

Chapter 10

Phytochemicals and bioactivities of *Garcinia gummi-gutta* (L.) N. Robson- A review

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Abstract

Among the different *Garcinia* species, *G. gummi-gutta* is the most widely distributed *Garcinia* species in Kerala, south India. The fruit is used as culinary spice, preservatives and also as a source of several nutraceutical products. The phytochemical analysis of *G. gummi-gutta* revealed the presence of several bioactive molecules such as xanthenes, benzophenones and organic acids. The fruit contains 10% to 30% (-) hydroxycitric acid (HCA), a well known hypo-lipidemic agent and an important constituent of food supplement for weight management. The species is a rich source of the bioactive benzophenones camboginol (garcinol) and cambogin (isogarcinol). The present review summarises the traditional uses, phytochemicals and pharmacological activities of *G. gummi-gutta*.

Keywords: *Garcinia gummi-gutta*, Hydroxy citric acid, Benzophenones, Camboginol, Cambogin

Introduction

Garcinia is the largest genus of the Clusiaceae family comprising nearly 250 species. *Garcinia gummi-gutta* (L.) Roxb. (Syn.: *Garcinia cambogia* (Gaertn.) Desr; Common name: Malabar tamarind), is one of the most important members of the Clusiaceae family (**Figure 1**). It is a small or medium sized tree up to 12 m tall with dark green and shining leaves. The leaves are elliptic obovate, 2-5 inch long and 1-3 inch broad. Fruits are ovoid, 2 inches in diameter, yellow when ripe, with 6-8 grooves; seeds 6-8 surrounded by succulent aril (Singh, 1993). The aril and the fleshy covering encasing the seed is edible when ripe. The differentiation between male and female trees is known only at the flowering stage which takes approximately 7 to 9 years (Kalia *et al.*, 2012). *G. gummi-gutta* is a common species found in the Western Ghats, from the Konkan southwards to Travancore eastwards. The species has now been introduced elsewhere in the subtropical region of Asia including China, Malaysia and the Philippines (Chuah *et al.*, 2013). The present chapter reviews the traditional uses, pharmacological activities and phytochemicals of *G. gummi-gutta*.



Figure 1. *Garcinia gummi-gutta* twig with fruits

1. Traditional uses

G. gummi-gutta is traditionally used as a condiment for flavouring curries and as a fish preservative. The traditionally smoke dried fruit rind of *G. gummi-gutta*, known as ‘Malabar tamarind’ was used for “Colombo curing” of fish, where the pickling was done in brine along with the smoke dried rinds of *G. gummi-gutta* (Sreenivasan and Venkataraman 1959; Lewis and Neelakantan, 1965). The species yield an yellow, adhesive gum resin similar to gamboge from *G. morella*, but of inferior quality and insoluble in water. The seeds yield an oil, which is used in medicine (Watt, 1890). The wood is grey, cross grained, shining, hard and can be used in furniture making (Watt, 1890). The dried rind was used for polishing gold and silver and also used as a substitute for acetic and formic acids in the coagulation of rubber latex (Anonymous, 1956).

Though the tree has been mentioned in the 17th century treatise of medicinal plants, *Hortus Malabaricus*, the species is not part of the Ayurvedic medicine of ancient India (Manilal, 2003). However, it was widely reputed in the folk herbal healing practices and has been used traditionally for the treatment of edema, delayed menstruation, ulcers, open sores, hemorrhoids, fever, rheumatism, and also against intestinal parasites (Majeed *et al.*, 1994, Semwal, *et al.*, 2015). The astringent properties of the rind make it an indispensable ingredient in gargles for weak gums, bowel complaints, constipation, diarrhoea and dysentery. The plant is used in veterinary medicine, for mouth diseases in livestock.

