



Garcinia

Garcinia cambogia

Nome botanico

Garcinia cambogia Desr. (*Guttiferae*)

Parti usate

Epicarpo del frutto.

Componenti principali

Acido (-)-idrossicitrico.

Attività farmacologica

Riduzione della biosintesi endogena dei lipidi. Incremento dell'utilizzazione dei grassi. Promuove la sintesi di glicogeno.

Impiego clinico

Ipertrigliceridemia e ipercolesterolemia. Coadiuvante in caso di condizioni di sovrappeso e obesità. Coadiuvante nell'attività sportiva.

Controindicazioni

Nessuna controindicazione nota.

Avvertenze e speciali precauzioni d'uso

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.

Interazioni

Nessuna nota.

Effetti indesiderati

Nessuno degno di nota.

Note Bibliografiche

Composizione

Il costituente principale del fitocomplesso dell'epicarpo del frutto di *Garcinia cambogia* è l'acido (-)-idrossicitrico (HCA) o idrossicitrato. Tra gli altri componenti del fitocomplesso troviamo mucillagini, flavonoidi, amine ed acidi alfa e beta garcinolici. Nell'estratto in dietilere dei frutti della *Garcinia* è inoltre presente il garcinolo insieme ai guttiferoni (I, J, K, M, N), composti appartenenti alla classe dei benzofenoni isoprenilati, noti per i loro effetti antibatterici e antiossidanti¹.

Attività biologiche ed impieghi clinici descritti in letteratura

Le attività biologiche ed i più noti impieghi clinici descritti per la *Garcinia cambogia* sono:

Riduzione del peso corporeo in soggetti con sovrappeso o obesità. La *Garcinia cambogia* è utilizzata per il trattamento coadiuvante di condizioni di sovrappeso ed obesità, in associazione a diete ipocaloriche ed a programmi fisici di riduzione del peso corporeo². L'integrazione con la droga sembra essere efficace soprattutto se associata a una dieta con una percentuale (rispetto alla quota calorica giornaliera) di carboidrati superiori alla media³.

¹ "In light of the wide range of biological activities of garcinol and with the aim of exploring some of them, we carried out its isolation from the fruits of *Garcinia cambogia* L. (Guttiferae). Surprisingly, **the fruits were also found to contain guttiferones I, J, and K, compounds never reported in *G. cambogia*, along with three new compounds, namely, guttiferone M, guttiferone N, and the oxidized derivative of guttiferone K. Oxy-guttiferone K is the first example of tetracyclic xanthone derived from the oxidation of a polyisoprenylated benzophenone from natural source.** The natural formation of oxy-guttiferone K is in agreement with the previously described cyclization of garcinol by DPPH." (Masullo M, Bassarello C, Suzuki H, Pizza C, Piacente S. *Polyisoprenylated Benzophenones and an Unusual Polyisoprenylated Tetracyclic Xanthone from the Fruits of *Garcinia cambogia*. J. Agric. Food Chem. 2008, 56, 5205–5210*).

² "**(-)-Hydroxycitric acid [(–)-HCA] is the principal acid of fruit rinds of *Garcinia cambogia*, *Garcinia indica*, and *Garcinia atroviridis*. (-)-HCA was shown to be a potent inhibitor of ATP citrate lyase (EC 4.1.3.8), which catalyzes the extramitochondrial cleavage of citrate to oxaloacetate and acetyl-CoA: citrate + ATP + CoA → acetyl-CoA + ADP + P(i) + oxaloacetate.** The inhibition of this reaction limits the availability of acetyl-CoA units required for fatty acid synthesis and lipogenesis during a lipogenic diet, that is, a diet high in carbohydrates. **Extensive animal studies indicated that (-)-HCA suppresses the fatty acid synthesis, lipogenesis, food intake, and induced weight loss.** In vitro studies revealed the inhibitions of fatty acid synthesis and lipogenesis from various precursors. However, a few clinical studies have shown controversial findings. This review explores the literature on a number of topics: the source of (-)-HCA; the discovery of (-)-HCA; the isolation, stereochemistry, properties, methods of estimation, and derivatives of (-)-HCA; and its biochemistry, which includes inhibition of the citrate cleavage enzyme, effects on fatty acid synthesis and lipogenesis, effects on ketogenesis, other biological effects, possible modes of action on the reduction of food intake, promotion of glycogenesis, gluconeogenesis, and lipid oxidation, (-)-HCA as weight-controlling agent, and some possible concerns about (-)-HCA, which provides a coherent presentation of scattered literature on (-)-HCA and its plausible mechanism of action and is provocative of further research." (Jena BS, Jayaprakasha GK, Singh RP, Sakariah KK. *Chemistry and biochemistry of (-)-hydroxycitric acid from *Garcinia*. J Agric Food Chem. 2002 Jan 2;50(1):10-22*).

³ "**(-)-Hydroxycitrate (HCA) might promote weight maintenance by limiting the capacity for de novo lipogenesis (DNL). It was investigated whether HCA may reduce DNL in humans during a persistent excess of energy intake as carbohydrate. In a double-blind, placebo-controlled, randomized and cross-over design,** 10 sedentary lean male subjects (mean±/S.D.,

L'attività del fitocomplesso della Garcinia è legata alla presenza di acido (-)-idrossicitrico (HCA), un ossiacido che è risultato efficace in alcuni modelli di obesità sperimentale⁴, in quanto coinvolto nelle reazioni cellulari del metabolismo lipidico⁵. L'acido idrossicitrico è stato infatti oggetto di numerosi studi che hanno potuto evidenziare, per la sua forma levogira⁶, una azione inibitoria competitiva nei confronti di un enzima citoplasmatico (individuato per la prima volta nel fegato) che svolge una azione primaria nella regolazione del metabolismo dei grassi⁷. Tra gli altri effetti dimostrati

