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ASSESSMENT REPORT GARCINIA CAMBOGIA

In this assessment report of Garcinia cambogia we i) characterize the preparations of the fruit, the phytochemical composition and traditional uses; ii) we summarize the safety; iii) we describe the mode of action and the intended use; and iv) mention the use recommendations. In annex you can find a few pictures and chemical structures of the phytochemicals of Garcinia species.

I. CHARACTERIZATION

The fruit rind of Garcinia gummi-gutta, commonly known as Garcinia cambogia, is extensively used traditionally as a flavoring in fish curries due to its sharp sour taste. Other ethnobotanical uses include its use as a digestive and a traditional remedy for bowel complaints, intestinal parasites and rheumatism. This small fruit, reminiscent of a pumpkin in appearance, is currently most popularly used and widely advertised as a weight-loss supplement.[1]

The use of dried fruits of *Garcinia gummi-gutta* (L.) Rob. has a documented long history of safe food use in India and several other countries. The safety of the food has been confirmed with compositional data and from experience of continued use for at least 25 years in the customary diet of a significant number of people in India and several other countries.

1. Name

1.1. Binomial scientific name of plant

Accepted binomial Latin name: *Garcinia gummi-gutta* (L.) Roxb

Family: *Clusiaceae* (also called *Guttiferae*)

Sub-Family: *Clusioideae*

Tribe: Garcinieae

Genera: *Garcinia*

Species: *Garcinia gummi-gutta* (L.) Roxb

Synonyms: *Garcinia cambogia* (Gaertn.) Desr., *Cambogia binucao* Blanco, *Cambogia gemmi-gutta* L., *Cambogia solitaria* Stokes, *Garcinia affinis* Wight & Arn.[2]

1.2. Common names

Indian berry, brindleberry, Malabar tamarind (EN); guttier (FR); Gummigutta, Malabar-Tamarinde (DE); tamarindo malabar (ES), guttegomboom (NL); tamaryndowiec malabarski (PL); garcinie kambodžská (CZ); malabar tamarind (DK); Kambodžas garsīnija (LV); vrsta garcinije (SL); kokam (IN).

2. Description of the herbal substance(s), herbal preparation(s) or combinations thereof

2.1. Plant and herbal substance

Garcinia gummi-gutta (L.) Roxb is one of several closely related *Garcinia* species from the plant family *Clusiaceae*.

Along the west coast of South India, Garcinia gummi-gutta is popularly termed "Malabar tamarind", and shares culinary uses with the tamarind (Tamarindus indica). The latter is a small and the former a quite large evergreen tree.

The fruit of *Garcinia gummi-gutta* and related species resembles a small pumpkin with a diameter ranging from 8 to 12 cm, comparable to an orange or grapefruit. The color can vary considerably from green to yellow, or sometimes dark red. When the rinds are dried and cured in preparation for storage and extraction, they turn dark brown or black in color (see pictures in Annex).

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1 Ruchi Badoni Semwal, Deepak Kumar Semwal, Ilze Vermaak, Alvaro Viljoen, A comprehensive scientific overview of Garcinia cambogia, Fitoterapia, Volume 102, 2015, p. 134-148, see http://www.sciencedirect.com/science/article/pii/S0367326X15000544

2 According to The Plant List: http://theplantlist.org/tpl1.1/record/kew-2816879

The Ayurvedic Pharmacopoeia of India[3] describes '*Dhārā Vṛkṣāmla*' which is the powdered dried fruits of *Garcinia gummi-gutta* (L.) Rob., a small tree, common in evergreen forests of Western ghats, from Konkan southwards to Travancore, and in the Shola forests of the Nilgiris up to an altitude of 1800 meter. The preparations contains not less than 5% hydroxycitric acid (HCA) and not less than 5% hydroxycitric acid lactone (HCAL) when assayed. This herbal substance is further described as follows:

a) Macroscopic: Fruits are ovoid, yellow or red when ripe and become black when dried. 6-8 grooves are seen up to the middle. Dried pieces of drug consists of longitudinal fragments of pericarp of various size and shapes strongly inwardly curved, boat or half-moon shaped, dark brownish black, wrinkled irregularly and internally smooth. Odor characteristic, taste sour, astringent and slightly bitter.

b) Microscopic: The transverse section of pericarp shows a layer of epicarp, composed of rectangular to tangentially elongated cells covered externally with thin cuticle; mesocarp very wide composed of 100 to 150 rows of parenchymatous cells of various size and shape which possess simple and compound starch grains and prismatic crystals of calcium oxalate; vascular bundles consists of phloem and xylem with spiral vessels, rectangular to irregular shaped parenchyma cells, traversing throughout the mesocarp but more prominently in inner zone of pericarp.

c) Powder: Shows isolated cells of mesocarp, containing dark reddish brown gummy exudates, prismatic crystals of calcium oxalate and starch grains; fragments of longitudinally cut spiral and annular vessels.

2.2. Herbal preparations

For preparations most often the fruit (exocarp) and the gum-resin is used.

The Ayurvedic Pharmacopoeia of India also describes the following two traditional derived preparations:

1) hydro-alcoholic extract of powdered dried fruits of Garcinia gummi-gutta: a dried and powdered extract prepared from the powdered dried fruits of *Garcinia gummi-gutta* (L.) Rob. The extract contains not less than 3% HCA and not less than 14% HCAL. The extract is prepared with 50% alcohol as solvent, three times the amount of raw material. The extract is then filtered, concentrated, dried, milled and sieved.
2) aqueous extract of powdered dried fruits of Garcinia gummi-gutta: dried and powdered extract prepared from powdered dried fruits of *Garcinia gummi-gutta* (L.) Rob. The extract contains not less than 6% HCA and not less than 20% HCAL. The extract is prepared with water, three times the amount of raw material. The extract is then filtered, concentrated, dried, milled and sieved.