2. Phytochemicals reported from *G. gummi-gutta*

Though *G. gummi-gutta* is an economically important species, widely cultivated in south India, only a few reports are available in literature on the phytochemistry of the plant (Table 1). The fruit is well known for the acidic nature and the chemistry and analytical techniques of hydroxycitric acid, the major organic acid in *G. gummi-gutta*, has been dealt with detail in literature (Jena *et al.*, 2002). Benzophenones are the major secondary metabolites in *G. gummi-gutta*, followed by xanthenes and biflavonoids.

2.1. Organic Acids

Organic acids are of great significance in plants as intermediates in the metabolic processes and are directly involved in growth and maturation of fruits. The organic acids play a key role in fruit flavour and taste. Most of the *Garcinia* fruits are well known for their sour taste and high acidity, and of the different acids reported from *Garcinia* fruits, (-)-hydroxycitric acid (HCA) is the important one, being an anti-obesity agent and a chiral molecule of wide utility in chiral synthesis (Jena, *et al.*, 2002). Malic acid, ascorbic acid, tartaric, oxalic acid and citric acids are also present to a lesser extent in *Garcinia* fruits.

Hydroxy citric acid: Hydroxycitric acid (HCA) is the major organic acid occurring in the fruits of *G. gummi-gutta*. The acid and its lactone were mistakenly identified as citric acid and tartaric acid, however, the acids failed to give positive result for pentabromacetone test for citric acid and cream of tartar test for tartaric acid (Sreenivasan and Venkataraman 1959, Lewis *et al.*, 1964). HCA has been first reported from nature by Lewis and Neelakantan in 1965 from the fruit rinds of *G. gummi-gutta* (Lewis and Neelakantan, 1965). HCA (1,2 dihydroxypropane-1,2,3- tricarboxylic acid) has four isomeric forms, since it contains two asymmetric carbons: (-)-HCA, (+)-HCA, (+)-allo-HCA and (-)-allo-HCA (**Figure 2**). (2S, 3S) Hydroxycitric acid is the major acid from the fruit rinds of *G. gummi-gutta*. The fruit contains 10% to 30% (-)HCA which can be isolated in the free form, as a mineral salt or as a lactone. An HPLC analysis showed 4.1-4.6% (-)-HCA in the leaves while 10.3-12.7% in the fruits of *G. indica* (Jayaprakasha and Sakariah, 2002).

The leaves also contain HCA and a recent LC-MS screening revealed that among 13 *Garcinia* species, *G. gummi-gutta* contains the highest quantity of acids (308mg/g leaf methanol extract) and the HCA content was 95mg/g (Pandey *et al.*, 2015). HCA is available in the market in the form of various salts such as calcium, magnesium and potassium as well as their mixtures (Yamada *et al.*, 2007). Citrin is the trade name given to the calcium salt of hydroxy citric acid. HCA lactone or garcinia lactone was also reported from the fruit. Other organic acids such as tartaric acid, citric acid and malic acid also have been reported as minor constituents. It also contains 1.5% phosphoric acid as calcium triphosphate.

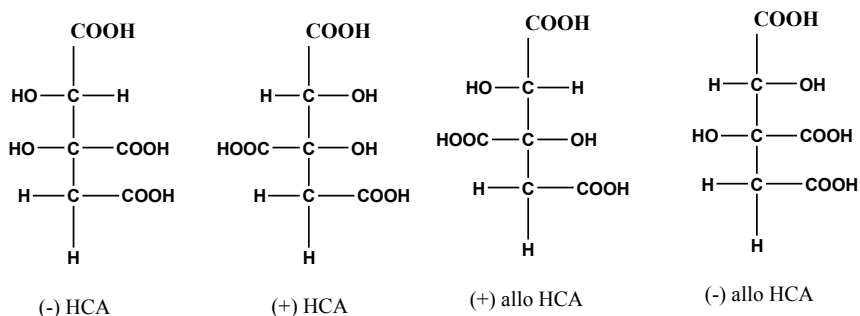


Figure 2. Isomeric forms of hydroxycitric acid

Though citric acid is a common acid in plants, hydroxy citric acid is distributed in limited plant species such as the flowers of *Hibiscus subdariffa* and *H. rosasinensis*. However, the stereochemistry of HCA from *Hibiscus* species is (+) allo form and is different from that of

Garcinia (Lewis *et al.*, 1964). Microbial strains such as *Streptomyces* sp. U121 and *Bacillus megaterium* G45C also produces HCA in trace amounts (Yamada *et al.*, 2007). Hydroxycitric acid has also been synthesized from citric acid, through dehydration to form aconitic acid, which forms hydroxycitric acid via oxidation (Chen *et al.*, 2001).