age: 24+/-5 years, BMI: 21.8+/-2.1 kg/m²) performed a glycogen depletion exercise test followed by a 3-day high-fat diet (F/CHO/P, 60/25/15% energy; 100% of energy expenditure (EE)) and a 7-day high-CHO diet (F/CHO/P, <5/>85/10% energy; 130-175% of EE; overfeeding). During overfeeding, they ingested 3 x 500 mg/day HCA or placebo (PLA). Each intervention ended with a 60-h stay in the respiration chamber (days 9 and 10). Body weight increased during overfeeding (mean+/-S.E., HCA: 2.9+/-0.2 kg, PLA: 2.8+/-0.2 kg). Respiratory quotient (RQ) was >1.00 in all subjects indicating that DNL was present. On day 9, 24-h EE was lower with HCA compared to PLA (P < 0.05). On day 10, resting metabolic rate and RQ during night were lower (P < 0.01 and P < 0.05, respectively). Non-protein RQ, fat balance and net fat synthesis as DNL tended to be lower (P < 0.1) with HCA compared to PLA indicating lower DNL; activity-induced EE was higher with HCA (P < 0.05) indicating the urge to eliminate the excess of energy ingested. We conclude that **an experimental condition resulting in DNL in humans was created and that treatment with HCA during overfeeding with carbohydrates may reduce DNL.**" (Kovacs EM, Westerterp-Plantenga MS. *Effects of (-)-hydroxycitrate on net fat synthesis as de novo lipogenesis. Physiol Behav. 2006 Jul 30;88(4-5):371-81.*)

⁴ "Recent advances in molecular biology combined with the wealth of information generated by the Human Genome Project have fostered the emergence of nutrigenomics, a new discipline in the field of nutritional research. Nutrigenomics may provide the strategies for the development of safe and effective dietary interventions against the obesity epidemic. (...) Among these supplements, **(-)-hydroxycitric acid (HCA), a natural extract isolated from the dried fruit rind of Garcinia cambogia**, and the micronutrient niacin-bound chromium(III) (NBC) have been shown to be safe and efficacious for weight loss. **Utilizing cDNA microarrays, we demonstrated for the first time that HCA-supplementation altered the expression of genes involved in lipolytic and adipogenic pathways in adipocytes from obese women and up-regulated the expression of serotonin receptor gene in the abdominal fat of rats.** Similarly, we showed that NBC-supplementation up-regulated the expression of myogenic genes while suppressed the expression of genes that are highly expressed in brown adipose tissue in diabetic obese mice. The potential biological mechanisms underlying the observed beneficial effects of these supplements as elucidated by the state-of-the-art nutrigenomic technologies will be systematically discussed in this review." (Lau FC, Bagchi M, Sen C, Roy S, Bagchi D. *Nutrigenomic analysis of diet-gene interactions on functional supplements for weight management. Curr Genomics. 2008 Jun;9(4):239-51.*)

⁵ "The feasibility of treating obesity by metabolic regulation has been explored in this study by examining the effect of (-)- hydroxycitrate on three types of experimentally induced obesity in the rodent. **(-)- Hydroxycitrate was utilized because it depressed fatty acid and cholesterol synthesis in vivo through its activity as a potent competitive inhibitor of APT citrate lyase.** In all models, the mature rat, the goldthiogluucose-induced obese mouse, and the ventromedial hypothalamic lesioned obese rat, food intake and **body weight gain were reduced significantly by the chronic oral administration of a nontoxic dose of (-)-hydroxycitrate.** Body composition analyses of mature rats treated with (-)- hydroxycitrate demonstrated a significant depression of body lipid levels and an unaltered body protein content. However, a citrate administration produced no significant effects on weight gain, food intake, or body lipid or protein levels when compared to controls." (Sullivan C, Triscari J. *Metabolic regulation as a control for lipid disorders. I. Influence of (-)-hydroxycitrate on experimentally induced obesity in the rodent. Am J Clin Nutr 1977; 30: 767-76.*)

⁶ Il componente principale della Garcinia cambogia è stato identificato come **acido (-)-idrossicitrico**. L'identificazione è stata resa possibile dal confronto con il lattone dell'acido (-)- idrossicitrico sintetico (Y.S. Lewis et al.1964). Anche nei calici del frutto dell'Hibiscus sabdariffa è presente acido idrossicitrico, ma si tratta dell'acido (+)-allo-idrossicitrico, ovvero della forma destrogira del composto. Queste due sostanze hanno proprietà chimico-fisiche diverse (punto di fusione, potere rotatorio specifico, ecc.), ma soprattutto è diversa anche l'azione a livello biologico, in quanto solo l'acido (-) idrossicitrico è risultato attivo nell'inibizione dell'enzima ATP-citratoliasi.

⁷ "Garcinia cambogia-derived (-)-hydroxycitric acid (HCA) is a popular and natural supplement for weight management. **HCA is a competitive inhibitor of the enzyme ATP citrate lyase, which catalyzes the conversion of citrate and coenzyme A**

per l'acido idrossicitrico troviamo poi una significativa riduzione dell'espressione della leptina negli adipociti del distretto addominale⁸ e una marcata riduzione della condizione di ipossia nel tessuto adiposo, fenomeno ritenuto alla base dello stato infiammatorio persistente responsabile delle alterazioni funzionali degli adipociti nei soggetti obesi⁹, tanto da poter definire l'obesità una *mild inflammation*, ovvero una malattia infiammatoria cronica correlata ad una condizione di basso grado di infiammazione locale del tessuto adiposo. Nel grande obeso, infatti, la massa cellulare degli