All procedures described in the available literature to obtain Garcinia cambogia extract (GCE) 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. Potassium or calcium salts of (-)-hydroxycitric acid extracts are generally known as GCE and are used in consumer products. A method to produce the potassium salt of HCA 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 hydroxy citrate extract is filtered, dried under vacuum, and packed under a nitrogen blanket.[4]

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[3] Ayurvedic Pharmacopoeia of India, Part 1, Vol. 9, 2016. See https://kupdf.net/download/api-pt-i-vol-9_5904eb70dc0d601764959e98.pdf

[4] Document 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, see https://bit.ly/3qD3nOS

Salts of HCA have been used in food supplements because this modification may increase the stability and prevent it from being converted into its lactone form. However, the calcium and magnesium salts of HCA are slightly soluble in aqueous media and, therefore, poorly absorbed in the gastrointestinal tract.

3. Compositional data

Many Garcinia species contain flavonoids in the leaf, stembark, and heartwood. Lipids commonly are concentrated in the fruits and seeds. The rind of many Garcinia species often contains xanthones, a class of compounds related to flavonoids. The latex of Garcinia cambogia contains the benzenoids cambogin and garcinol (camboginol). HCA was identified as the principal acid in the highly acidic fruits of Garcinia cambogia and Garcinia indica[5] based on chemical and spectroscopic studies.[6,7,8] Besides organic acids, Garcinia fruits are also a rich source of anthocyanins and polyisoprenylated benzophenone derivatives like garcinol, camboginol, guttiferones and xanthochymol (structures see Annex I). HCA is a derivative of citric acid that is found in a variety of tropical plants including Garcinia cambogia and Hibiscus subdariffa. As is common in many citrus fruits, traces of succinic and tartaric compounds are found in the fruit of this species.

Nutritional values of Garcinia gummi-gutta fruits according to literature:

The rind of Garcinia gummi-gutta comprises of tannin (1.7%), pectin (0.9%), fat (1.4%), moisture (80%), protein (1%) and sugars (4.1%). The seed is an excellent source of stearic triglycerides, stearic and oleic acid. Also, the plant contains a minimal amount of citric and hydroxyl citric acid lactones.[9]

Phytochemical composition of the fruit according to literature:

- citric acids at 10-30% dry weight, of which a large part consists of hydroxycitric acids (HCA);[6] HCAs come in four isomers, (-)-hydroxycitric acid, (+)-hydroxycitric acid, (-)-allo-HCA, and (+)-allo-HCA;[1,10]
- polyisoprenylated benzophenones garcinol (camboginol)[11] and isogarcinol[12], xanthochymol and isoxanthochymol[13], guttiferone I, J, K, N and M[14,15];

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5 *Garcinia indica* (Thouars) Choisy, see http://theplantlist.org/tpl1.1/record/kew-2816906

6 Chemical formula: 3-C-Carboxy-2-deoxypentaric acid or 1,2-dihydroxy-1,2,3-propanetricarboxylic acid, CAS n° 6205-14-7

7 Lewis et al., Isolation and properties of hydroxycitric acid, Methods in Enzymology, Academic Press, Volume 13, 1969, p. 613-619. See http://www.sciencedirect.com/science/article/pii/0076687969130852

8 Lewis, Neelakantan, (-)-Hydroxycitric acid—the principal acid in the fruits of *Garcinia cambogia* desr., Phytochemistry. 1965;4:619–625, see https://www.sciencedirect.com/science/article/abs/pii/S003194220086224X

9 Vazhacharickal et al, Phytochemical profiling of Garcinia gummi-gutta (Malabar tamarind) and in vitro analysis of cholesterol lowering effect, 2017, Munich, GRIN Verlag, https://www.grin.com/document/370625

10 Márquez, et al. Evaluation of the safety and efficacy of hydroxycitric acid or Garcinia cambogia extracts in humans, Crit Rev Food Sci Nutr., 2012, 52(7):585-94, see https://pubmed.ncbi.nlm.nih.gov/22530711/

11 Chattopadhyay SK, Kumar S. A rapid liquid chromatography-tandem mass spectrometry method for quantification of a biologically active molecule camboginol in the extract of Garcinia cambogia. Biomed Chromatogr., Jan;21(1):55-66, 2007, see https://pubmed.ncbi.nlm.nih.gov/17080506/. Camboginol (CAS 78824-30-3)

12 N. Krishnamurthy, Y.S. Lewis, B. Ravindranath, On the structures of garcinol, isogarcinol and camboginol, Tetrahedron Letters, Volume 22, Issue 8, 1981, Pages 793-796, see http://www.sciencedirect.com/science/article/pii/0040403981801542

13 Sunil K. Chattopadhyay, Satyanshu Kumar, Identification and quantification of two biologically active polyisoprenylated benzophenones xanthochymol and isoxanthochymol in Garcinia species using liquid chromatography–tandem mass spectrometry, Journal of Chromatography B, Volume 844, Issue 1, 2006, Pages 67-83, http://www.sciencedirect.com/science/article/pii/S1570023206005587

14 Masullo M, et al. Polyisoprenylated benzophenones and an unusual polyisoprenylated tetracyclic xanthone from the fruits of Garcinia cambogia. J Agric Food Chem, 2008, Jul 9;56(13):5205-10, see https://pubmed.ncbi.nlm.nih.gov/18533663/

15 Kolodziejczyk J, et al. 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, see https://pubmed.ncbi.nlm.nih.gov/19852687/

- tetracyclic polyisoprenylated xanthones namely oxy-guttiferone I, K, K2 and M;[16]
- polyphenols, luteolin, and kaempferol;[17]
- low amounts of other organic acids like heterocyclic amines, tartaric acid, malic acid; and
- amino acids (e.g. arginine, asparagine, glutamine, threonine, glycine, proline, γ-aminobutyric acid, leucine, isoleucine, ornithine and lysine).[1,18]

4. Data from experience of continued use

4.1. Outside of the European Union

Garcinia cambogia, also known as Malabar tamarind, and known as Garcinia, is a plant native to Southeast Asia. The dried rind has been extensively used for centuries throughout Southeast Asia as a culinary spice, a food preservative, flavoring agent and carminative, and is now popularly used as an ingredient of food supplements for weight loss in developed countries. It was originally found only in the western peninsular coastal regions and the adjoining Western Ghats in the states of Maharashtra, Goa, Karnataka and Kerala, India as well as parts of Eastern India in the states of West Bengal, Assam and North Eastern Hill regions, but is today found growing in other parts of peninsular India

Various Garcinia plants have had a long history of human use in the traditional botanical medicine of India. Several other species of this genus are also listed in the Indian Materia Medica as therapies for a host of ailments.

