Garcinia cambogia Extract

90045-23-1

OVERVIEW

This material was prepared for the National Cancer Institute (NCI) for consideration by the Chemical Selection Working Group (CSWG) by Technical Resources International, Inc. under contract no. N02-07007.

Garcinia cambogia extract came to the attention of the NCI Division of Cancer Biology in follow-up to a previous nomination of ephedra to the National Toxicology Program (NTP). Used alone or with other ingredients, *Garcinia cambogia* extract is marketed as an ephedra-free diet aid.

Although studies supporting its use have been published, no information supporting the safety of this product was identified in the available literature. Some distributors of dietary supplements containing *Garcinia cambogia* extract do not recommend its use for persons with diabetes or dementia, or for pregnant or lactating women. However, studies concerning these safety issues were not found in the available literature.

NOMINATION OF *GARCINIA CAMBOGIA* EXTRACT TO THE NTP

Based on a review of available relevant literature and the recommendations of the Chemical Selection Working Group (CSWG) on December 17, 2003, NCI nominates this substance for testing by the National Toxicology Program (NTP) and forwards the following information:

- The attached Summary of Data for Chemical Selection
- Copies of references cited in the Summary of Data for Chemical Selection
- CSWG recommendations to:

  (1) Evaluate the extract and the lactone for genetic toxicology,

  (2) Evaluate the extract for toxicity in a 90-day subchronic study,

  (3) Expand the toxicological review of this extract for the following endpoint: developmental toxicology.

PRIORITY

The CSWG suggested that the recommended testing be conducted with high priority.

COMMENTS

Garcinia cambogia is used for weight reduction, raising concerns about developmental endpoints, such as fetal size and ossification.

At least one member of the CSWG felt that a structure-activity analysis could be based on pure hydroxycitric acid.

Following the CSWG meeting in December 2003, important new information relevant to the assessment of *Garcinia cambogia* was published.

Using the preincubation method and doses of 492-5,000 µg/plate, Super CitriMax, a calcium/potassium-hydroxycitrate extract (HCA-SX) was not mutagenic in the presence or absence of metabolic activation in *Salmonella typhimurium* strains TA98 and TA102. HCA-SX-induced increases in the number of revertants in other strains (TA100 and TA1535 in the absence of metabolic activation and in strain TA1537 in the presence of metabolic activation). No dose relationship was observed. Tests in *S. typhimurium* using the plate incorporation method were negative (Soni *et al.*, 2004).

Shara and coworkers (2004) 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 for periods of up to 90 days. Histopathological evaluation was performed at 90 days. The animals were administered 0, 0.2, 2.0, and 5.0% HCA-SX in feed and were killed at 30, 60, or 90 days. A time-, but not dose-dependent increase in hepatic lipid peroxidation was observed. Under identical conditions, HCA-SX caused no effect on hepatic DNA fragmentation. Selected organ weights individually and as a percent 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 results. Histopathological evaluation of 26 tissue/organ sites showed no changes due to HCA-SX treatment with the exception of the gastric mucosa. The mucosa of the glandular stomach of one animal was atrophied and mineralizedl and foci of glandular dilatation were noted in a number of animals.

Rhabdomyolysis following the ingestion of weight-loss herbal medicine was reported in an otherwise healthy 54-year-old woman. Three hours after ingestion of a herbal medicine containing ma huang (12 mg ephedrine), guarana (190 mg), chitosan (250 mg), *Gymnena sylvestre* (100 mg), *Garcinia cambogia* (50% hydroxycitric acid) (50 mg), and chromium (200 mg), the patient suffered chest pain that continued for two hours and resolved gradually. Laboratory investigation showed the presence of rhabdomyolysis with peak serum creatine kinase (CK) of 1028 IU/L, which gradually decreased and normalized after the herbal medicine was discontinued. The role of hydroxycitric acid is uncertain (Mansi & Huang, 2004).

Citations to these three reports are included in the reference list and full articles are included in the attached references.