to oxaloacetate and acetyl coenzyme A (acetyl CoA) in the cytosol. Acetyl CoA is used in the synthesis of fatty acids, cholesterol and triglycerides, and in the synthesis of acetylcholine in the central nervous system. Studies have demonstrated the efficacy of a novel 60% calcium-potassium salt of HCA derived from *Garcinia cambogia* (HCA-SX, Super CitriMax) in weight management. **Results have shown that HCA-SX promotes fat oxidation, enhances serotonin release and availability in the brain cortex, normalizes lipid profiles, and lowers serum leptin levels in obese subjects.** Acute oral, acute dermal, primary dermal irritation and primary eye irritation toxicity, as well as Ames bacterial reverse mutation studies and mouse lymphoma tests have demonstrated the safety of HCA-SX. However, no detailed long-term safety of HCA-SX or any other HCA extract has been previously assessed. We evaluated the dose- and time-dependent effects of HCA-SX in Sprague-Dawley rats on body weight, selected organ weights, hepatic lipid peroxidation and DNA fragmentation, hematology and clinical chemistry over a period of 90 days. Furthermore, a 90-day histopathological evaluation was conducted. The animals were treated with 0, 0.2, 2.0 and 5.0% HCA-SX of feed intake and were sacrificed on 30, 60 or 90 days of treatment. The body weight and selected organ weights were assessed and correlated as a % of body weight and brain weight at 90 days of treatment. A significant reduction in body weight was observed in treated rats as compared to control animals. An advancing age-induced marginal increase in hepatic lipid peroxidation was observed in both male and female rats, while no such difference in hepatic DNA fragmentation was observed as compared to the control animals. Furthermore, selected organ weights individually and as a % of body weight and brain weight at 90 days of treatment exhibited no significant difference between the groups. No difference was observed in hematology and clinical chemistry or the histopathological evaluation. Taken together, these results show that 90 day treatment of HCA-SX results in a reduction in body weight, and does not cause any changes in major organs or in hematology, clinical chemistry, and histopathology." (*Shara M, Ohia SE, Schmidt RE, Yasmin T, Zardetto-Smith A, Kincaid A, Bagchi M, Chatterjee A, Bagchi D, Stohs SJ. Physico-chemical properties of a novel (-)-hydroxycitric acid extract and its effect on body weight, selected organ weights, hepatic lipid peroxidation and DNA fragmentation, hematology and clinical chemistry, and histopathological changes over a period of 90 days. Mol Cell Biochem. 2004 May;260(1-2):171-86.*)

⁸ "Obesity is a global public health problem, with about 315 million people worldwide estimated to fall into the WHO-defined obesity categories. Traditional herbal medicines may have some potential in managing obesity. Botanical dietary supplements often contain complex mixtures of phytochemicals that have additive or synergistic interactions. **The dried fruit rind of *Garcinia cambogia*, also known as Malabar tamarind, is a unique source of (-)-hydroxycitric acid (HCA), which exhibits a distinct sour taste and has been safely used for centuries in Southeastern Asia to make meals more filling.** Recently it has been demonstrated that HCA-SX or Super Citrimax, a novel derivative of HCA, is safe when taken orally and that HCA-SX is bioavailable in the human plasma as studied by GC-MS. Although HCA-SX has been observed to be conditionally effective in weight management in experimental animals as well as in humans, its mechanism of action remains to be understood. **We sought to determine the effects of low-dose oral HCA-SX on the body weight and abdominal fat gene expression profile of Sprague-Dawley rats. We observed that at doses relevant for human consumption dietary HCA-SX significantly contained body weight growth. This response was associated with lowered abdominal fat leptin expression while plasma leptin levels remained unaffected. Repeated high-density microarray analysis of 9960 genes and ESTs present in the fat tissue identified a small set (approximately 1% of all genes screened) of specific genes sensitive to dietary HCA-SX.** Other genes, including vital genes transcribing for mitochondrial/nuclear proteins and which are necessary for fundamental support of the tissue, were not affected by HCA-SX. Under the current experimental conditions, HCA-SX proved to be effective in restricting body weight gain in adult rats. Functional characterization of HCA-SX-sensitive genes revealed that upregulation of genes encoding serotonin receptors represent a distinct effect of dietary HCA-SX supplementation." (*Roy S, Rink C, Khanna S, Phillips C, Bagchi D, Bagchi M, Sen CK. Body weight and abdominal fat gene expression profile in response to a novel hydroxycitric acid-based dietary supplement. Gene Expr. 2004;11(5-6):251-62.*)

⁹ *Trayhurn P, Wang B, Wood IS. Hypoxia in adipose tissue: a basis for the dysregulation of tissue function in obesity? Br J Nutr. 2008 Aug;100(2):227-35.*

adipociti nel tessuto adiposo appare aumentata rispetto al numero ed estensione dei vasi, anche se dati precisi al riguardo non sono presenti in letteratura. Si verrebbe a creare, quindi, un microambiente ipossico che, mediante i segnali del danno necrotico, potrebbe essere in relazione all'attivazione di risposta genica proinfiammatoria attraverso il signalling HIF- α /NF- κ B e/o al reclutamento di cellule staminali la cui proliferazione contribuirebbe a mantenere l'ipertrofia/iperplasia del tessuto adiposo dell'obeso¹⁰.

La demolizione finale degli zuccheri, dei grassi e delle proteine assunti con l'alimentazione avviene a livello dei mitocondri attraverso il ciclo di Krebs, con produzione di energia attraverso la catena respiratoria a questo collegata. Nei principali tessuti lipogenici quali fegato, intestino e tessuto adiposo, quando l'ingestione di cibo e in particolare di zuccheri eccede le necessità dell'organismo, una parte del citrato prodotto nel ciclo di Krebs viene immesso nel citoplasma, dove viene scisso in acido ossalacetico e Acetil-CoA. E l'acido ossalacetico costituisce il prodotto di partenza per la sintesi endogena dei grassi, che vengono poi immagazzinati principalmente a livello del tessuto adiposo sottocutaneo. Più precisamente, l'acido (-)-idrossicitrico agisce inibendo la ATP-citrato-liasi, enzima deputato alla liberazione nel citoplasma cellulare dell'acetil-CoA proveniente dai mitocondri e starter della liposintesi endogena. L'acetil-CoA, presente all'interno del mitocondrio – proveniente sia dalla glicolisi anaerobica sia dalla β -ossidazione degli acidi grassi – viene infatti utilizzato in parte per la produzione di ATP ed in parte trasportato nel citosol dove da inizio alla biosintesi di tutti i lipidi dell'organismo (acidi grassi, trigliceridi, colesterolo, ecc.). Più la quantità di glucidi e lipidi assunti con la dieta eccede il fabbisogno energetico, maggiore è la concentrazione di acetil-CoA all'interno del mitocondrio, e maggiore è l'entità della liposintesi endogena. L'acetil-CoA, per passare nel citosol, è trasformato – per unione con l'acido ossalacetico – in acido citrico (acetil-CoA + ac. ossalacetico = ac. citrico), che può così attraversare la membrana mitocondriale (tricarboxylic acid carrier). Nel citosol l'acido citrico è nuovamente idrolizzato da una citrato liasi in acido ossalacetico e acetil-CoA, il quale poi, unendosi con un'altra molecola di acetil-CoA, forma malonil-CoA e dà inizio alla biosintesi degli acidi grassi. L'acido ossalacetico è trasformato, a sua volta, in acido malico da una malico deidrogenasi (MDH) citosolica e, successivamente, in acido piruvico da un enzima malico (ME). L'acido piruvico riattraversa infine la membrana del mitocondrio all'interno del quale è trasformato di nuovo in acido ossalacetico da una piruvato carbossilasi attivata dalle elevate concentrazioni di acetil-CoA. In definitiva quindi, per azione dell'acido idrossicitrico si formeranno meno grassi endogeni disponibili per l'accumulo da parte dell'organismo (fegato, tessuto adiposo)¹¹ ed inoltre sarà disponibile una