Paper chromatographic method (solvent system: n-butanol: acetic acid:water (BAW) in the ratio (4:1:5) separates and detects hydroxy citric acid, along with its lactone, on Whatman No.1 paper using bromophenol blue as spray reagent. The acid content of the fruits can be estimated by titrating against 0.1 N sodium hydroxide using phenolphthalein as indicator. However, in this method the concentrations of (-)-HCA and lactone cannot be estimated separately (Jayaprakasha and Sakariah, 1998). HCA can be estimated spectrophotometrically by the formation of reddish orange color complex between HCA and sodium meta vanadate (Antony *et al.*, 1999). Quantification of HCA was also possible through HPLC analysis of aqueous solution, where (-)-HCA and its lactone can be quantified separately (Majeed *et al.*, 1994, Jayaprakasha and Sakariah, 1998, 2000, 2002). The acid can also be detected and estimated using gas chromatography of the trimethyl derivative (Lowenstein and Brunengraber, 1981). In a recent report, UHPLC-QqQLIT-MS/MS method has been applied for the validated estimation of HCA and lactone separately in leaf samples of different *Garcinia* species (Pandey *et al.*, 2015).

The fatty acid content of *G. gummi-gutta* seeds were 46.5%, and the major fatty acid was stearic acid (30.6%), followed by oleic acid (26.2%), linoleic acid (11.4%), elaidic acid (9.5%), palmitic acid (6.3%) and arachidic acid (5.4%) (See chapter 12 for further details).

The amino acid profile of *G. gummi-gutta* fruits was also reported. The amount of total free amino acids was determined to be less than 60 mg in 100 g of *G. gummi-gutta* fruit. The amino acids such as arginine, asparagine, glutamine, threonine, glycine, proline, γ -amino butyric acid, leucine, isoleucine, ornithine and lysine were detected in the fruits (Carratu *et al.*, 2008).

Volatile chemical profiling of the leaves of *G. gummi-gutta* revealed sesquiterpenoids as the major class of volatile compounds and α -copaene has been reported as the major compound (30.2%) (refer chapter 5 for details).

2.2. Benzophenones

Rama Rao *et al.* in the late 1970's, isolated the benzophenones camboginol (garcinol) and cambogin (isogarcinol; xanthochymol) from the latex of *G. gummi-gutta* in large quantities (37.0% and 5.5% respectively) (Rao *et al.*, 1973). Camboginol (m.p. 132°C) was obtained in 37% yield from the latex of *G. gummi-gutta* by a simple crystallisation from pet-ether. Silica gel column chromatography of the remaining residue using hexane as the eluting solvent gave cambogin (Rao *et al.*, 1973). Cambogin has identical chemical and spectral properties as isoxanthochymol but having exactly opposite specific rotation, clearly indicating the compound as an enantiomer of isoxanthochymol. Later Iinuma, *et al.* has also isolated garcinol and isogarcinol from the barks of *G. gummi-gutta* (Iinuma, *et al.*, 1998). Phytochemical investigation of the fruits of *G. gummi-gutta* resulted in the isolation and characterisation of the benzophenones garcinol and guttiferones I, J, K, M, N (Masullo *et al.*, 2008, 2010). In a recent report, the content of garcinol was highest in *G. gummi-gutta* (0.593mg/g) leaf methanol extract among the 13 *Garcinia* species screened (Pandey *et al.*, 2015).