SUMMARY OF DATA FOR CHEMICAL SELECTION

CHEMICAL IDENTIFICATION

CAS Registry Number: 90045-23-1

Chemical Abstracts Service Name: *Garcinia cambogia* extract (ChemID, 2003)

Synonyms and Trade Names: Brindal Berry; Gamboge; Gorikapuli; Malabar Tamarind; Mangosteen; Uppagi (Drug Digest, 2003; HerbalProvider.com, 2003; Kalyx.com, 2003)

Chemical and Physical Properties:

Description: Off-white to pale brown powder (Siris Impex, 2003)

Solubility: Soluble in ethanol and water (MDidea, 2001)

Reactivity: Stable at room temperature in closed containers; incompatible with oxidizing agents; decomposes in carbon monoxide and carbon dioxide among other products (MDidea, 2001)

Technical Products and Impurities: *Garcinia cambogia* is a small- or medium-sized tree, with drooping branches and ovoid fruits, native to Southeast Asia. Several compounds have been isolated from certain species of *Garcinia*, including xanthones, xanthones derivatives, and (-)-hydroxycitric acid [CAS No. 27750-10-3]. (-)-Hydroxycitric acid is present in the pericarp of the fruit of *Garcinia cambogia* up to 30% by weight. Commercially available *Garcinia cambogia* extracts are prepared from the fruit rind and contain 50% (-)-hydroxycitric acid (Jena *et al*., 2002; Mattes & Bormann, 2000; Siris Impex, 2003).

Sigma-Aldrich (2002) offers *Garcinia cambogia* extract as the (-)-calcium threo-hydroxycitrate tribasic hydrate salt.

Garcinia cambogia extract powder (100%) and *Garcinia cambogia* extract liquid (100%), standardized to 50% and 30% of (-)-hydroxycitric acid, respectively, can also be obtained from Premier Specialties (Premier Specialties, 2003).

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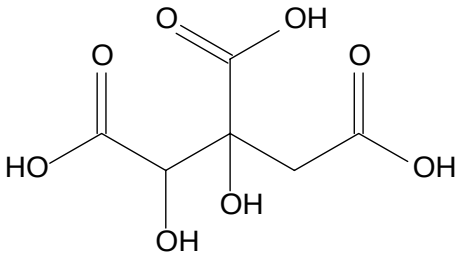
Among the components of the *Garcinia cambogia* extract, (-)-hydroxycitric acid exists as a free acid and as hydroxycitric acid lactone forms. The free acid form is considered to be biologically active. However, the free acid is unstable and is converted to its more stable lactone form. For consumer products, the free acid is often stabilized by forming salts of (-)-hydroxycitric acid (Majeed *et al*., 1998).



(-)-Hydroxycitric acid

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EXPOSURE INFORMATION

Production and Producers:

Manufacturing process: All procedures described in the available literature to obtain *Garcinia cambogia* extract were ultimately conducted to produce extracts with a high content of (-)-hydroxycitric acid.

(-)-Hydroxycitric acid extracts can be prepared from *Garcinia cambogia* rind by water extraction. The crude extract is loaded on an anion exchange column to adsorb (-)-hydroxycitric acid, and elution is carried out with sodium/potassium hydroxide. This fraction is then passed through a cation exchange column to yield the free acid. The final extract contains 54% (-)-hydroxycitric acid (Moffet *et al*., 1996).

Potassium or calcium salts of (-)-hydroxycitric acid extracts are generally known as *Garcinia cambogia* extracts and are used in consumer products. A method to produce the potassium salt of (-)-hydroxycitric acid extract involves the extraction of the fruit rind with methanol. This process is repeated several times. After the extracts are combined, they are treated with methanolic potassium hydroxide. The resulting precipitated potassium hydroxycitrate extract is filtered, dried under vacuum, and packed under a nitrogen blanket (Majeed *et al*., 1998).

Producers and importers: One US producer or distributor of *Garcinia cambogia* is listed by Chemical Sources International (2003).