¹⁰ Halberg N, Khan T, Trujillo ME, Wernstedt-Asterholm I, Attie AD, Sherwani S, Wang ZV, Landskroner-Eiger S, Dineen S, Magalang UJ, Brekken RA, Scherer PE. Hypoxia-inducible factor 1 α induces fibrosis and insulin resistance in white adipose tissue. *Mol Cell Biol.* 2009 Aug;29(16):4467-83.

¹¹ **“Our objective was to examine whether etomoxir (ETO), an inhibitor of NEFA oxidation, or (-)-hydroxycitrate (HCA), an inhibitor of lipogenesis which may indirectly stimulate NEFA oxidation, alters satiety.** Post-lunch satiety was measured in eight normal-weight male subjects who were deprived of time cues and received on three occasions either ETO (320 mg), HCA (2 g) or placebo (PLA) in random order. Between lunch and dinner, blood was withdrawn continuously and collected

quantità maggiore di energia a livello cellulare per una più rapida degradazione degli acidi grassi¹². Inibendo la citrato liasi che avvia la sintesi lipidica a partire dal citrato, l'acido (-)-idrossicitrico favorisce la combustione completa del glucosio nel ciclo di Krebs con produzione di energia e conferisce senso di sazietà. Esso stimola poi la sintesi epatica di glicogeno, con aumento del suo deposito di riserva nel fegato. Ciò produce una inibizione del nucleo ipotalamico della fame, e questo meccanismo spiega in parte l'effetto ipopressizzante dell'estratto secco di Garcinia. Altri meccanismi legati alla sazietà potrebbero essere legati ad un aumento della biodisponibilità della serotonina a livello cerebrale¹³. Uno studio ha valutato l'effetto dell'acido idrossicitrico sulla liberazione di serotonina da parte del cervello del ratto sia basale sia indotta dalla depolarizzazione

every 10 min for measures of plasma concentrations of glucose, insulin, lactate, TAG, NEFA, beta-hydroxybutyrate (BHB), leptin and ghrelin. **Results showed that HCA began to decrease hunger and desire to eat compared to PLA and ETO 210 min after lunch and increased satiety duration compared to PLA by 70 (se 23) min (P < 0.05), but did not modify energy intake at dinner.** ETO did not affect any variable of satiety. HCA increased NEFA concentrations during the pre-dinner period, whereas ETO increased and decreased plasma concentrations of NEFA and BHB, respectively. Mean differences in plasma NEFA concentrations between HCA and PLA were predictive of the differences in satiety duration between treatments (r^2 0.71, $P < 0.01$). Among treatments, plasma leptin concentration at dinner onset was the only blood variable correlated with energy intake at this meal ($r = 0.75$, $P < 0.0005$). **In healthy, normal-weight men, acute HCA increased the intensity and duration of satiety possibly via increased NEFA disposal for oxidation.**" (Gatta B, Zuberbuehler C, Arnold M, Aubert R, Langhans W, Chapelot D. *Acute effects of pharmacological modifications of fatty acid metabolism on human satiety.* *Br J Nutr.* 2009 Jun;101(12):1867-77).

¹² "In this study, subcutaneous preadipocytes collected from obese women with body mass index >25 kg/m² were differentiated to adipocytes for 2 weeks in culture. **The effects of low-dose HCA-SX on lipid metabolism and on the adipocyte transcriptome were tested.** Results: **HCA-SX caused droplet dispersion facilitating lipase action on the lipids. HCA-SX markedly induced leptin expression in the adipocytes.** In the microarray analyses, a total of 54,676 probe sets were screened. **HCA-SX resulted in significant down-regulation of 348, and induction of 366 fat- and obesity-related genes. HCA-SX induced transactivation of hypoxia inducible factor (HIF), a novel approach in the management of obesity.**" (Roy S, Shah H, Rink C, Khanna S, Bagchi D, Bagchi M, Sen CK. *Transcriptome of primary adipocytes from obese women in response to a novel hydroxycitric acid-based dietary supplement.* *DNA Cell Biol.* 2007 Sep;26(9):627-39).