Garcinia gummi-gutta is used in cooking, including in the preparation of curries. The fruit rind and extracts of Garcinia species are called for in many traditional recipes[19], and various species of Garcinia are used similarly in food preparation in (southern) India, Thailand, Malaysia, Burma, and other Southeast Asian countries. In the Indian Ayurvedic medicine, "sour" flavors are said to activate digestion. The extract and rind of Garcinia gummi-gutta is a curry condiment in India. It is an essential souring ingredient in the southern Thai variant of “kaeng som”, a sour curry.[20] Dried rinds are powdered and marketed to be used as acidulant for traditional curries. The Garcinia rinds are commercially used to prepare concentrated syrups which on appropriate dilution gives the ready to use cool health drinks. The local community of Goa also uses the rinds to prepare wine.[21]

The gum resins extracted from many genera within *Guttiferae* are used therapeutically in traditional medicine, especially as emetics and cathartics. The capsular fruits common to many of the genera in *Guttiferae* are covered by an astringent rind which, like the rinds of lemons and limes, is touted as a culinary spice as well as a remedy.

In addition to their healing virtues, some of the trees in *Guttiferae* are economically important as sources of timber and edible fruit. Although this species was not part of the traditional Ayurvedic medicine of ancient India, it has had widespread usage in the folk herbal healing of the Indian peasantry.

The astringent and antiseptic properties of the rind of Garcinia cambogia make it a useful ingredient in gargles for weak and spongy gums. In oral form, it is taken for stomach problems and chronic indigestion. The rind of the berry, the same part of the plant used as a condiment, is made into a tea for treating rheumatism and bowel complaints.

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16 Santo et al., Medicinal Potential of Garcinia Species and Their Compounds. Molecules 2020, 25, 4513, see https://www.mdpi.com/1420-3049/25/19/4513?type=check_update&version=1

17 Sulaiman, Balachandran, LC/MS characterization of phenolic antioxidants of Brindle berry (Garcinia gummi-gutta (L.) Robson), Natural Product Research, 2017, 31 (10): 1191–1194

18 Hargunani et al., Garcinia cambogia: an ancient fruit rind with recently discovered therapeutic activity, Journal of Medical Pharmaceutical and Allied Sciences, V 9-I 1, 892. March-April 2020, 2391-2397, https://jmpas.com/admin/assets/article_issue/1588008252JMPAS_MARCH_-APRIL_2020.pdf

19 Drury, Heber, Garcinia gambogia (Desrous) N.0. Clusiaceae, The Useful Plants of India, 1873, 2nd edition, p. 220

20 Sanitha Philip, Garcinea gummi-gutta -A Herbal Drug, Research Journal of Pharmaceutical, Biological and Chemical Sciences Pharmacological Review of Pazhampuli, see https://www.rjpbcs.com/pdf/2015_6(3)/[39].pdf

21 Rasha HM, Salha A, Thanai A, Zahar A (2015) The Biological Importance Of Garcinia Cambogia: A review. J Nutr Food Sci S5: 004, see https://www.researchgate.net/publication/299406036_The_Biological_Importance_Of_Garcinia_Cambogia_A_review

In addition a cross-cultural survey of the ethnomedical uses of Garcinia species shows that many trees and shrubs in this genus are used therapeutically (often for similar afflictions) in other parts of the world outside of South Asia.

Early scientific laboratory research conducted in India on Garcinia focused mainly on the species described in Ayurvedic medicine, including, for example, Garcinia indica (Garcinia purpurea) and Garcinia mangostana.

More recently, Indian scientists have begun investigating the effects of traditional Indian folk medicines used by rural and forest peoples. India is a vast country with considerable cultural heterogeneity. Certain folk medicinal plants, and the indigenous rationales for using them, lie outside of the canons of the medical beliefs upon which Ayurveda was founded. Some of the folk medicinal herbs used by the peasant classes were not used historically in Ayurveda. Today, however, Indian plant drug researchers have rediscovered that within the geographic boundaries of their historically rich nation is a wealth of unknown and potentially efficacious medicinal plants. By broadening their searches of Indian ethnobotany beyond those plants commonly associated with Ayurveda, Indian scientists have identified more botanical medicines about which they previously knew very little. Garcinia cambogia is one such plant.

Garcinia species are distributed widely throughout the Old world, especially Asia and Africa. In some cases, a related species of a well-known medicinal plant may contain an altogether unique compound, or it may have a higher concentration of a medicinally valuable constituent.

Garcinia cambogia is an example of a plant closely related to several important botanical species used in the traditional medicine of India. Chemists in India who had investigated different species of Garcinia reported the presence of hydroxycitrate in the rind of one species in particular, Garcinia cambogia. Aware of the chemists' finding on a natural analogue of citric acid, pharmacologists found that Garcinia cambogia provided an easily accessible source of this compound. Garcinia cambogia initially was recognized for its utility as a culinary spice. Pharmacological studies of this species were eventually launched because other Garcinia species were used in traditional Ayurvedic medicine. The outcome of this research was that an age-old food spice and folk herbal remedy found a novel application in a therapeutic, or nutritional, category for which it had not originally been used in traditional medicine.

Garcinia fruits are widely collected and commercially exploited for their medicinal value, and the fruit rinds of *Garcinia gummi-gutta* (L.) Roxb. are traditionally used to treat constipation, piles, rheumatism, oedema, irregular menstruation and intestinal parasites, and are also used as a food flavoring agent and preservative.[22]

4.2. Within the European Union

According to the Novel Food Catalogue the fruit of Garcinia cambogia is not considered to fall under the novel food regulation.[23]

II. SAFETY

1. APHA Botanical Safety Handbook

According to the APHA Botanical Safety Handbook[24], *Garcinia cambogia* (Gaertn.) Desr. has Safety Class 1, which means that it can be safely consumed when used appropriately and:

- History of safe traditional use;
- No case reports of significant adverse events with high probability of causality;
- No significant adverse events in clinical trials;
- No identified concerns for use during pregnancy or lactation;

[22] Semwal, R. B., Semwal, D. K., Vermaak, I. & Viljoen, A. A comprehensive scientific overview of Garcinia cambogia. Fitoterapia 102, 134–148, 2015.

