema nervoso centrale, con rafforzamento dell'attività intellettiva ed aumento del livello di vigilanza e del tono psichico, è principalmente da attribuire alla presenza nella droga di caffeina ed altre metilxantine. Tale azione tonica generale del fitocomplesso può essere di utilità in tutti i casi di astenia psicofisica.

Azione diuretica. Le metilxantine, specialmente la teofillina, fanno aumentare la produzione di urina e potenziano l'escrezione di acqua ed elettroliti. Studi di farmacologia dimostrano che la teofillina aumenta la velocità di filtrazione glomerulare ed il flusso ematico renale, specialmente nella midollare. Nell'uomo, invece, l'infusione di aminofillina sembra inibire il riassorbimento di soluti sia nel nefrone prossimale sia nel segmento diluente senza provocare una variazione apprezzabile né della velocità di filtrazione glomerulare né della velocità del flusso ematico renale totale[20].

Azione antiossidante. I ROS che si formano nell'organismo a seguito degli stress ossidativi producono danni alle cellule accelerando il processo di invecchiamento e lo sviluppo di patologie cronico-degenerative. I composti polifenolici del The verde inibiscono significativamente la formazione delle ROS favorendo la loro cattura (radical scavengers) e risparmiando gli antiossidanti fisiologici (SOD, glutatione perossidasi, ecc.). In particolare, il potenziale antiossidante del The verde è associato all'elevato contenuto in (-)-epigallocatechina gallato (EGCG)[21], anche se la miscela delle varie catechine presenti nel The verde ha dimostrato un'azione antiossidante superiore rispetto ai singoli componenti, confermando l'ormai accettata tesi secondo cui i fitocomplessi sono molto più attivi dei loro singoli componenti isolati. Le catechine hanno potere chelante dovuto alla presenza del gruppo catecolico nella loro struttura; in questo modo legano gli ioni ferrici e ferrosi che sono necessari per la formazione dei radicali liberi dell'ossigeno. L'azione di rimozione dei radicali liberi,

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with the feces. Epidemiological studies suggest a protective effect of tea against various human cancers, including colon and rectum. The bactericidal property of tea catechins plays several roles in the digestive tract. In the small intestine, **catechins inhibit α-amylase activity**, and a certain amount is absorbed into the portal vein. Although catechins are bactericidal, they do not affect lactic acid bacteria. Including tea catechins in the diet for several weeks decreases putrefactive products and increases organic acids by lowering pH. These changes were achieved in tube-fed patients by administering 100 mg of tea catechins (equivalent to a cup of green tea) three times daily with meals for 3 weeks. When catechin administration ceased, the effects reversed after 1 week. Catechins should be considered further in colon carcinogenesis studies" *(Hara Y. Influence of tea catechins on the digestive tract. J Cell Biochem 1997; 27 (Supplement): 52-8).*

19 *Murase T. et al. Green tea extract improves running endurance in mice by stimulating lipid utilization during exercise. Am J Physiol Regul Integr Comp Physiol. 290(6):R1550-6, 2006.*

20 *Rall TW. Farmaci usati nel trattamento dell'asma. Le metilxantine, il cromoglicato e altri agenti. In: Goodman & Gilman, Le Basi Farmacologiche della Terapia. Zanichelli, 8° Edizione, Bologna, 1990, pag. 570-572.*

21 *Ohmori R, Iwamoto T, Tago M, Takeo T, Unno T, Itakura H, Kondo K. Antioxidant activity of various teas against free radicals and LDL oxidation. Lipids. 2005; 40(8):849-53.*

attribuita ad EGCG, EGC ed ECG, si manifesta nell'eliminazione di molecole come radicali anionici superossidi e idrossilici, specie reattive dell'ossigeno in grado di indurre danni al DNA e ad altre strutture della cellula. Inoltre le catechine reagiscono con i radicali perossidi ed in questo modo interrompono la catena di reazioni che porta alla perossidazione lipidica[22].