¹³ "A growing body of evidence demonstrates the efficacy of Garcinia cambogia-derived natural (-)-hydroxycitric acid (HCA) in weight management by curbing appetite and inhibiting body fat biosynthesis. However, the exact mechanism of action of this novel phytopharmaceutical has yet to be fully understood. In a previous study, we showed that in the rat brain cortex a novel HCA extract increases the release/availability of radiolabeled 5-hydroxytryptamine or serotonin ([3H]-5-HT), a neurotransmitter implicated in the regulation of eating behavior and appetite control. **The aim of the present study was 2-fold: (a) to determine the effect of HCA-SX on 5-HT uptake in rat brain cortex in vitro; and (b) to evaluate the safety of HCA-SX in vivo.** Isolated rat brain cortex slices were incubated in oxygenated Krebs solution for 20 min and transferred to buffer solutions containing [3H]-5-HT for different time intervals. In some experiments, tissues were exposed to HCA-SX (10 microM - 1 mM) and the serotonin receptor reuptake inhibitors (SRRIs) fluoxetine (100 microM) plus clomipramine (10 microM). Uptake of [3H]-5-HT was expressed as d.p.m./mg wet weight. A time-dependent uptake of [3H]-5-HT occurred in cortical slices reaching a maximum at 60 min. HCA-SX, and fluoxetine plus clomipramine inhibited the time-dependent uptake of [3H]-5-HT. At 90 min, HCA-SX (300 microM) caused a 20% decrease, whereas fluoxetine plus clomipramine inhibited [3H]-5-HT uptake by 30%. In safety studies, acute oral toxicity, acute dermal toxicity, primary dermal irritation and primary eye irritation, were conducted in animals using various doses of HCA-SX. Results indicate that the LD50 of HCA-SX is greater than 5,000 mg/kg when administered once orally via gastric intubation to fasted male and female Albino rats. No gross toxicological findings were observed under the experimental conditions. Taken together, these in vivo toxicological studies demonstrate that HCA-SX is a safe, natural supplement under the conditions it was tested. Furthermore, **HCA-SX can inhibit [3H]-5-HT uptake (and also increase 5-HT availability) in isolated rat brain cortical slices in a manner similar to that of SRRIs, and thus may prove beneficial in controlling appetite,** as well as treatment of depression, insomnia, migraine headaches and other serotonin-deficient conditions." (Ohia SE, Opere CA, LeDay AM, Bagchi M, Bagchi D, Stohs SJ. *Safety and mechanism of appetite suppression by a novel hydroxycitric acid extract (HCA-SX).* *Mol Cell Biochem.* 2002 Sep;238(1-2):89-103).

potassica. Si è visto che l'acido idrossicitrico alla dose di 10 microM aumenta moderatamente i livelli basali di serotonina, ma non influenza quelli conseguenti a depolarizzazione potassica. Questi risultati aiutano a spiegare l'effetto iposessizzante dell'estratto secco di *Garcinia*¹⁴. Inibendo la liposintesi endogena, oltre che alla normalizzazione del quadro lipidico la *Garcinia cambogia* contribuisce e alla riduzione del peso corporeo, come dimostrato da evidenze sperimentali in soggetti obesi e in sovrappeso^{15,16}. Particolarmente efficace è anche l'azione dell'HCA unito al

¹⁴ **"There is evidence that hydroxycitric acid (HCA), an extract of dried fruit rind of South Asian trees of the genus *Garcinia cambogia*, can reduce food intake in experimental animals. In the present study, we investigated the effect of HCA on basal and potassium-depolarization evoked increase in radiolabeled serotonin ([3H]-5-HT) release from rat brain cortex slices in vitro.** HCA (10 microM-1 mM) altered the baseline of spontaneous tritium efflux but had no significant effect on potassium-evoked release of [3H]-5-HT. When applied on its own, HCA (10 microM-1 mM) elicited a concentration-dependent increase in efflux of [3H]-5-HT reaching a maximum at 300 microM. **We conclude that HCA can increase the release of radiolabeled 5-HT from the isolated rat brain cortex.**" (*Ohia SE, Awe SO, LeDay AM, Opere CA, Bagchi D. Effect of hydroxycitric acid on serotonin release from isolated rat brain cortex. Res Commun Mol Pathol Pharmacol. 2001 Mar-Apr;109(3-4):210-6.*)

¹⁵ **"The weight-loss efficacy of a novel, water-soluble, calcium-potassium salt of (-)-hydroxycitric acid (HCA-SX) was re-examined in 90 obese subjects (BMI: 30-50.8 kg/m²).** We combined data from two previously reported randomized, double-blind, placebo-controlled clinical studies in order to achieve a better statistical evaluation based on a larger population. This re-examination of data also allowed us to reflect more intensely on various aspects of weight loss studies. **Subjects were randomly divided into three groups: group A received a daily dose of HCA-SX 4,667 mg (providing 2,800 mg HCA per day); group B was given a daily dose of a combination of HCA-SX 4,667 mg, niacin-bound chromium (NBC) 4 mg (providing 400 microg elemental chromium), and *Gymnema sylvestre* extract (GSE) 400 mg (providing 100 mg gymnemic acid); and group C received a placebo in three equally divided doses 30-60 min before each meal.** All subjects were provided a 2,000 kcal diet/day and participated in a supervised walking program for 30 min/day, 5 days/week. Eighty-two subjects completed the study. At the end of 8 weeks, in group A, both body weight and BMI decreased by 5.4%, low-density lipoprotein and triglycerides levels were reduced by 12.9% and 6.9%, respectively, while high-density lipoprotein levels increased by 8.9%, serum leptin levels decreased by 38%, serotonin levels increased by 44.5% and urinary excretion of fat metabolites increased by 32-109%. Group B demonstrated similar beneficial changes, but generally to a greater extent. No significant adverse effects were observed. **The combined results confirm that HCA-SX and, to a greater degree, the combination of HCA-SX plus NBC and GSE reduce body weight and BMI, suppress appetite, improve blood lipid profiles, increase serum leptin and serotonin levels and increase fat oxidation more than placebo.** We conclude that dosage levels, timing of administration, subject compliance and bioavailability of HCA-SX significantly affect results and that when taken as directed, HCA-SX is a highly effective adjunct to healthy weight control." (*Preuss HG, Garis RI, Bramble JD, Bagchi D, Bagchi M, Rao CV, Satyanarayana S. Efficacy of a novel calcium/potassium salt of (-)-hydroxycitric acid in weight control. Int J Clin Pharmacol Res. 2005; 25(3):133-44.*)