[23] See https://ec.europa.eu/food/safety/novel_food/catalogue/search/public/index.cfm

[24] American Herbal Products Association's Botanical Safety Handbook, 2nd edition, 2013, CRC Press Taylor & Francis Group

- No innately toxic constituents;
- Toxicity associated with excessive use is not a basis for exclusion from this class; and
- Minor or self-limiting side effects are not bases for exclusion from this class.

The following characteristics are also listed:

- interaction Class: A;
- Contraindications: None known;
- Other Precautions: None known; and
- Drug and Supplement Interactions: None known.

This monograph also mentions that Garcinia fruit rind naturally contains approximately 16 to 26% HCA.[25,26] Much of the research on garcinia is focused on a standardized extract referred to as 'HCA-SX', an extract with 60% HCA.[27]

Adverse Events and Side Effects

Cases of liver toxicity have been reported in patients taking weight-loss products containing garcinia and other botanical and mineral ingredients.[28,29,30,31,32,33] The relationship between these cases and garcinia is not clear.[34]

Pregnancy and Lactation

Multigeneration animal studies have indicated no adverse effects of HCA-SX on pregnancy or fetal development.[35] No information on the safety of garcinia in lactation was identified in the scientific or traditional literature. While this review did not identify any concerns for use while nursing, safety has not been conclusively established.[36]

Drug and Supplement Interactions

- No clinical trials of drug or supplement interactions were identified.

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25 Antony, J.I.X., P.D. Josan, and M.L. Shankaranarayana. 1998. Quantitative analysis of (–)-hydroxycitric acid and (–)-hydroxycitric acid lactone in Garcinia fruits and Garcinia products. J. Food Sci. Technol. 35:399-402.

26 Jayaprakasha, G.K., and K.K. Sakariah. 1998. Determination of organic acids in Garcinia cambogia (Desr.) by high-performance liquid chromatography. J. Chromatogr. A 806(2):337-339.

27 Soni, M.G., G.A. Burdock, H.G. Preuss, et al. 2004. Safety assessment of (–)-hydroxycitric acid and Super CitriMax, a novel calcium/potassium salt. Food Chem. Toxicol. 42(9):1513-1529.

28 Actis, G.C., E. Bugianesi, A. Ottobrelli, and M. Rizzetto. 2007. Fatal liver failure following food supplements during chronic treatment with montelukast. Dig. Liver Dis. 39(10):953-955.

29 Dara, L., J. Hewett, and J.K. Lim. 2008. Hydroxycut hepatotoxicity: A case series and review of liver toxicity from herbal weight loss supplements. World J. Gastroenterol. 14(45):6999-7004.

30 Jones, F.J., and A.H. Andrews. 2007. Acute liver injury associated with the herbal supplement Hydroxycut in a soldier deployed to Iraq. Am. J. Gastroenterol. 102(10):2357-2358.

31 Shim, M., and S. Saab. 2009. Severe hepatotoxicity due to Hydroxycut: A case report. Dig. Dis. Sci. 54(2):406-408.

32 Stevens et al., Two patients with acute liver injury associated with use of the herbal weight-loss supplement Hydroxycut. Ann. Intern. Med., 2005, 142(6):477-478.

33 LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012. Garcinia Cambogia, see https://www.ncbi.nlm.nih.gov/books/NBK548087/

34 Stohs, S.J., H.G. Preuss, S.E. Ohia, et al. 2009. No evidence demonstrating hepatotoxicity associated with hydroxycitric acid. World J. Gastroenterol. 15(32):4087-4089.

35 Deshmukh, N.S. 2008b. Safety of a novel calcium/potassium salt of hydroxycitric acid (HCA-SX): I. Two-generation reproduction toxicity study. Toxicol. Mech. Meth. 18(5):433-442.

36 Deshmukh, N.S. 2008a. Safety of a novel calcium/potassium salt of (–)-hydroxycitric acid (HCA-SX): II. Developmental toxicity study in rats. Toxicol. Mech. Meth. 18(5):443-451.

- No case reports of suspected drug or supplement interactions were identified.
- No animal trials of drug or supplement interactions were identified.

Toxicity Studies

1) Acute Toxicity

The oral LD_{50} of garcinia extract (60% HCA) in rats could not be determined at doses up to 5 g/kg. The dermal LD_{50} of garcinia extract (60% HCA) in rabbits could not be determined at doses up to 2 g/kg.[37]

2) Short-Term Toxicity

In female rats fed diets containing 7.3% garcinia extract HCA-SX (41% HCA) for 2 or 4 weeks, no changes in reproductive hormones were observed.[38]

3) Subchronic Toxicity

In rats fed diets containing 0.2, 2, or 5% of a garcinia extract HCA-SX (60% HCA) for 90 days, an advancing age induced marginal increase in hepatic lipid peroxidation was observed as compared to control animals. No differences were observed in hematology, clinical chemistry, histopathological evaluation, hepatic DNA fragmentation, or testicular lipid peroxidation. Relative organ weights, including liver, testis, and brain, were comparable to the control group.[39,40]

In obese rats fed diets containing 0.5, 2.4, 4.9, or 7.3% (77, 388, 778, or 1244 mg/kg body weight HCA) garcinia extract for 92 days, animals on the 4.9% or higher diets had testicular atrophy and toxicity.[41] The design of this study has been questioned for accuracy as a test of testicular toxicity.[42]

In male rats fed diets containing 4.9% garcinia extract HCA-SX (41% HCA) for 2 or 4 weeks, a decrease in the serum level of inhibin B and increase in follicle-stimulating hormone was observed. The level of testis meiosis-activating sterol was statistically lower in the testes of rats on the garcinia diet as compared to control.[43]