According to a recent issue of a chemical buyer's directory, *Garcinia cambogia* extract is manufactured and/or distributed by Alchem International Ltd.; Ampak Co., Inc.; Barrington Chemical Corp.; Buckton Scott Nutrition, Inc.; CPB International, Inc.; Fabrichem, Inc.; Har-Met International Inc.; Indo German Alkaloids; International Sourcing Inc.; MDS Chemical Co.; M.M.P., Inc.; Pharmachem Laboratories, Inc.; Pharmed Medicare (P) Ltd.; Pharmline, Inc.; Paul Schueller International Inc.; Spectrum Chemical Mfg. Corp.; and Unibar Corp. (Tilton, 2002).

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Production/import/export level: *Garcinia cambogia* extract is not listed in the TSCA Inventory (ChemID, 2003).

Information on *Garcinia cambogia*, (-)-hydroxycitric acid extract, and *Garcinia cambogia* extract were combined to assess the import level of *Garcinia cambogia* extract. The Port Import/Export Reporting Service (PIERS) reported imports with a cargo weight of 497,540 pounds over the 41 month period from March 2000 to September 2003. Additional import entries of *Garcinia*-derived products were found in the PIERS database but were not included in this calculation (Dialog Information Services, 2003).

Use Pattern:

Dietary Supplement: *Garcinia cambogia* extract, used alone or in combination with other ingredients, is marketed as a dietary aid that suppresses the appetite, inhibits the synthesis of lipids, and burns fat via thermogenesis (HerbalProvider.com, 2003; InterHealth, 2003).

Over 50% of the US population is overweight and about 25% of the US population is obese. In a recent survey, 42% of US adults reported that they had tried one or more forms of alternative medicine in 1997 and it is estimated that 38% of women and 24% of men are trying to lose weight at any point in time (Allison *et al.*, 2001; Williamson & Bowman, 2001).

Several limited clinical trials studying the effectiveness of *Garcinia cambogia* extract on weight loss have produced contradictory results. Supporting evidence for its efficacy is largely based on studies with small sample sizes, without placebo-treated groups or with inaccurate measures of body lipid changes. A 12-week, randomized, double-blind, placebo-controlled trial was conducted in 42 subjects that received 3,000 mg of *Garcinia cambogia* extract per day. *Garcinia cambogia* extract failed to produce significant weight loss and fat mass loss beyond that observed with placebo (Heymsfield *et al.*, 1998).

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Another limited study reported that Super Citrimax™, an extract of *Garcinia cambogia* with a content of calcium/potassium salt of 60% (-)-hydroxycitric acid, increased serum serotonin levels and HDL cholesterol and lowered serum leptin levels, LDL cholesterol, and triglycerides in human subjects in an 8-week clinical trial (InterHealth, 2002).

Garcinia cambogia extracts are commonly added to weight loss supplements containing other ingredients, such as chromium picolinate and L-carnitine, and in appetite-suppressor products including snack bars, drinks, and chewing gums. In these products, the calcium salt of (-)-hydroxycitric acid is usually used (InterHealth, 2003; Springwater Beverages Ltd, 2003; Woodward, 2002).

Examples of products that contain *Garcinia cambogia* extracts are listed in Table 1.

Table 1. Consumer Products that Contain *Garcinia cambogia* extract

Product Name	Company	Description
Super Citrimax™	InterHealth	*Garcinia cambogia* extract standardized to 60% (-)-hydroxycitric acid.
Metabolife® Ephedra-Free	Metabolife	Tablets, 50 mg calcium (as hydroxycitrate and dicalcium phosphate), 150 mg chromium (as chromium picolinate), 60 mg sodium, 30 mg potassium, green tea extract, *Garcinia cambogia* extract, *Guarana* extract, yerba mate extract.
Garcinia 1,000	Nature's Life	Tablets, 1 g *Garcinia cambogia* rind concentrate (50% (-)-hydroxycitric acid)
Procuts	Sci-fit	Capsules, 2 g *Garcinia cambogia* (50% (-)-hydroxycitric acid), 334 mg ma huang extract (6% ephedra), 910 mg *Guarana* extract (22% caffeine), 150 mg white willow bark, 100 mg L-carnitine, and 300 mcg chromium picolinate.
Awe Slim	Now Foods	Liquid, 750 mg *Garcinia cambogia* extract (60% (-)-hydroxycitric acid), 750 mg L-carnitine, 500 mg arginine, 500 mg lysine, 500 mg ornithine & other ingredients.