¹⁶ **"*Garcinia cambogia*-derived (-)-hydroxycitric acid (HCA) is a safe, natural supplement for weight management. HCA is a competitive inhibitor of ATP citrate lyase, a key enzyme which facilitates the synthesis of fatty acids, cholesterol and triglycerides.** Previous studies in our laboratories have demonstrated the superior bioavailability of a novel calcium-potassium salt of HCA derived from *Garcinia cambogia* (HCA-SX, Super CitriMax). Greater bioavailability of HCA-SX was observed when taken on an empty stomach. **HCA-SX was also shown to exhibit concentration-dependent release of serotonin in isolated rat brain cortex, which may explain its appetite suppressive action.** Acute oral, acute dermal, primary dermal irritation, primary eye irritation and 90-day chronic toxicity studies, as well as Ames bacterial reverse mutation and mouse lymphoma tests, were assessed to determine the safety of HCA-SX. In the 90-day toxicity study, dose- and time-dependent effects of HCA-SX were assessed on body weight, selected organ weights, hepatic and testicular lipid peroxidation and DNA fragmentation, hematology and clinical chemistry, and histopathology in male and female Sprague-Dawley rats. No remarkable toxicity results were detected, demonstrating the safety of HCA-SX. Furthermore, **clinical studies to evaluate the safety and efficacy of HCA-SX over a period of eight weeks were conducted in 60 human volunteers. Subjects were given a 2,000 kcal diet/day, participated in a 30 min walking exercise program 5 days/week and given an oral dose of placebo or 4666.7 mg HCA-SX (providing 2,800 mg HCA) in three equally divided doses 30-60 min before meals,** Body weight, BMI, lipid profiles, serum leptin, serotonin and excretion of urinary fat metabolites were determined at 0, 4 and 8 weeks of treatment. **At the end of 8 weeks, body weight and BMI decreased by 5.4% and 5.2%, respectively. Food intake, total cholesterol, LDL, triglycerides and serum leptin levels were significantly reduced, while HDL and serotonin levels, and excretion of**

Cromo (un oligolemento che influisce positivamente sul metabolismo glucidico), alla Carnitina (un aminoacido che il corpo utilizza per convertire i grassi in energia)¹⁷ o ad altri fitocomplessi attivi sulla riduzione del peso come p.e. il Glucomannano^{18,19}.

Attività ipolipemizzante. L'acido (-)-idrossicitrico (HCA) interferisce con la sintesi endogena degli acidi grassi in quanto è in grado di abbassare indirettamente la quantità di Acetil-CoA utilizzato come substrato per la biosintesi degli acidi grassi e del colesterolo. L'inibizione dell'enzima ATP-citrato liasi può pertanto portare ad una diminuzione del flusso di atomi di carbonio durante la biosintesi del colesterolo. In questo modo i recettori per le LDL risultano più attivi, captando una maggiore quantità di lipoproteine LDL e diminuendo così la loro concentrazione nel circolo ematico. Quindi, inibendo la citrato liasi – enzima deputato alla liberazione nel citoplasma cellulare dell'acetil-CoA proveniente dai mitocondri e starter della liposintesi endogena – la *Garcinia cambogia* determina un effetto ipolipemizzante, particolarmente evidente sui trigliceridi ematici. La droga è tuttavia anche in grado di ridurre moderatamente la colesterolemia.

Molte condizioni di ipertrigliceridemia sono in effetti determinate da una aumentata sintesi di trigliceridi e lipoproteine VLDL a livello epatico, specialmente nel soggetto obeso. Sperimentalmente, è stato dimostrato che il trattamento con acido (-)-idrossicitrico riduce la lipidosintesi epatica e, contemporaneamente, la trigliceridemia²⁰. Nei soggetti con obesità androide soprattutto, ciò

urinary fat metabolites (a biomarker of fat oxidation) significantly increased. No significant adverse effects were reported. These results demonstrate the safety, bioavailability and efficacy of HCA-SX in weight management." (*Preuss HG, Rao CV, Garis R, Bramble JD, Ohia SE, Bagchi M, Bagchi D. An overview of the safety and efficacy of a novel, natural(-)-hydroxycitric acid extract (HCA-SX) for weight management. J Med. 2004;35(1-6):33-48.*)

¹⁷ Yonei Y, Takahashi Y, Hibino S, Watanabe M, Yoshioka T. Effects on the Human Body of a Dietary Supplement Containing L-Carnitine and *Garcinia cambogia* Extract: A Study using Double-blind Tests. *J Clin Biochem Nutr.* 2008 Mar;42(2):89-103.

¹⁸ "Hydroxycitric acid (HCA), the main compound of *Garcinia cambogia* extract, is a competitive blocker of ATP-citrate-lyase, presenting a potential inhibition of fatty acid biosynthesis. Glucomannan fibers, abundant in *Amorphophallus konjac*, seem to reduce the absorption kinetics of dietary fat. Therefore, the aim of this double-blind randomized study was to evaluate the pharmacotherapeutic efficacy of standardized extracts of *G. cambogia* (52.4% HCA) plus *A. konjac* (94.9% glucomannan) in the treatment of obesity. Fifty-eight obese subjects (BMI 30.0-39.9 kg/m²) were assigned to the placebo group (n = 26) or the treatment group (n = 32); no dietary restrictions were applied. Over a 12-week period, subjects were given daily doses of either *Garcinia* (2.4 g) plus *Konjac* (1.5 g) or placebo prior to their main meals (3 times/day). Before the start of treatment, and every 4 weeks thereafter, the following were recorded: height, weight, circumferences and body composition, resting energy expenditure (REE), lipid profile and glucose levels. The treatment had no significant effect on anthropometric parameters, REE, triglycerides or glucose levels. However, a significant reduction was observed in total cholesterol (-32.0 +/- 35.1 mg/dL) and LDL-c levels (-28.7 +/- 32.7 mg/dL) in the treated group, the final levels being significantly lower than those of the placebo group (p = 0.008 and p = 0.020, respectively). The results obtained suggest that the treatment had a significant hypocholesterolemic effect, without influencing the anthropometric or calorimetric parameters tested." (*Vasques CA, Rossetto S, Halmenschlager G, Linden R, Heckler E, Fernandez MS, Alonso JL. Evaluation of the pharmacotherapeutic efficacy of *Garcinia cambogia* plus *Amorphophallus konjac* for the treatment of obesity. Phytother Res. 2008 Sep;22(9):1135-40.*)

¹⁹ Yonei Y, Takahashi Y, Hibino S, Watanabe M, Yoshioka T. Effects on the Human Body of a Dietary Supplement Containing L-Carnitine and *Garcinia cambogia* Extract: A Study using Double-blind Tests. *J Clin Biochem Nutr.* 2008 Mar;42(2):89-103.