In male rats orally administered 100 or 200 mg/kg of an ethanol extract of garcinia seed 6 days per week for 6 weeks, changes in the testes were observed along with an increase in sperm counts.[44]

4) Genotoxicity

In the micronucleus test with HCA intraperitoneally administered to mice at doses of 20, 100, 500, 2,500, or 12,500 µmol/kg, HCA was found to increase the number of micronucleated polychromatic erythrocytes (Lee and Lee 2007). A commentary on this study noted that the route of administration (intraperitoneal instead of oral) and the use of DMSO

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37 Ohia, S.E., C.A. Opere, A.M. LeDay, et al. 2002. Safety and mechanism of appetite suppression by a novel hydroxycitric acid extract (HCA-SX). Mol. Cell. Biochem. 238(1-2):89-103

38 Kiyose, C., K. Kubo, and M. Saito. 2006a. Effect of Garcinia cambogia administration on female reproductive organs in rats. J. Clin. Biochem. Nutr. 38(3):188-194

39 Shara, M., S.E. Ohia, R.E. Schmidt, et al. 2004. 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. 260(1-2):171-186.

40 Shara, M., S.E. Ohia, T. Yasmin, et al. 2003. Dose- and timedependent effects of a novel (−)-hydroxycitric acid extract on body weight, hepatic and testicular lipid peroxidation, DNA fragmentation and histopathological data over a period of 90 days. Mol. Cell. Biochem. 254(1-2):339-346.

41 Saito, M., M. Ueno, S. Ogino, et al. 2005. High dose of Garcinia cambogia is effective in suppressing fat accumulation in developing male Zucker obese rats, but highly toxic to the testis. Food Chem. Toxicol. 43(3):411-419.

42 Burdock, G., M. Soni, M. Bagchi, and D. Bagchi. 2005. Garcinia cambogia toxicity is misleading. Food Chem. Toxicol. 43(11):1683-1684; author reply 1685-1686.

43 Kiyose, C., S. Ogino, K. Kubo, M. Takeuchi, and M. Saito. 2006b. Relationship between Garcinia cambogia-induced impairment of spermatogenesis and meiosis-activating sterol production in rat testis. J. Clin. Biochem. Nutr. 38(3):180-187.

44 Oluyemi, K.A., O.R. Jimoh, O.A. Adesanya, et al. 2007. Effects of crude ethanolic extract of Garcinia cambogia on the reproductive system of male Wistar rats (Rattus novergicus). Afr. J. Biotechnol. 6(10):1236-1238.

as part of the treatment but not the control group were likely to produce results different than those seen after oral use of HCA.[45] No mutagenic activity of the compound (–)-hydroxycitric acid (HCA) was observed in the Ames test for mutagenicity with or without metabolic activation, or in the chromosomal aberration test.[46,47]

2. Literature review

With regard to toxicity and safety, it is important to note that except in rare cases, studies conducted in experimental animals have not reported increased mortality or significant toxicity. Furthermore, at the doses usually administered, no differences have been reported in terms of side effects or adverse events (those studied) in humans between individuals treated with Garcinia cambogia and controls.[48]

According one literature review, Garcinia cambogia reportedly does not have any known adverse effects in healthy adults, but there are some people who are advised not to take it. According to experts, this includes children, pregnant and lactating women, those diagnosed with diabetes mellitus, and people with Alzheimer's or other forms of dementia disease. In the case of Alzheimer's patients, it is thought HCA might form acetylcholine in the brain, while diabetics could be affected by HCA's tendency to lower blood sugar. Conversely, in healthy adults this latter effect can purportedly curb cravings for sweets and carbohydrates. It is advisable to discuss this with your health care professional.

According to the same review, various animal and human studies have been conducted on the safety of HCA. In summary, no serious or significant untoward effects were reported in any of those studies. All reported effects were comparable to placebo-treated animals and human subjects. Dose-dependent studies in animals assessed acute oral toxicity, as well as acute dermal toxicity, primary dermal irritation, and primary eye irritation. No gross toxicological findings were observed, and the authors concluded that HCA is safe under the experimental conditions employed.[18]

According to another review of 2012, a comprehensive safety profile of a Garcinia cambogia extract high in HCA (GCE) as food supplements for treating obesity has been established based on the results obtained in an array of toxicological and safety studies. Cytotoxicity study, genotoxicity study, acute toxicity studies (such as acute oral, acute dermal, primary dermal irritation, and primary eye irritation toxicity studies), sub-chronic 90-day safety study, two-generation reproductive and teratogenicity studies, and clinical studies on the GCE support its safety demonstrating a wide margin of safety for human consumption. Recent animal and clinical toxicology studies have shown that the GCE is generally safe and is classified as NOAEL up to 1240 mg/kg/day. In experimental animal studies at up to 233 times the human equivalency dose of HCA (1500 mg/day of HCA), toxicological studies revealed no death, remarkable body weight changes, or gross necropsy findings in Albino rats.

Furthermore, the fact that the GCE has been widely used as an anti-obesity herbal supplement for decades around the world without a birth defect or reproductive problem suggests that HCA is unlikely to cause reproductive or developmental toxicity. However, most randomized control trials have been conducted on small samples and mainly over a short term. None of them have shown whether the efficacy and safety of the GCE consumption persist beyond 12 weeks of intervention. Thus, more long term clinical trials or follow-ups could be conducted, especially on consumers who have been taking HCA for a long period of time to add value to the NOAEL for long-term consumption.[49]

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[45] Lau, F.C., M. Bagchi, and D. Bagchi. 2008. Refuting "Evaluation of the genotoxicity of (–)-hydroxycitric acid (HCA-SX) isolated from Garcinia cambogia." J. Toxicol. Environ. Health A 71(5):348-349.

[46] Aujoulat, M. 2003. Cited in Soni, M.G., G.A. Burdock, H.G. Preuss, S.J. Stohs, S.E. Ohia, and D. Bagchi. 2004. Safety assessment of (–)-hydroxycitric acid and Super CitriMax, a novel calcium/ potassium salt. Food Chem. Toxicol. 42(9):1513-1529.