2.3. Xanthenes

The xanthenes garbogiol and rheediaxanthone A were isolated from the barks and roots of *G. gummi-gutta* (Inuma, *et al.*, 1998). Oxy-guttiferones M, K2, I and K were isolated from the fruits of *G. gummi-gutta* (Masullo *et al.*, 2008, 2010). Oxy-guttiferones are tetracyclic xanthenes derived from the oxidation of the corresponding polyisoprenylated benzophenones.

2.4. Biflavonoids

In a recent report, the biflavonoids fukugicide, GB-1 and amentoflavone were reported from *G. gummi-gutta* leaf extracts through a validated LC-MS analysis (Pandey *et al.*, 2015). However, the biflavonoid content was lowest in *G. gummi-gutta* among all the screened *Garcinia* species. The phenolic acid and flavonoids were also lower compared to other *Garcinia* species (Pandey *et al.*, 2015).

The major secondary metabolites benzophenones, xanthenes and biflavonoids reported from the species are listed in **Table 1**.

Table 1. Phytochemicals reported from *Garcinia gummi-gutta*

Plant Part	Compounds	References
Leaf	Cambogic acid, mangostin, garcinol, fukugicide, GB-1 and amentoflavone	Pandey <i>et al.</i> , 2015
Heart wood	Morelloflavone, dihydromorelloflavone, isomorellic acid	Venkataraman, 1973
Bark	Rheediaxanthone, guttiferone E and isogarcinol	Inuma <i>et al.</i> , 1998
Latex	Cambogin (isogarcinol) and camboginol (garcinol)	Rao <i>et al.</i> , 1973
Root	Garbogiol	Inuma <i>et al.</i> , 1998
	Morelloflavone, dihydromorelloflavone, isomorellic acid	Venkataraman, 1973
Fruit	Guttiferones - K, I, J, M and N; oxy-guttiferones M, K, K2 and I	Masullo <i>et al.</i> , 2008, 2010

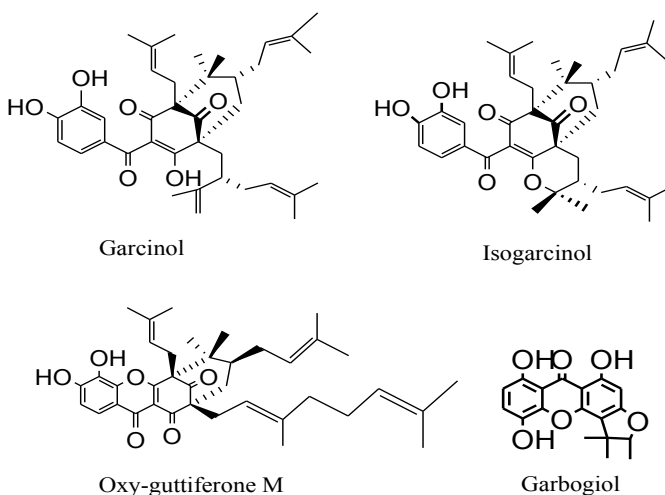


Figure 3. Structures of some secondary metabolites isolated from *G. gummi-gutta*