Uno studio nel ratto indica che il the verde e i suoi principali componenti hanno un'azione protettiva contro i danni polmonari provocati dal fumo di sigaretta, sia a livello sistemico sia a livello polmonare nel ratto. Gli animali venivano esposti al fumo per 1 ora al giorno per 56 giorni, al termine dei quali venivano sacrificati con prelievo dei loro polmoni e del siero, per effettuare gli opportuni accertamenti. La distrofia muscolare di Duchenne è caratterizzata dall'assenza di distrofina nelle cellule muscolari, il che le rende molto suscettibili allo stress ossidativo. Uno studio ha valutato se 3 settimane di sforzo fisico di durata in ratti giovani di sesso maschile potessero eliminare lo stress ossidativo e migliorare la funzionalità delle cellule muscolari distrofiche e se tali effetti potessero essere aumentati dal The verde. Si è visto che Il The verde riduceva l'attività della creatinchinasi sierica e la lipoperossidazione nel cuore e nel muscolo gastrocnemio e aumentava l'attività della citrato sintetasi. Lo studio indica che il The verde migliora la funzionalità muscolare in ratti con distrofia muscolare di Duchenne in sinergia con l'esercizio fisico di durata[23]. Si è visto che il fumo di sigaretta provocava un inizio di enfisema polmonare e l'iperplasia delle cellule mucinose bronchiali, effetti che il The verde preveniva validamente; il fumo causava anche aumento dei livelli sierici di 8-isoprostano ($p<0,01$), di superossido desmutasi e di catalasi ($p<0,05$), e anch'essi erano prevenuti dal The verde[24]. Uno studio clinico indica che il The verde migliora lo stato antiossidante globale dell'organismo e riduce lo stress ossidativo nel plasma e negli eritrociti nell'uomo. Sono stati reclutati 34 soggetti adulti, dei quali si valutava lo stress ossidativo plasmatico ed eritrocitario pre e post trattamento (stato antiossidante totale, malondialdeide, 4-idrossinonenale ed emoglobina legata alla membrana dei globuli rossi). Per 4 settimane essi dovevano bere 1 litro al giorno di The verde. Al termine dello studio vi era una significativa riduzione dei livelli sierici di malondialdeide e di idrossinonenale e dello stress ossidativo negli eritrociti, come confermato da un'evidente riduzione dell'emoglobina legata alla membrana dei globuli rossi. Si osservava anche un significativo incremento della capacità antiossidante plasmatica totale[25].

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22 *Liao S, Kao YH, Hiipakka RA. Green tea: Biochemical and biological basis for health benefits.Vitamins and Hormones 2001;26:1-94.*

23 *Call J.A. et al. Endurance capacity in maturing mdx mice is markedly enhanced by combined voluntary wheel running and green tea extract. J Appl Physiol. 2008;105(3):923-32.*

24 *Chan K.H. et al. Chinese green tea ameliorates lung injury in cigarette smoke-exposed rats. Respir Med. 2009 Nov;103(11):1746-54.*

25 *Coimbra S, Castro E, Rocha-Pereira P, Rebelo I, Rocha S, Santos-Silva A. The effect of green tea in oxidative stress. Clin Nutr. 2006 Oct;25(5):790-6.*

Azione antimutagena e anticancerogena. Le catechine hanno effetti antimutagenici, anticarcinogenici ed antinfiammatori[26], e la maggior parte degli studi riferiscono proprio all'azione protettiva di queste sostanze l'osservazione che l'incidenza di tumori è inferiore nelle popolazioni che fanno un uso abbondante di the[27]. Il The verde, ma soprattutto l'EGCG, nella sua forma pura, è attualmente in studio in ambito oncologico in considerazione delle sue attività anti-angiogenetiche ed anti-metastatiche, più volte riportate in letteratura[28]. Sono stati eseguiti studi di antimutagenicità su microorganismi, valutata la capacità di inibizione della crescita neoplastica su molte linee cellulari ed eseguiti esperimenti su diversi modelli animali, ottenendo unanimemente risultati positivi ed incoraggianti. La valutazione dell'effetto antineoplastico attraverso trial clinici è stata principalmente rivolta all'apparato gastro-intestinale, sia per l'importanza epidemiologica, sia, forse, per l'effetto di contatto, in grado di innalzare i livelli di catechine nelle cellule della mucosa digestiva per passaggio diretto, ovviando alla scarsa biodisponibilità dei flavonoidi e della EGCG in particolare[29]. Studi epidemiologici hanno suggerito che il The verde ha il potenziale di ridurre il rischio di gastrite atrofica cronica, di cancro gastrico e intestinale, di neoplasie della pelle[30]. Alcuni Autori hanno trovato un rapporto di rischio (odds ratio - OR) per cancro allo stomaco tra bevitori di The verde e non bevitori di 0.52 (CI al 95% da 0.29 a 0.94), e un OR per gastrite cronica (una importante tappa pre-maligna della lesione neoplastica), di 0.49 (IC_{50} al 95% da 0.31 a 0.77). Gli stessi Autori trovano anche una correlazione dose-risposta per anni di assunzione di The[31]. Tuttavia, in

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26 *Mukhtar H, Ahmad N. Tea polyphenols: prevention of cancer and optimizing health. Am J Clin Nutr 2000; 71: Suppl 6: 1698S-1702S.*

27 "Green tea is now an acknowledged cancer preventive in Japan… **Cancer onset of patients who had consumed over 10 cups of green tea per day was 8.7 years later among females and 3.0 years later among males, compared with patients who had consumed under three cups per day**. The mechanisms of action of (-)-epigallocatechin gallate (EGCG) were briefly discussed with regard to inhibition of tumor necrosis factor-α (TNF-α) release." *(Fujiki H, Suganuma M, Okabe S, Sueoka N, Komori A, Sueoka E, Kozu T, Tada Y, Suga K, Imai K, Nakachi K. Cancer inhibition by green tea. Mutation Research 1998; 402: 307-10).*