[47] Lee, K.H., and B.M. Lee. 2007. Evaluation of the genotoxicity of (–)-hydroxycitric acid (HCA-SX) isolated from Garcinia cambogia. J. Toxicol. Environ. Health A 70(5):388-392.

[48] Márquez F, Babio N, Bulló M, Salas-Salvadó J. Evaluation of the safety and efficacy of hydroxycitric acid or Garcinia cambogia extracts in humans. Crit Rev Food Sci Nutr. 2012;52(7):585-94. See https://pubmed.ncbi.nlm.nih.gov/22530711/

[49] Chuah et al., In vitro and in vivo toxicity of garcinia or hydroxycitric Acid: a review, Evid Based Complement Alternat Med.;2012:197920. Epub 2012 Aug 9.

An ever increasing number of well-designed and appropriately controlled studies in animals and humans have indicated that HCA is both safe and efficacious.[50]

The potential drug interactions of the GCE 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 hypokalaemia; and risk of arrhythmia when combined with depolarizing muscle relaxants or terfenadine.[4]

Case reports

There are numerous case reports of hepatoxicity associated with a supplement known as 'Hydroxycut'.[51] Fifteen clinical studies involving approximately 900 patients documented very mild adverse reactions, with the most common adverse reactions including headache, dizziness, dry mouth, and gastro-intestinal complaints such as nausea and diarrhea. 'Hydroxycut' food supplements for weight loss were voluntarily recalled from the US market in 2009 because of concerns about hepatotoxicity. Although Garcinia cambogia was an ingredient in some formulations of 'Hydroxycut', its role in cases of hepatotoxicity associated with 'Hydroxycut' is unclear. Other cases of hepatotoxicity have been reported as "probably" related to ingestion of supplements containing Garcinia cambogia.

One study from 2018 presents four cases of acute liver failure in women taking a product with Garcinia cambogia extract for weight loss, and a literature review of clinical evidences about hepatic toxicity in patients taking food supplements containing GCE.[52,53]

One article describes the a case of fulminant hepatic failure associated with a food supplement with Garcinia. In this case the product contained 80 mg of a 5:1 extract of Garcinia cambogia equivalent to 400 mg of standard preparation. While evidence from a case report rarely offers indisputable proof of causality, this case, in conjunction with known cases of hepatotoxicity and liver failure associated with other Garcinia cambogia-containing supplements warrants a high index of suspicion. Conditions predisposing patients to liver toxicity associated with Garcinia cambogia and like products remain unidentified. Acute liver failure from supplement ingestion appears relatively rare compared to their widespread use. Certain patients may have genetic predisposition or pre-existing liver damage, compounding hepatotoxicity. While additional research is necessary to further identify the link between Garcinia Cambogia and severe liver damage, public warning to potentially deadly side effects is necessary.[54]

Some cases have been reported of acute pancreatitis secondary to the use of Garcinia cambogia. The pathogenesis of how such an increased risk of acute pancreatitis may occur is not clear; however, there is evidence that active oxygen species may play a central role in this pathogenesis. Garcinia cambogia increases lipidic peroxidation and positively regulates the expression of superoxide dismutase and glutathione peroxidase messenger ribonucleic acid (RNA). Lipidic peroxidation also increases oxidative stress and can increase the risk of acute pancreatitis in patients using the species. Garcinia cambogia can cause other severe adverse events, including hepatoxicity and secondary acute hepatic insufficiency. Other studies have also shown acute necrotizing eosinophilic myocarditis, rhabdomyolysis, serotonin toxicity, and nephropathy secondary to the use of Garcinia cambogia.[55]

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50 Sidney et al., Safety and Efficacy of Hydroxycitric Acid Derived from Garcinia cambogia – A Literature Review, HerbalGram. 2010; American Botanical Council, Issue: 85 Page: 58-63, see https://bit.ly/2VFJIQ2

51 Lobb A. Hepatoxicity associated with weight-loss supplements: a case for better post-marketing surveillance. World J Gastroenterol. 2009 Apr 14;15(14):1786-7. See https://pubmed.ncbi.nlm.nih.gov/19360927/

52 Crescioli, G., Lombardi, N., Bettiol, A. *et al.* Acute liver injury following *Garcinia cambogia* weight-loss supplementation: case series and literature review. Intern Emerg Med 13, 857–872 (2018). See: https://pubmed.ncbi.nlm.nih.gov/29802521/

53 Jiten P. Kothadia, Monica Kaminski, Hrishikesh Samant, Marco Olivera-Martinez, "Hepatotoxicity Associated with Use of the Weight Loss Supplement Garcinia cambogia: A Case Report and Review of the Literature", Case Reports in Hepatology, vol. 2018, Article ID 6483605, 5 pages, 2018, https://www.hindawi.com/journals/crihep/2018/6483605/

54 Lunsford, Keri E et al. "Dangerous dietary supplements: *Garcinia cambogia*-associated hepatic failure requiring transplantation." *World journal of gastroenterology* vol. 22,45 (2016): 10071-10076, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5143754/

55 Santo et al., Medicinal Potential of Garcinia Species and Their Compounds. Molecules 2020, 25, 4513, see https://www.mdpi.com/1420-3049/25/19/4513?type=check_update&version=1

Identification and quantification of adulteration

A study of 2016 to develop and validate an accurate and efficient method for the detection of any adulteration in Garcinia cambogia products. For this purpose, high performance liquid chromatography (HPLC) was used to analyze the ethanolic fruit rind extracts of Garcinia cambogia, Garcinia indica, their formulations, and eleven commercial products. The analytical methods were validated by quality assurance parameters of linearity, sensitivity, precision and accuracy. Two marker peaks were detected in Garcinia indica fruit extract, whereas Garcinia cambogia did not show these peaks. The detected peaks were identified as anthocyanins; cyanidin-3-O-sambubioside and cyanidin-3-O-glucoside. From this study, it was found that the HPLC method used for the detection of adulteration in Garcinia cambogia products is rapid and accurate.[56]