Source: InterHealth, 2003; Metabolife, 2003; Nature's Life, 2003; Now Foods, 2003; Sci-fit, 2003

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Garcinia cambogia extract has been used traditionally in Indian medicine to treat tumors, ulcers, hemorrhoids, diarrhea, dysentery, fever, open sores, and parasites. It has been reported to be indicated for constipation, rheumatism, dyspepsia, obesity, and high levels of triglycerides and cholesterol (Duke *et al*., 2002; Mahendran & Shyamala Devi, 2001; Springwater Beverages Ltd, 2003; Tru Health, 2003).

Other Uses: *Garcinia cambogia* extracts are listed as a cosmetic raw material (Premier Specialties, 2003).

Garcinia cambogia is used as a condiment in southeastern Asia cuisine. The *Garcinia cambogia* fruit rinds are used to preserve fish as well (Drug Digest, 2003; Jena *et al*., 2002; Ohia *et al*., 2002; Springwater Beverages Ltd, 2003).

As of October 2003, a total of 35 patents that apply to *Garcinia cambogia* were filed with the US Patent and Trademark Office (USPTO) since 1976 (US Patents and Trademark Office, 2003).

Human Exposure:

Consumer Exposure: The primary exposure to *Garcinia cambogia* extract occurs through its use as an herbal supplement (Mattes & Bormann, 2000).

According to directions by distributors, the recommended daily dosage of *Garcinia cambogia* extract is 4,500-6,000 mg (InterHealth, 2003; Woodward, 2002).

Other potential sources of exposure include the use of cosmetics containing *Garcinia cambogia* extract, consumption of foods that utilize this substance as a culinary spice, or medications (Jena *et al*., 2002; Premier Specialties, 2003).

Environmental Occurrence: *Garcinia cambogia* extracts are produced from the *Garcinia cambogia* trees. This species is a member of the Guttiferae family (Nutritionfocus.com,

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2003). No other information was found in the available literature identifying *Garcinia cambogia* extract in the environment.

Regulatory Status:

No standards or guidelines have been set by the National Institute of Occupational Safety and Health (NIOSH) or the Occupational Safety and Health Administration (OSHA) for occupational exposure to or workplace allowable levels of *Garcinia cambogia* extract. *Garcinia cambogia* extract are not listed on the American Conference of Governmental Industrial Hygienists (ACGIH) list of compounds for which recommendations for a Threshold Limit Value (TLV) or Biological Exposure Index (BEI) are made.

Since 1994, dietary supplements have been regulated under the Dietary Supplement Health and Education Act (DSHEA). For dietary supplements on the market prior to October 15, 1994, the DSHEA requires no proof of safety in order for them to remain on the market. The labeling requirements for supplements allow warnings and dosage recommendations as well as substantiated "structure or function" claims. All claims must prominently note that they have not been evaluated by the FDA, and they must bear the statement "This product is not intended to diagnose, treat, cure, or prevent any disease" (FDA, 1995).

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TOXICOLOGY INFORMATION

Human Data:

No epidemiological studies or case reports investigating the association of exposure to *Garcinia cambogia* extract and cancer risks in humans were identified in the available literature.

According to distributor warning labels, the consumption of *Garcinia cambogia* extract is contraindicated in diabetic patients, subjects with Alzheimer's syndrome or any other dementia syndromes, and in pregnant and lactating women (Woodward, 2002).

The potential drug interactions of *Garcinia cambogia* extract described by distributors include interference with antiarrhythmics, nitrates, and calcium-channel blockers; antagonism of beta-adrenoreceptor blocking drugs; potentiation of cardiac glycosides; increased risk of hypokalemia; and risk of arrhythmia when combined with depolarizing muscle relaxants or terfenadine (Nutritionfocus.com, 2003).