28 "**(-)-Epigallocatechin-3-gallate (EGCG), the principal polyphenol in green tea, has been shown to be a potent chemopreventive agent. Recently, 67-kDa laminin receptor (67LR) has been identified as a cell surface receptor for EGCG that mediates the anticancer activity of EGCG**. **Indeed, expression of 67LR confers EGCG responsiveness to tumor cells; however, the molecular basis for the anticancer activity of EGCG in vivo is not entirely understood**. Here we show that (i) using a direct genetic screen, eukaryotic translation elongation factor 1A (eEF1A) is identified as a component responsible for the anticancer activity of EGCG; (ii) through both eEF1A and 67LR, EGCG induces the dephosphorylation of myosin phosphatase targeting subunit 1 (MYPT1) at Thr-696 and activates myosin phosphatase; and (iii) silencing of 67LR, eEF1A, or MYPT1 in tumor cells results in abrogation of EGCG-induced tumor growth inhibition in vivo. Additionally, we found that eEF1A is up-regulated by EGCG through 67LR. Overall, **these findings implicate both eEF1A and MYPT1 in EGCG signaling for cancer prevention through 67LR.**" *(Umeda D, Yano S, Yamada K, Tachibana H. Green tea polyphenol epigallocatechin-3-gallate signaling pathway through 67-kDa laminin receptor. J Biol Chem. 2008 Feb 8;283(6):3050-8).*

29 *Auger C, Mullen W, Hara Y, Crozier A. Bioavailability of polyphenon E flavan-3-ols in humans with an ileostomy. J Nutr. 2008 Aug;138(8):1535S-1542S.*

30 *Carlson JR, Bauer BA, Vincent A, Limburg PJ, Wilson T. Reading the tea leaves: anticarcinogenic properties of (-)-epigallocatechin-3-gallate. Mayo Clin Proc 2007; 82(6) 725-732.*

31 *Setiawan VW, Zhang ZF, et al. Protective effect of green tea on the risks of chronic gastritis and stomach cancer. Int J Cancer: 2001; 92:600-604.*

un articolo apparso sul New England Journal of Medicine, gli AA. non trovano alcuna associazione tra ingestione di una o due, tre o quattro e cinque o più tazze di The verde al giorno e rischio di cancro allo stomaco - RR = 1.1 (CI al 95% da 0.8 a 1.9), RR = 1.0 (CI al 95% da 0.7 a 1.4), RR = 1.2 (CI al 95% da 0.9 a 1.6) rispettivamente – evidenziando come l'effetto protettivo nei vari trial compaia solitamente nei bevitori di 10 o più tazze di the al giorno e sia assente per livelli intermedi[32]. Il The verde è infatti la bevanda più popolare in Giappone, dove molte persone arrivano a consumarne più di un litro al giorno.

Sono poi stati condotti alcuni studi che suggerirebbero un possibile ruolo protettivo del The verde nella prevenzione del cancro al seno ed alla prostata[33]. Tuttavia, in base ai risultati di una revisione voluta dalla Food and Drug Administration (FDA), basata sulla valutazione sistematica dei dati scientifici disponibili, sembra altamente improbabile che il The verde riduca il rischio di tumori al seno, come anche il rischio di cancro alla prostata[34]. Uno studio ha esaminato gli effetti di uno dei principali costituenti del The verde, l'epigallocatechina-3-gallato (EGCG), sulle cellule B nella leucemia linfocitica cronica, isolate da pazienti leucemici[35]. Queste cellule sono caratterizzate dalla resistenza all'apoptosi poiché secernono e legano una potente citochina angiogenica (VEGF), che agisce anche come fattore cruciale di sopravvivenza delle cellule tumorali. I ricercatori hanno dimostrato che l'addizione di EGCG a queste cellule, provoca una significativa diminuzione della fosforilazione dei recettori VEGF e conduce ad una interruzione della via autocrina VEGF-dipendente che protegge queste cellule dall'apoptosi e dalla morte cellulare. Tali conclusioni supportano osservazioni precedenti[36] sulla potente inibizione dell'attività del recettore tirosina chinasi per il

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32 *Tsubono Y, Nishino Y, et al. Green tea and the risk of gastric cancer in Japan. N Engl J Med. 2001 Mar 1;344(9):632-6.*

33 *Stuart EC, Scandlyn MJ, Rosengren RJ. Role of epigallocatechin gallate (EGCG) in the treatment of breast and prostate cancer. Life Sci. 2006 Nov 17;79(25):2329-36.*

34 *Chen D, Milacic V, Chen MS, Wan SB, Lam WH, Huo C, Landis-Piwowar KR, Cui QC, Wali A, Chan TH, Dou QP. Tea polyphenols, their biological effects and potential molecular targets. Histol Histopathol. 2008 Apr;23(4):487-96.*