Another article describes a rapid, simple and efficient method with minimal sample treatment for authentication of Garcinia cambogia fruit peel powder, along with determining undeclared active pharmaceutical ingredients (APIs) in its herbal slimming food supplements using near infrared spectroscopy combined with chemometrics. The Near infrared spectral data matrix of authentic Garcinia cambogia fruit peel and specimens degraded by intentional contamination with the five selected APIs was subjected to hierarchical clustering analysis to investigate their bundling figure. The suggested approach can be applied to enhance and guarantee the safety and quality of Garcinia fruit peel powder as raw material and in dietary supplements.[57]

III. MODE OF ACTION AND INTENDED USES

1. Literature

The leaves and fruits are described as sour, astringent, thermogenic, constipating and digestive. The herbal preparations made from Garcinia rinds are traditionally used in the treatment of inflammatory ailments, for rheumatic pains and bowel complaints. The fruit is considered to be anthelmintic and cardiotonic. The juice from the rind is used for piles, hemorrhoids, colic problems, ulcers, inflammations, treat sores, dermatitis, diarrhea, dysentery, ear infection, to facilitate digestion and to prevent over perspiration or hyper perspiration. Garcinia is a natural antacid and the preparation of the rind, yogurt and salt is supposed to relieve gastric ulcerations and burning sensation. Garcinia butter has been proven useful in dysentery, diarrhea, phthisis pulmonalis and scorbutic disease.[18] The Ayurvedic Pharmacopoeia of India mentions the therapeutic uses for digestive impairment, piles, and constipation.

Garcinia has also been historically used to treat gastric ulcers. Garcinol is known to lower acidity in the stomach and protects the gastric mucosa. The rind of garcinia cambogia is also astringent, which is why it was also historically used in the treatment of diarrhea and dysentery as well as having the added benefit in the treatment of gastric and duodenal ulcers. Several studies have been done regarding reduction of blood lipid and cholesterol levels. More recently, it has been proposed that Garcinia cambogia has a hepato-protective ability against external toxins, such as alcohol. A recent study showed that Garcinia prevented liver cells from becoming fibrotic and stopped cell damage caused by high blood lipid levels.[18]

The main use of products with Garcinia preparations is for weight loss through fat loss (i.e. increased fat oxidation, and regulation of endogenous lipid biosynthesis[58]) and appetite reduction. HCA appears to be a competitive inhibitor of the enzyme ATP citrate lysase[59], which is an enzyme in the biosynthetic pathway of fatty acids (de novo lipogenesis) and its inhibition results in suppressed formation of acetyl-CoA from citrate and less substrate for fatty acid synthesis

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[56] Jamila et al., Identification and quantification of adulteration in Garcinia cambogia commercial products by chromatographic and spectrometric methods, Food Additives & Contaminants: Part A, 2016, 33. 1751-1760, see https://bit.ly/2W3u559

[57] Selim et al., Detection and quantification of active pharmaceutical ingredients as adulterants in Garcinia cambogia slimming preparations using NIR spectroscopy combined with chemometrics, Records of Pharmaceutical and Biomedical Sciences, Article 8, Volume 4, Issue 1, Winter and Spring 2020, Page 62-71, see https://journals.ekb.eg/article_74421.html

[58] Rajinder et al., Chapter 48 - Garcinia cambogia, Nutraceuticals, 2016, Pages 669-680, see http://www.sciencedirect.com/science/article/pii/B9780128021477000486

[59] Watson JA, Lowenstein JM. Citrate and the conversion of carbohydrate into fat. Fatty acid synthesis by a combination of cytoplasm and mitochondria. J Biol Chem., 1970, see https://pubmed.ncbi.nlm.nih.gov/5484459/

in vitro.[60] The (+)- isomer of hydroxycitric acid does not have this same inhibitory potential, and is instead a substrate of the enzyme. Other studies mention that HCA can increase fat metabolism, which may be associated with a decrease in glycogen utilization during the same intensity exercise and enhanced exercise performance.[61]

Another study showed that the GCE presented hypolipidemic[62], antiadipogenic, and appetite-suppression effects in experimental animals through the inhibition of the expression of the early adipogenic transcription factor CCAAT enhancer-binding protein alpha, which regulates adipogenesis. The hypolipidemic effect of the GCE has been attributed to its high content of flavonoids.[50]
A recent systematic review and dose-response meta-analysis of 2020 was executed to determine the effect of Garcinia cambogia supplement on the obesity indices in human randomized controlled trials. The supplement had a significant effect on body weight, body mass index, percentage of fat mass, and waist circumference. There was a non-linear association between Garcinia cambogia dosage and changes in the weight and BMI.

The polyisoprenylated benzophenone and xanthone derivatives (i.e. garcinol, camboginol, guttiferones and xanthochymol) are known for their antioxidant, anti-inflammatory, antibacterial, anti-viral, anti-fungal, anti-ulcer and anti-protozoal properties.

Other effects mentioned in the literature include:

- Effects on insulin metabolism: no differences in body weight were observed between two groups of female 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.
- In vitro effects on serotonin levels: a Garcinia cambogia extract increased the release of tritium-labelled 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. An increase in serotonin levels has been linked to appetite suppression in many studies.
- 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 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.
- Reduction of gastric ulcers: rats pre-treated 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.[4]

The above mentioned effects have been confirmed in different other studies and systematic reviews.[63,64,65,66, 67]

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60 Lowenstein JM., Effect of (-)-hydroxycitrate on fatty acid synthesis by rat liver in vivo, J Biol Chem., 1971, see https://pubmed.ncbi.nlm.nih.gov/5542676/

61 Lim et al., (-)-Hydroxycitric acid ingestion increases fat utilization during exercise in untrained women. J Nutr Sci Vitaminol (Tokyo). 2003 Jun;49(3):163-7, see https://pubmed.ncbi.nlm.nih.gov/12953793/

62 Chen, S.X.; Wan, M.; Loh, B.N. Active constituents against HIV-1 protease from Garcinia mangostana. Planta Med. 1996, 62, 381–382

63 Ventura et al., Short-term effects of Garcinia cambogia extract on the pharmacokinetics of lamotrigine given as a single-dose in Wistar rats, Food and Chemical Toxicology, Volume 128, 2019, Pages 61-67, see http://www.sciencedirect.com/science/article/pii/S0278691519301796