²⁰ "These studies were designed to determine whether genetically and experimentally induced hypertriglyceridemia were correlated with hyperlipogenesis, and whether inhibiting fatty acid synthesis would reduce serum triglyceride levels... Zucker

potrebbe comportare una significativa riduzione del rischio di malattia cardiovascolare²¹. Uno studio in vitro ha dimostrato che la garcinia inibisce l'accumulo citoplasmatico di lipidi e la differenziazione in senso adipogenico dei preadipociti. Il meccanismo che regola l'inibizione della differenziazione insulino indotta da parte della Garcinia include l'inibizione dell'espressione di un fattore trascrizionale precoce adipogenico, il CCAAT element binding protein (C/EBP)alpha che regola l'adipogenesi²². Alcuni composti isolati dal frutto della *Garcinia cambogia*, quali garcinolo e guttiferone K, hanno inoltre dimostrato una buona attività antiossidante nei confronti della perossidazione lipidica su piastrine e plasma umano²³ nonché una interessante azione antiinfiammatoria²⁴.

obese rats demonstrated significantly increased rates of fatty acid synthesis and levels of serum triglycerides compared to their lean litter mates; **lipogenic rates and circulating triglycerides were reduced markedly by the oral administration of (-)-hydroxycitrate**. Fructose administered in the diet or drinking water induced a hypertriglyceridemia which was associated with a marked increase in hepatic lipogenesis, and (-)-hydroxycitrate reduced significantly both parameters... (-)-Hydroxycitrate reduced serum triglyceride levels and hepatic lipogenic rates equivalently in the Triton-treated and nontreated rats." (Sullivan AC, Triscari J, Spiegel JE. *Metabolic regulation as a control for lipid disorders. II. Influence of (-)-hydroxycitrate on genetically and experimentally induced hypertriglyceridemia in the rat. Am J Clin Nutr* 1977; 30: 777-84).

²¹ "It should be obvious from the foregoing discussion that, at the present time, there is not an acceptably safe and effective pharmacological treatment for obesity. This patent inadequacy of present drug regimens has spawned the investigation into the diverse pharmacological approaches reviewed in this paper as well as investigation into the intestinal bypass operation (see Chapter 10). We feel that the eventual, safe and effective therapy for obesity will come from the pharmacological realm. **Glucose-blocking drugs, growth hormone analogues, and hydroxycitrate are three of the potentially safe and effective approaches to the problem for the future.** It will be truly fascinating to watch the development in the treatment of obesity and, specifically, the pharmacological treatment for this problem over the next five to ten years." (Bray GA, Greenway FL. *Pharmacological approaches to treating the obese patient. Clin Endocrinol Metab* 1976; 5: 455-79).

²² "It Garcinia extract was used as a potential anti-obesity agent. In this study, we found that **Garcinia extract inhibits the cytoplasmic lipid accumulation as well as adipogenic differentiation of preadipocytes.** The mechanisms that regulate the inhibition of insulin-induced differentiation by Garcinia extracts include the inhibition of expression of the early adipogenic transcription factor, CCAAT element binding protein (C/EBP)alpha that regulate adipogenesis. **These results suggest that the specific targets of Garcinia extract on differentiation process of 3T3-L1 cells could be, at least, early adipogenic differentiation factor.**" (Kim MS, Kim JK, Kwon DY, Park R. *Anti-adipogenic effects of Garcinia extract on the lipid droplet accumulation and the expression of transcription factor. Biofactors.* 2004; 22(1-4):193-6).

²³ "**The effects of garcinol and guttiferone K, two polyisoprenylated benzophenones occurring a food plant called Garcinia cambogia, on oxidative/nitrative protein damage (determined by parameters such as levels of protein carbonyl groups and nitrotyrosine residues) in human blood platelets and plasma after treatment with peroxynitrite (ONOO(-)) were studied in vitro. We also investigated the effects of garcinol and guttiferone K on lipid peroxidation in blood platelets and plasma induced by ONOO(-) (100 microM).** Exposure of blood platelets or plasma to peroxynitrite (100 microM) resulted in an increased level of carbonyl groups and nitrotyrosine residues in proteins, and an increase of lipid peroxidation measured by the level of thiobarbituric acid reactive species (TBARS). In the presence of garcinol and guttiferone K (0.1-25 microg/ml), a distinct reduction in the formation of carbonyl groups in plasma and platelet proteins together with the decrease of TBARS caused by 100 microM peroxynitrite, was observed. However, garcinol and guttiferone K did not inhibit plasma and platelet protein nitration induced by peroxynitrite. **Polyisoprenylated benzophenones present in human diet such as garcinol or guttiferone K in vitro have protective effects against lipid and protein oxidation and may have some promising effects in vivo because they are good antioxidants in the tested models in vitro. Garcinol and guttiferone K can be also useful as protecting factors against diseases associated with oxidative stress.**" (Kolodziejczyk J, Masullo M, Olas B, Piacente S, Wachowicz B. *Effects of garcinol and guttiferone K isolated from Garcinia cambogia on oxidative/nitrative modifications in blood platelets and plasma. Platelets.* 2009 Nov;20(7):487-92).

²⁴ "**Garcinol (camboginol) from the fruit rind of Guttiferae species shows anti-carcinogenic and anti-inflammatory properties, but the underlying molecular mechanisms are unclear. Here we show that garcinol potently interferes**