35 "We recently reported that chronic lymphocytic leukemia (CLL) cells synthesize and release vascular endothelial growth factor (VEGF) under normoxic and hypoxic conditions. CLL B cells also express VEGF membrane receptors (VEGF-R1 and VEGF-R2), suggesting that they use VEGF as a survival factor. To assess the mechanism of apoptosis resistance related to VEGF, **we determined the impact of VEGF on CLL B cells, and we studied the impact of epigallocatechin-3-gallate (EGCG), a known receptor tyrosine kinase (RTK) inhibitor, on VEGF receptor status and viability of CLL B cells**. VEGF165 significantly increased apoptotic resistance of CLL B cells, and immunoblotting revealed that VEGF-R1 and VEGF-R2 are spontaneously phosphorylated on CLL B cells. EGCG significantly increased apoptosis/cell death in 8 of 10 CLL samples measured by annexin V/propidium iodide (PI) staining. The increase in annexin V/PI staining was accompanied by caspase-3 activation and poly-adenosine diphosphate ribose polymerase (PARP) cleavage at low concentrations of EGCG (3 microg/mL). Moreover, EGCG suppressed the proteins B-cell leukemia/lymphoma-2 protein (Bcl-2), X-linked inhibitor of apoptosis protein (XIAP), and myeloid cell leukemia-1 (Mcl-1) in CLL B cells. Finally, EGCG (3-25 microg/mL) suppressed VEGF-R1 and VEGF-R2 phosphorylation, albeit incompletely. Thus, these results suggest that VEGF signaling regulates survival signals in CLL cells and that interruption of this autocrine pathway results in caspase activation and subsequent leukemic cell death." *(Lee YK, Bone ND, Strege AK, Shanafelt TD, Jelinek DF, Kay NE. VEGF receptor phosphorylation status and apoptosis is modulated by a green tea component, epigallocatechin-3-gallate (EGCG), in B-cell chronic lymphocytic leukemia. Blood. 2004 Aug 1;104(3):788-94).*

36 *Lamy S, Gingras D, Béliveau R. Green tea catechins inhibit vascular endothelial growth factor receptor phosphorylation. Cancer*

VEGF da parte dei componenti del The verde, ed offrono solide prove che questo effetto inibitorio possa avere profonde ripercussioni sui tumori la cui progressione sia legata a questa citochina. Ciò suggerisce l'interessante possibilità che il The verde possa essere utilizzato come un agente concomitante nel trattamento della leucemia. Una recente Cochrane review, che ha condotto un'accurata revisione critica della letteratura pubblicata fino al gennaio 2009 ed inerente gli effetti anticarcinogenici del The verde, conclude infine che mancano le evidenze per poter raccomandare la droga nella prevenzione dei tumori[37].

Attività sull'apparato cardiovascolare. A partire dagli anni '90, alcune evidenze epidemiologiche avevano suggerito una possibile correlazione inversa tra consumo di The verde e salute cardiovascolare. La ricerca, dopo aver individuato nella (-)-epigallocatechina-3-gallato (EGCG) la molecola di maggior interesse, ha indagato i possibili ruoli protettivi su alcuni importanti fattori di rischio: controllo glicemico, lipidi ematici, fattori endoteliali, ecc.

Uno studio nel ratto ha evidenziato che il The verde può prevenire lo stress ossidativo renale causato dall'ipertensione arteriosa e dal diabete. Si utilizzavano allo scopo ratti spontaneamente ipertesi SHR diabetici e non, che dovevano ingerire quotidianamente 13,3 g/L di The verde o un placebo per 3 mesi. Le catechine del The verde riducevano significativamente sia la glicemia sia il danno renale, valutato misurando l'espressione della 8-idrossidesossiguanosina (8-OHdG) e della

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Res. 2002 Jan 15;62(2):381-385.

[37] "…Objectives: To critically assess any associations between green tea consumption and the risk of cancer incidence and mortality. Search strategy: We searched eligible studies up to January 2009 in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, Amed, CancerLit, Psych INFO and Phytobase and reference lists of previous reviews and included studies. We included all prospective, controlled interventional studies and observational studies, which either assessed the associations between green tea consumption and risk of cancer incidence or that reported on cancer mortality. (…) Main results: **Fifty-one studies with more than 1.6 million participants were included. Twenty-seven of them were case-control studies, 23 cohort studies and one randomised controlled trial (RCT).Twenty-seven studies tried to establish an association between green tea consumption and cancer of the digestive tract, mainly of the upper gastrointestinal tract, five with breast cancer, five with prostate cancer, three with lung cancer, two with ovarian cancer, two with urinary bladder cancer one with oral cancer**, three further studies included patients with various cancer diagnoses. The methodological quality was measured with the Newcastle-Ottawa scale (NOS). The 9 nested case-control studies within prospective cohorts were of high methodological quality, 13 of medium, and 1 of low. One retrospective case-control study was of high methodological quality and 21 of medium and 5 of low. **Results from studies assessing associations between green tea and risk of digestive tract cancer incidence were highly contradictory. There was limited evidence that green tea could reduce the incidence of liver cancer. The evidence for esophageal, gastric, colon, rectum, and pancreatic cancer was conflicting. In prostate cancer, observational studies with higher methodological quality and the only included RCT suggested a decreased risk in men consuming higher quantities green tea or green tea extracts. However, there was limited to moderate evidence that the consumption of green tea reduced the risk of lung cancer, especially in men, and urinary bladder cancer or that it could even increase the risk of the latter. There was moderate to strong evidence that green tea consumption does not decrease the risk of dying from gastric cancer. There was limited moderate to strong evidence for lung, pancreatic and colorectal cancer**. Authors' conclusions: There is insufficient and conflicting evidence to give any firm recommendations regarding green tea consumption for cancer prevention. The results of this review, including its trends of associations, need to be interpreted with caution and their generalisability is questionable, as the majority of included studies were carried out in Asia (n = 47) where the tea drinking culture is pronounced." *(Lee YK, Bone ND, Strege AK, Shanafelt TD, Jelinek DF, Kay NE. VEGF receptor phosphorylation status and apoptosis is modulated by a green tea component, epigallocatechin-3-gallate (EGCG), in B-cell chronic lymphocytic leukemia. Blood. 2004 Aug 1;104(3):788-94).*