64 Maia-Landim et al., Long-term effects of Garcinia cambogia/Glucomannan on weight loss in people with obesity, PLIN4, FTO and Trp64Arg polymorphisms. BMC Complement Altern Med. 2018 Jan 24;18(1):26, see https://pubmed.ncbi.nlm.nih.gov/29361938/

65 Espirito Santo et al., Medicinal Potential of Garcinia Species and Their Compounds. Molecules 2020, *25*, 4513, see https://www.mdpi.com/1420-3049/25/19/4513

66 Badr AM, EL- Orabi NF, Ali RA (2019) The implication of the crosstalk of Nrf2 with NOXs, and HMGB1 in ethanol-induced gastric ulcer: Potential protective effect is afforded by Raspberry Ketone. PLoS ONE 14(8): e0220548. https://doi.org/10.1371/journal.pone.0220548

67 Chuah LO, Ho WY, Beh BK, Yeap SK. Updates on Antiobesity Effect of Garcinia Origin (-)-HCA. Evid Based Complement Alternat Med. 2013;2013:751658. doi: 10.1155/2013/751658. Epub 2013 Aug 6. PMID: 23990846; PMCID: PMC3748738.

2. EFSA Claims evaluation

According to EFSA evaluation reports following claims are pending for the fruits of Garcinia Cambogia:

Health relationship	Proposed claim	Proposed conditions of use	Entry ID
Weight management, appetite	Contributes to weight management; Helps in weight control; Contributes to reduce fat storage; Reduces sense of appetite	The equivalent of 750 mg HCA per day	2057
metabolism of fats, management weight	helps to control body weigh helps to reduce sense of hunger and appetite for goodies helps to keep normal sugar and fat level in blood	500 mg HCA per day	2643
Lipids metabolism, Weight management & loss	HCA supresses the lipogenesis and their accumulating in the body, food intake, and induced weight loss	at least 100 mg/day	2651

IV. USE RECOMMENDATIONS

1. Recommended doses

The Ayurvedic Pharmacopoeia of India mentions a dose of 3-6 g of the powdered dried rind of the fruit.

The dosages of the GCE used in clinical trials ranged from 1,500 to 4,667 mg/day (25 to 78 mg/kg/day). The equivalent HCA dosage in the trials ranged from 900 to 2,800 mg/day (15 to 47 mg/kg/day).

Many commercially available products contain Garcinia cambogia in capsule or tablet form with an extract containing 50% HCA and with a maximum daily dosage of 1,500 mg. This dosage is often divided into three doses of 500 mg to be taken with water, 30' to 60' before meals to.

Taking the preparation on an empty stomach takes advantage of the appetite-curbing effect of Garcinia, whilst maximising bio-availability. Nutrient absorption can be further increased by adding a black pepper extract high in piperine, which inhibits key enzymes responsible for metabolising nutrients.

According to directions by distributors in the US, the recommended daily dosage of Garcinia cambogia extract is between 4,500-6,000 mg. Most products contain levels of HCA between 20 and 60%.[4]

2. Contraindications

According to some 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.[4,68,69]

[68] Drugs and Lactation Database (LactMed), Bethesda (MD): National Library of Medicine (US); 2006, Garcinia, See from: https://www.ncbi.nlm.nih.gov/books/NBK501896/

[69] See https://www.drugs.com/npp/garcinia-hydroxycitric-acid.html

V. ANNEX: Pictures

1. Garcinia tree

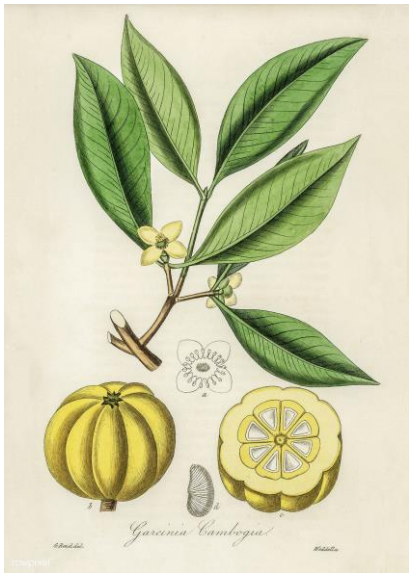
2. Garcinia fruits (green)

3. Garcinia fruits (yellow and green)

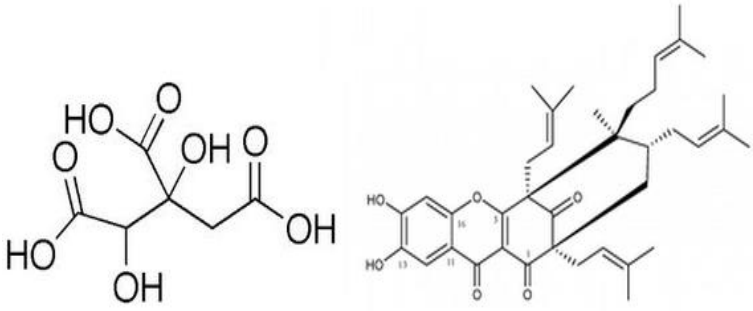
4. Garcinia fruits (red)

5. Garcinia fruits (dried)

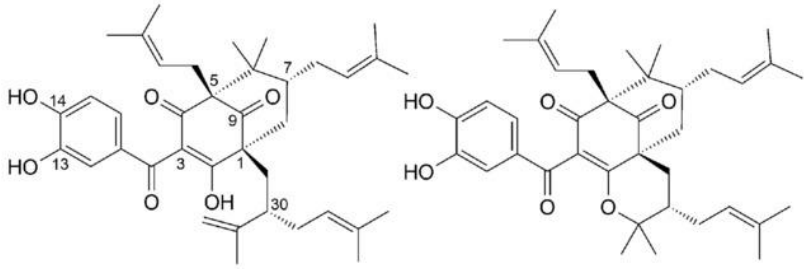
6. Botanical drawings



7. Chemical structures of hydroxycitric acid, guttiferone K



8. Chemical structures of garcinol and isogarcinol



9. Chemical structures of xanthochymol and isoxamthochymol