Attività ipoglicemizzante. Durante l'esercizio fisico prolungato è essenziale mantenere adeguati livelli di glucosio nel sangue, e ciò viene ottenuto soprattutto tramite la gluconeogenesi a livello epatico. Una scarsa gluconeogenesi causa infatti progressivo abbassamento della glicemia, con conseguente ipoglicemia ed esaurimento muscolare. La somministrazione di *Garcinia cambogia* prima dello sforzo muscolare, stimolando la gluconeogenesi, potrebbe quindi migliorare l'utilizzazione dei glicidi nelle cellule muscolari durante un esercizio fisico prolungato²⁵. Questo effetto – che sembra anch'esso mediato dall'acido(-)-idrossicitrico – può contribuire significativamente a migliorare i risultati dei programmi fisici (camminate, jogging, ecc), mirati al controllo o alla riduzione del peso corporeo nei soggetti in sovrappeso. Uno studio clinico controllato ha valutato l'effetto dell'acido idrossicitrico sulla performance sportiva di un gruppo di donne non allenate. Sono state arruolate 6 donne apparentemente sane, che ricevevano per os 250 mg/die di acido idrossicitrico o un placebo per 5 giorni, al termine dei quali venivano sottoposte a sforzo fisico massimale al cicloergometro. Si è visto che le donne trattate con l'acido idrossicitrico avevano un significativo ($p < 0,05$) prolungamento dello sforzo prima dell'esaurimento, con una riduzione del respiratory exchange ratio e dell'ossidazione dei carboidrati. I risultati di questo studio indicano che l'acido idrossicitrico

with 5-lipoxygenase (EC 7.13.11.34) and microsomal prostaglandin (PG)E₂ synthase (mPGES)-1 (EC 5.3.99.3), enzymes that play pivotal roles in inflammation and tumorigenesis. In cell-free assays, garcinol inhibited the activity of purified 5-lipoxygenase and blocked the mPGES-1-mediated conversion of PGH₂ to PGE₂ with IC₅₀ values of 0.1 and 0.3 microM, respectively. Garcinol suppressed 5-lipoxygenase product formation also in intact human neutrophils and reduced PGE₂ formation in interleukin-1beta-stimulated A549 human lung carcinoma cells as well as in human whole blood stimulated by lipopolysaccharide. Moreover, garcinol interfered with isolated cyclooxygenase (COX)-1 (EC 1.14.99.1, IC₅₀ = 12 microM) and with the formation of COX-1-derived 12(S)-hydroxy-5-cis-8,10-trans-heptadecatrienoic acid and thromboxane B₂ in human platelets. In contrast, neither Ca²⁺-ionophore (A23187)-induced arachidonic acid release in neutrophils nor COX-2 activity in A549 cells or whole blood, measured as formation of 6-keto PGF₁alpha, or isolated human recombinant COX-2 were significantly affected by garcinol (< or = 30 microM). **Together, the high potency of garcinol to selectively suppress PGE₂ synthesis and 5-lipoxygenase product formation provides a molecular basis for the anti-inflammatory and anti-carcinogenic effects of garcinol and rationalizes its therapeutic use.**" (Koeberle A, Northoff H, Werz O. Identification of 5-lipoxygenase and microsomal prostaglandin E₂ synthase-1 as functional targets of the anti-inflammatory and anti-carcinogenic garcinol. *Biochem Pharmacol.* 2009 May 1;77(9):1513-21).

²⁵ "Owing to a substantial increase in glucose uptake by working muscle, glucose homeostasis during sustained aerobic exercise requires a severalfold increase in hepatic glucose output... **Pre-administration of (-)-hydroxycitrate, a potent inhibitor of citrate lyase found in fruits of the genus *Garcinia*, may aid endurance during post-absorptive aerobic exercise by promoting gluconeogenesis.**" (McCarty MF. Inhibition of citrate lyase may aid aerobic endurance. *Med Hypotheses* 1995; 45: 247-54).

umenta il metabolismo dei grassi e la resistenza allo sforzo fisico^{26,27}.

Tollerabilità. In base agli studi tossicologici esistenti, l'estratto secco ottenuto dall'epicarpo del frutto di *Garcinia cambogia* non presenterebbe alcuna tossicità^{28,29}.



²⁶ “(-)-Hydroxycitric acid (HCA) is a competitive inhibitor of the enzyme ATPcitrate-lyase, which inhibits lipogenesis in the body. Moreover, **HCA increases endurance exercise performance in trained mice and athletes**. However, had not been investigated in untrained animals and humans. Therefore, **we investigated the effects of short-term HCA ingestion on endurance exercise performance and fat metabolism in untrained women**. In two experiments designed as a double-blind crossover test, six subjects ingested 250 mg of HCA or placebo (same amount of dextrin) via capsule for 5 d and then participated in cycle ergometer exercise. They cycled at 40% VO₂max for 1 h and then the exercise intensity was increased to 60% VO₂max until exhaustion on day 5 of each experiment. **HCA tended to decrease the respiratory exchange ratio (RER) and carbohydrate oxidation during 1 h of exercise. In addition, exercise time to exhaustion was significantly enhanced (p<0.05). These results suggest that HCA increases fat metabolism, which may be associated with a decrease in glycogen utilization during the same intensity exercise and enhanced exercise performance.**” (Lim K, Ryu S, Nho HS, Choi SK, Kwon T, Suh H, So J, Tomita K, Okuhara Y, Shigematsu N. (-)-Hydroxycitric acid ingestion increases fat utilization during exercise in untrained women. *J Nutr Sci Vitaminol (Tokyo)*. 2003 Jun;49(3):163-7).

²⁷ “We have been interested in the ergogenic aid effects of food components and supplements for enhancing endurance exercise performance. For this purpose, **acute or chronic (-)-hydroxycitrate (HCA) ingestion might be effective because it promotes utilization of fatty acid as an energy source. HCA is a competitive inhibitor of the enzyme ATP: citrate lyase, thereby increasing inhibition of lipogenesis in the body**. Many researchers have reported that less body fat accumulation and sustained satiety cause less food intake.” (Lim K, Ryu S, Suh H, Ishihara K, Fushiki T. (-)-Hydroxycitrate ingestion and endurance exercise performance. *J Nutr Sci Vitaminol (Tokyo)*. 2005 Feb;51(1):1-7).

²⁸ Stohs SJ, Preuss HG, Ohia SE, Kaats GR, Keen CL, Williams LD, Burdock GA. No evidence demonstrating hepatotoxicity associated with hydroxycitric acid. *World J Gastroenterol*. 2009 Aug 28;15(32):4087-89.

²⁹ Lee KH, Lee BM. Evaluation of the genotoxicity of (-)-hydroxycitric acid (HCA-SX) isolated from *Garcinia cambogia*. *J Toxicol Environ Health A*. 2007 Mar 1;70(5):388-92.