nitro-tirosina, nei ratti diabetici. Anche l'albuminuria e l'espressione del collagene IV nel rene erano significativamente più elevati nei ratti diabetici trattati col placebo rispetto a quelli che ricevevano le catechine del the verde, che ristabilivano lo stato riduttivo nel rene e riducevano gli indici di nefropatia senza alterare la glicemia e la pressione arteriosa sistolica[38]. Uno studio clinico controllato mostra che un estratto acquoso decaffeinato di The verde può ridurre la pressione arteriosa, il colesterolo LDL e i markers di flogosi cronica indicativi dello stress ossidativo nell'uomo, suggerendo la droga nella prevenzione nei confronti delle malattie cardiovascolari[39]. Un estratto acquoso di The verde ostacola l'ipertensione e il danno d'organo indotto dall'angiotensina II nel ratto, grazie soprattutto alla sua energica azione antiossidante[40], e un altro studio indica che un estratto di The verde ostacola l'invecchiamento del tessuto cardiaco legato all'età nel ratto[41]. Un recente studio di popolazione effettuato in Cina sembra infine dimostrare la correlazione inversa tra il consumo di The verde e il rischio di ictus cerebrale[42].

In maggior misura del caffè, i preparati a case di The verde possono anche contare su di una possibile azione coronarodilatatrice tipica della teofillina; l'infuso di the potrebbe dunque trovare idonea applicazione quale blando rimedio coadiuvante nella prevenzione e nella cura degli accessi stenocardici e quale diuretico nelle forme cardiache con stasi. Sia gli estratti di The verde che le catechine del fitocomplesso producono inoltre una diminuzione della pressione ematica[43] e della

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38 *Ribaldo P.D. et al. Green tea (Camellia sinensis) Attenuates Nephropathy by Downregulating Nox4 NADPH Oxidase in Diabetic Spontaneously Hypertensive Rats. J Nutr. 2009 Jan; Vol. 139, No. 1, 96-100.*

39 *Nantz M.P. et al. Standardized capsule of Camellia sinensis lowers cardiovascular risk factors in a randomized, double-blind, placebo-controlled study. Nutrition. 2008 Oct 8. [Epub ahead of print].*

40 *Antonello M. et al. Prevention of hypertension, cardiovascular damage and endothelial dysfunction with green tea extracts. Am J Hypertens. 2007; 20(12):1321-8.*

41 *Kumaran V.S. et al. Senescence mediated redox imbalance in cardiac tissue: Antioxidant rejuvenating potential of green tea extract. Nutrition. 2009; 25(7-8):847-54.*

42 *Liang W. et al. Tea Consumption and Ischemic Stroke Risk. A Case-Control Study in Southern China. Stroke. 2009 May 28. [Epub ahead of print].*

43 "**Epigallocatechin gallate (EGCG), a bioactive polyphenol in green tea, may augment metabolic and vascular actions of insulin**. **Therefore, we investigated effects of EGCG treatment to simultaneously improve cardiovascular and metabolic function in spontaneously hypertensive rats (SHR; model of metabolic syndrome with hypertension, insulin resistance, and overweight).** In acute studies, EGCG (1-100 microM) elicited dose-dependent vasodilation in mesenteric vascular beds (MVB) isolated from SHR ex vivo that was inhibitable by N(omega)-nitro-L-arginine methyl ester (L-NAME; nitric oxide synthase antagonist) or wortmannin [phosphatidylinositol (PI) 3-kinase inhibitor]. In chronic studies, 9-wk-old SHR were treated by gavage for 3 wk with EGCG (200 mg.kg(-1).day(-1)), enalapril (30 mg.kg(-1).day(-1)), or vehicle. A separate group of SHR receiving L-NAME (80 mg/l in drinking water) was treated for 3 wk with either EGCG or vehicle. Vasodilator actions of insulin were significantly improved in MVB from EGCG- or enalapril-treated SHR (when compared with vehicle-treated SHR). Both EGCG and enalapril therapy significantly lowered systolic blood pressure (SBP) in SHR. EGCG therapy of SHR significantly reduced infarct size and improved cardiac function in Langendorff-perfused hearts exposed to ischemia-reperfusion (I/R) injury. In SHR given L-NAME, beneficial effects of EGCG on SBP and I/R were not observed. Both enalapril and EGCG treatment of SHR improved insulin sensitivity and raised plasma adiponectin levels. **We conclude that acute actions of EGCG to stimulate production of nitric oxide from endothelium using PI 3-kinase-dependent pathways may explain, in part, beneficial effects of EGCG therapy to simultaneously improve metabolic and cardiovascular pathophysiology in SHR**. These findings may