Animal Data:

No 2-year carcinogenicity studies or subchronic toxicity studies of *Garcinia cambogia* extract in animals were identified in the available literature.

The LD_{50} values for an extract of *Garcinia cambogia* with a content of calcium/potassium salt of 60% (-)-hydroxycitric acid (Super Citrimax™) are given in Table 2.

Table 2. Acute Toxicity Values for *Garcinia cambogia* extract

Species	Route of administration	LD_{50} (mg/kg)
rat	gavage	> 5,000
rabbit	dermal	> 2,000

Source: Ohia *et al.*, 2002

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Garcinia cambogia extract (Super Citrimax™) was non-irritating to rabbits when given a single, 4-hour, semi-occluded exposure to 500 mg onto shaved intact skin (Ohia *et al*., 2002).

Garcinia cambogia extract (Super Citrimax™) was classified as a mild ocular irritant after a dose of 54 mg was instilled in the right eye of rabbits (Ohia *et al*., 2002).

Short-Term Tests:

No *in vitro* or *in vivo* studies evaluating *Garcinia cambogia* extract for mutagenic activity were found in the available literature.

Metabolism:

(-)-Hydroxycitric acid is the only component of the *Garcinia cambogia* extract for which pharmacokinetics has been studied.

Salts of (-)-hydroxycitric acid have been used in dietary supplements because this modification may increase the stability of (-)-hydroxycitric acid and prevent it from being converted into its lactone form. However, the calcium and magnesium salts of (-)-hydroxycitric acid are slightly soluble in aqueous media and, therefore, poorly absorbed in the gastrointestinal tract (Clouatre & Dunn, 2002).

Calcium and magnesium salts of (-)-hydroxycitric acid are broken down by bile acids and fats in the gut and become bound to fibers, pectins, or other substances in the diet or secreted during digestion (Clouatre & Dunn, 2002).

The peak plasma level of (-)-hydroxycitric acid was 8.4 µg/ml at two hours after the oral administration of 2 g of *Garcinia cambogia* extract (Super Citrimax™) to normal subjects, suggesting a limited efficiency of (-)-hydroxycitric acid absorption. (-)-Hydroxycitric acid was also detected in the urine (Loe *et al*., 2001).

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Other Biological Effects:

Effects on Insulin Metabolism: No differences in body weight were observed between two groups of female Std ddY mice that were fed either a high sucrose diet or the same diet with 3.3% *Garcinia cambogia* extract for 4 weeks. Serum insulin and leptin levels in treated mice were lower than those of control mice (Hayamizu *et al.*, 2003).

In Vitro Effects on Serotonin Levels: *Garcinia cambogia* extract (Super Citrimax™) increased the release of tritium-labeled serotonin from cultured brain cortex slices in a dose-dependent manner. The maximum release of serotonin was comparable to a response elicited by K^+ depolarizing stimuli (Ohia *et al*., 2001).

Anti-oxidant Properties: Administration of *Garcinia cambogia* extract (1 g/kg bw) to ethanol-treated male albino rats for 45 days inhibited the rise in lipid levels in both serum and liver tissue induced by ethanol and also prevented ethanol-induced peroxidative damage. The group given *Garcinia cambogia* extract and ethanol had levels similar to normalcy (non-treated animals) of total lipids and liver enzymes in the serum and liver, and of anti-oxidant enzymes, lipid peroxide, glutathione, and conjugated dienes in the liver (Mahendran & Shyamala Devi, 2001).

Rats pretreated with *Garcinia cambogia* extract at 1 g/kg bw, at days 7 and 15 prior to ulcer induction with hydrochloric acid and ethanol, significantly reduced the number of lesions and showed a decrease in lipid peroxidative damage in animals orally administered HCl and ethanol (Mahendran *et al*., 2002).

Structure Activity Relationships:

The structure-activity analysis generally performed for summary sheets is based on carcinogenicity and genotoxicity data for similar compounds. Such an analysis is not appropriate for *Garcinia cambogia* extract.

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