glicemia nell'uomo[44,45], inibiscono l'aggregazione piastrinica[46], riducono la proliferazione delle fibrocellule muscolari lisce di arteria rallentando la formazione di una placca aterosclerotica[47], e

be relevant to understanding potential benefits of green tea consumption in patients with the metabolic syndrome." *(Potenza MA, Marasciulo FL, Tarquinio M, Tiravanti E, Colantuono G, Federici A, Kim JA, Quon MJ, Montagnani M. EGCG, a green tea polyphenol, improves endothelial function and insulin sensitivity, reduces blood pressure, and protects against myocardial I/R injury in SHR. Am J Physiol Endocrinol Metab. 2007 May;292(5):E1378-87).*

[44] "…**We investigated the effects of acute ingestion of green tea extract (GTE) on glucose tolerance and fat oxidation during moderate-intensity exercise in humans**. Design: Two studies were performed, both with a counter-balanced crossover design. In study A, 12 healthy men performed a 30-min cycling exercise at 60% of maximal oxygen consumption (VO2max) before and after supplementation. In study B, 11 healthy men took an oral-glucose-tolerance test before and after supplementation. In the 24-h period before the experimental trials, participants ingested 3 capsules containing either GTE (total: 890 +/- 13 mg polyphenols and 366 +/- 5 mg EGCG) or a corn-flour placebo (total: 1729 +/- 22 mg). Results: **Average fat oxidation rates were 17% higher after ingestion of GTE than after ingestion of placebo** (0.41 +/- 0.03 and 0.35 +/- 0.03 g/min, respectively; $P < 0.05$). **Moreover, the contribution of fat oxidation to total energy expenditure was also significantly higher, by a similar percentage, after GTE supplementation**. **The insulin area under the curve decreased in both the GTE and placebo trials** (3612 +/- 301 and 4280 +/- 309 microIU/dL . 120 min, respectively; $P < 0.01$), **and there was a concomitant increase of 13% in insulin sensitivity**. Conclusions: **Acute GTE ingestion can increase fat oxidation during moderate-intensity exercise and can improve insulin sensitivity and glucose tolerance in healthy young men**." *(Venables MC, Hulston CJ, Cox HR, Jeukendrup AE. Green tea extract ingestion, fat oxidation, and glucose tolerance in healthy humans. Am J Clin Nutr. 2008 Mar;87(3):778-84).*

[45] "Tea is a popular beverage with a number of putative beneficial health effects. **A recent large epidemiological study in Japan demonstrates that increased tea consumption is associated with decreased cardiovascular mortality (but not cancer mortality) in a dose-dependent manner**. The polyphenol epigallocatechin-3-gallate (EGCG) is the most abundant tea catechin. Beneficial effects of EGCG therapy have been reported in a number of human and animal studies. **Emerging evidence suggests that EGCG may improve endothelial function, hypertension, coronary heart disease, obesity, insulin resistance, as well as glucose and lipid metabolism. Studies in cultured cells and animal models suggest molecular mechanisms for EGCG to activate specific cellular signaling pathways that may play major roles in prevention and amelioration of cardiovascular and metabolic diseases**. In this review, the beneficial health effects of tea and molecular mechanisms of EGCG related to cardiovascular and metabolic diseases will be discussed." *(Kim JA. Mechanisms underlying beneficial health effects of tea catechins to improve insulin resistance and endothelial dysfunction. Endocr Metab Immune Disord Drug Targets. 2008 Jun;8(2):82-8).*

[46] "We have previously reported that green tea catechins (GTC) showed an antithrombotic activity, which might be due to antiplatelet effect rather than anticoagulation. **The present study was performed to investigate the effect of GTC on the arachidonic acid (AA) metabolism in order to elucidate a possible antiplatelet mechanism**. GTC inhibited the collagen-, AA- and U46619-induced rabbit platelet aggregation in vitro in a concentration-dependent manner, with IC50 values of 61.0+/-2.5, 105.0+/-4.9 and 67.0+/-3.2 microg/ml, respectively. Moreover, GTC administered orally into rats inhibited the AA-induced platelet aggregation ex vivo by 46.9+/-6.1% and 95.4+/-2.2% at the doses of 25 and 50 mg/kg, respectively. [3H]AA liberation induced by collagen in [3H]AA incorporated rabbit platelets was significantly suppressed by GTC compared to the control. GTC also significantly inhibited the thromboxane A2 (TXA2) and prostaglandin D2 (PGD2) generations induced by addition of AA. in intact rabbit platelets. GTC significantly inhibited TXA2 synthase activity in a concentration-dependent manner. Moreover, adenosine triphosphate (ATP) release from dense granule was inhibited by GTC in washed platelets. **These results suggest that the antiplatelet activity of GTC may be due to the inhibition of TXA2 formation through the inhibition of AA. liberation and TXA2 synthase**." *(Son DJ, Cho MR, Jin YR, Kim SY, Park YH, Lee SH, Akiba S, Sato T, Yun YP. Antiplatelet effect of green tea catechins: a possible mechanism through arachidonic acid pathway. Prostaglandins Leukot Essent Fatty Acids. 2004 Jul;71(1):25-31).*

[47] "Since ancient times green tea has been considered a health-promoting beverage. In recent years, scientists throughout the world have investigated the potential benefits of green tea and its most abundant catechin, epigallocatechin gallate (EGCG). The anti-cancer effects of green tea and EGCG were the focus of early research, and encouraging data from in vitro, animal model, and human studies have emerged. **Due to the dominant role of cardiovascular disease and the dramatic rise of obesity and type 2 diabetes mellitus as major and interlinked healthcare problems, green tea and EGCG are increasingly being investigated in these areas**. **Dose-response relationships observed in several epidemiological studies have indicated that pronounced cardiovascular and metabolic health benefits can be obtained by regular consumption of 5-6 or more cups of green tea per day**. **Furthermore, intervention studies using similar amounts of green tea, containing 200-300**

così risultano attivi nel prevenire i rischi di patologie coronariche[48] e cardiovascolari in genere[49]. L'attività antiaterosclerotica delle catechine - la A(-)-epicatechina e la (-)-epigallocatechina - sembra mediata, in parte, anche da un ridotto assorbimento dei lipidi a livello intestinale[50], in parte da una ridotta ossidazione delle lipoproteine LDL[51]. Gli effetti delle catechine sono stati confermati da un ampio studio epidemiologico che ha dimostrato una relazione inversa fra consumo di The e livelli plasmatici di colesterolo e di lipoproteine LDL[52].

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mg of EGCG, have demonstrated its usefulness for maintaining cardiovascular and metabolic health. Additionally, there are numerous in vivo studies demonstrating that green tea and EGCG exert cardiovascular and metabolic benefits in these model systems. **Therefore, green tea and EGCG can be regarded as food components useful for the maintenance of cardiovascular and metabolic health.** To prove the effectiveness for disease prevention or treatment, several multi-center, long-term clinical studies investigating the effects of one precisely-defined green tea product on cardiovascular and metabolic endpoints would be necessary. The aim of this manuscript is to provide an overview of the research investigating the effects of green tea and green tea catechins on cardiovascular and metabolic health." *(Wolfram S. Effects of green tea and EGCG on cardiovascular and metabolic health. J Am Coll Nutr. 2007 Aug;26(4):373S-388S).*

48 *Moore RJ, Jackson KG, Minihane AM. Green tea (Camellia sinensis) catechins and vascular function. Br J Nutr. 2009 Dec;102(12):1790-802.*

49 "…It has been shown that green tea, when consumed on a daily basis, supports health. Many of the beneficial effects of green tea are related to its catechin, particularly (-)-epigallocatechin-3-gallate (EGCG), content. There is conclusive evidence from in vitro and animal studies which provide the concepts for underlying functional mechanisms of green tea catechins and their biological actions. An increasing number of human studies have explored the effects of green tea catechins on the major MetS conditions such as obesity, type-2 diabetes and cardiovascular risk factors. **This article provides a comprehensive overview of the human studies addressing the potential benefits of green tea catechins on the MetS. The number of human studies in this field is still limited. However, the majority of human epidemiological and intervention studies demonstrate beneficial effects of green tea or green tea extracts, rich in EGCG on weight management, glucose control and cardiovascular risk factors**. The optimal dose has not yet been established. The current body of evidence in humans warrants further attention. In particular, well-controlled long-term human studies would help to fully understand the protective effects of green tea catechins on parameters related to the MetS." *(Thielecke F, Boschmann M. The potential role of green tea catechins in the prevention of the metabolic syndrome - a review. Phytochemistry. 2009 Jan;70(1):11-24).*

50 "A(-)-epicatechin (EC) and (-)-epigallocatechin (EGC) mixture and a mixture of their gallates (ECG and EGCG, respectively) markedly lowered lymphatic cholesterol absorption... **These results clearly show that tea catechins, in particular their gallate esters, effectively reduce cholesterol absorption from the intestine by reducing solubility of cholesterol in mixed micelles. The observation accounts for the hypocholesterolemic effect of tea catechins.**" *(Ikeda I, Imasato Y, Sasaki E, Nakayama M, Nagao H, Takeo T, Yayabe F, Sugano M. Tea catechins decrease micellar solubility and intestinal absorption of cholesterol in rats. Biochim Biophys Acta 1992; 1127: 141-6).*

51 "We have reported in our previous paper that several flavan-3-ol derivatives (tea polyphenols) inhibited the $Cu(2^{+})$-mediated low density lipoprotein (LDL) oxidation in vitro. **(-)-Epigallocatechin gallate (EGCG), in particular, exhibited strong inhibition..."** *(Miura S, Watanabe J, Sano M, Tomita T, Osawa T, Hara Y, Tomita I. Effects of various natural antioxidants on the Cu(2+)-mediated oxidative modification of low density lipoprotein. Biol Pharm Bull 1995; 18: 1-4).*

52 "**Animal experiments have shown a hypocholesterolemic effect of green tea extracts.** Only few epidemiological studies have addressed the relation between green tea consumption and serum total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C)… After adjustment for body mass index, waist-hip ratio, smoking, alcohol use, exercise, rank, and hospital, **green tea consumption was inversely associated with serum levels of TC and LDL-C, but not with either high density lipoprotein cholesterol or triglycerides**. Daily drinking of 10 cups of green tea was associated with differences of 6.2 mg/dl in TC (95% confidence interval [CI] 0.4-12.1) and 6.2 mg/dl in LDL-C (95% CI 0.7-11.7). **These findings of association of green tea with blood cholesterol hint at a possible causal relationship, which requires confirmation by further studies in humans using different methods.**" *(Kono S, Shinchi K, Wakabayashi K, Honjo S, Todoroki I, Sakurai Y, Imanishi K, Nishikawa H, Ogawa S, Katsurada M. Relation of green tea consumption to serum lipids and lipoproteins in Japanese men. J Epidemiol 1996; 6: 128-33).*

Altre attività. Uno studio in vitro indica che l'epigallocatechin-gallato (EGCG) può avere azione protettiva contro i danni causati alla cute dai raggi UVB, in quanto riduce la formazione di H_2O_2 e l'attivazione conseguente delle chinasi ERK1/2, p38 e JNK[53]. Anche un altro studio mostra come l'applicazione topica del The verde abbia azione fotoprotettiva contro i raggi UV nell'uomo[54]. Uno studio pubblicato di recente suggerisce infine le potenzialità del The verde nel trattamento delle allergie[55], anche se le opinioni in merito a tale applicazione sono discordanti[56].

Tollerabilità. Una recente revisione sistematica voluta dalla Farmacopea Americana ha valutato gli studi esistenti sulla sicurezza del the verde, definendola una droga generalmente sicura[57]. Si sono tuttavia verificati rari casi di intossicazione epatica in pazienti che assumevano dosi elevate di estratti di The verde; tali casi si risolvevano peraltro spontaneamente in pochi giorni sospendendo l'assunzione della droga. Ciò suggerisce comunque prudenza in pazienti affetti da problemi epatici[58]. Gli autori di una recente review attribuiscono le reazioni epatiche sospette da The Verde alle catechine in esso contenute. La biodisponibilità delle catechine è ridotta in seguito a somministrazione orale, ma può aumentare fino a determinare livelli plasmatici tossici in condizioni particolari quali p.e. digiuno e somministrazioni ripetute. L'epatotossicità può essere attribuita alla capacità di EGCG o dei suoi metaboliti di indurre stress ossidativo nel fegato. Dato che la maggior parte dei casi di riscontrati è insorta in soggetti di sesso femminile, può inoltre essere ipotizzata una suscettibilità del genere femminile allo sviluppo di danno epatico da The Verde. In alcuni casi non può essere escluso un meccanismo idiosincrasico o un meccanismo immuno-allergico[59].

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53 *Huang C.C. et al. (-)- Epicatechin-3-gallate, a green tea polyphenol is a potent agent against UVB-induced damage in HaCaT keratinocytes. Molecules. 2007; 12(8):1845-58.*

54 *Camouse M.M. et al. Topical application of green and white tea extracts provides protection from solar-simulated ultraviolet light in human skin. Exp Dermatol. 18(6):522-6, 2009.*

55 *Heo JC, Rho JR, Kim TH, Kim SY, Lee SH. An aqueous extract of green tea Camellia sinensis increases expression of Th1 cell-specific anti-asthmatic markers. Int J Mol Med. 2008 Dec;22(6):763-7.*

56 *Murr C, Schroecksnadel K, Winkler C, Ledochowski M, Fuchs D. Antioxidants may increase the probability of developing allergic diseases and asthma. Med Hypotheses. 2005;64(5):973-7.*

57 *Sarma DN, Barrett ML, Chavez ML, Gardiner P, Ko R, Mahady GB, Marles RJ, Pellicore LS, Giancaspro GI, Low Dog T. Safety of green tea extracts: a systematic review by the US Pharmacopeia. Drug Saf. 2008;31(6):469-84.*

58 *Molinari M, Watt KD, Kruszyna T, Nelson R, Walsh M, Huang WY, Nashan B, Peltekian . Acute liver failure induced by green tea extracts: case report and review of the literature. Liver Transpl. 2006 Dec;12(12):1892-5.*

59 "**Our analysis of the published case reports suggests a causal association between green tea and liver damage. The hepatotoxicity is probably due to (-)-epigallocatechin gallate or its metabolites which, under particular conditions related to the patient's metabolism, can induce oxidative stress in the liver**. In a few cases, toxicity related to concomitant medications could also be involved." *(Mazzanti G, Menniti-Ippolito F, Moro PA, Cassetti F, Raschetti R, Santuccio C, Mastrangelo S. Hepatotoxicity from green tea: a review of the literature and two unpublished cases. Eur J Clin Pharmacol 2009; 65:331–341).*