3. Biological activities reported for *Garcinia gummi-gutta*

3.1. Bioactivities of *G. gummi-gutta* crude extracts: The crude extract and isolated constituents from *G. gummi-gutta* exerted wide spectra of biological activities such as anthelmintic, anticholinesterase, diuretic, antifungal, gastroprotective and hepatoprotective activities in various *in vitro* and *in vivo* models (Semwal, *et al.*, 2015). *G. gummi-gutta* also showed effect on reproductive system, lipid peroxidation, blood viscosity, haematology and plasma biochemistry (Semwal *et al.*, 2015). *G. gummi-gutta* extract has shown significant antidiabetic property by efficiently improving glucose metabolism and displaying leptin like activity (Hayamizu *et al.*, 2003). Remarkable antibacterial effect has been observed for various extracts of *G. gummi-gutta* (Jacob *et al.*, 2015, Rani and Lawrence, 2015, Maridass *et al.*, 2010). Different extracts of *G. gummi-gutta* fruits have shown good antioxidant property in various *in vitro* assays such as DPPH, hydroxyl radical, ferric reducing and lipid peroxidation (Jacob *et al.*, 2015, Ranjani *et al.*, 2014, Shivakumar *et al.*, 2013, Subhashini *et al.*, 2011). *G. gummi-gutta* extracts showed significant anti-inflammatory activity in various experimental systems. In TNBS-induced colitis rats, the extract showed significant anti-inflammatory activity and it could be related to a reduction in DNA damage in isolated colonocytes, observed with the comet assay. The extract also improved the macroscopic damage and caused substantial reductions in MPO activity, COX-2 and iNOS expression. It was also observed that treatment using *Garcinia* extract reduced PGE2 and IL-1 β colonic levels. The leaves of *G. gummi-gutta* showed significant anti-inflammatory activity, especially against carrageenan induced paw oedema in rats and also exhibited moderate *in vitro* anti-inflammatory action in hRBC membrane stabilization method (Prasanth *et al.*, 2013). Several compounds such as garcinol, guttiferone K and guttiferone M isolated from *G. gummi-gutta* also possess anti-inflammatory activity (Semwal *et al.*, 2015). *G. gummi-gutta* decreases the acidity and increase the mucosal defence in the gastric areas, thereby it can be used as an anti-ulcerogenic agent (Mahendran *et al.*, 2002). The oral administration of a fruit extract of *G. gummi-gutta* at doses of 1000 mg/kg BW/day for 5, 10 or 15 days exerted protective effects against indomethacin-induced damage of the gastric mucosa in rats. *G. gummi-gutta* fruit extract showed anti-tumour activity against the cell viability in the murine neuroblastoma cell line (Neuro-2A cells) (Mazzio and Soliman, 2009). Garcinol, the major secondary metabolite in *G. gummi-gutta* was effectively used against different cancer types such as breast cancer, Burkitt lymphoma, colon cancer, esophageal cancer, hepatocellular carcinoma, HeLa cells, kidney cancer, leukemia, lung cancer, medulloblastoma, multiple myeloma, pancreatic cancer, prostate cancer and tongue cancer (Saadat and Gupta, 2012).

3.2. Antiobesity property of hydroxyl citric acid (HCA): (-)-HCA is one of the important supplements for anti-obesity and weight management (Chuah *et al.*, 2013). The inhibition of fatty acid synthesis *in vivo* by HCA was first reported by Lowenstein *et al.*, in 1971. (-)-HCA at 1 mmole per kg of body weight inhibited fatty acid synthesis by about 75% (Lowenstein *et al.*, 1981). Sullivan *et al.*, reported that fatty acid and cholesterol synthesis were blocked significantly by HCA and also that rats fed with HCA tended to eat less compared to the control animals (Sullivan *et al.*, 1974). They have also reported that HCA lowered body fat levels with no loss of body protein in test animals (Sullivan *et al.*, 1974). Followed by these

observations, there has been a plethora of experiments on different models to test the anti obesity activity of HCA (Majeed *et al.*, 1994).

HCA exhibited antiobesity activity by inhibiting the ATP-citrate lyase, a catalyst for the conversion process of citrate to acetyl-coenzyme A, the building block for fatty acid and cholesterol synthesis (Tharachand *et al.*, 2013, Downs *et al.*, 2005). In human trails HCA significantly improved blood lipid profiles by reducing total cholesterol, LDL and triglycerides levels significantly (Preuss *et al.*, 2005). HCA promotes weight loss in humans without causing any stimulation in the central nervous system and produce only short term anorexia and does not carry the risk of being addictive (Majeed *et al.*, 1994, Downs *et al.*, 2005). HCA also regulated the serotonin levels related to satiety and decreased lipogenesis.

Garcinia extracts and HCA have widely been used for obesity and weight control treatments and the long term continuous consumption demands systematic toxicity evaluation and a number of reports about the toxicity of *G. gummi-gutta* fruits and supplements are available in literature (Majeed *et al.*, 1994). However, the potential contributions of HCA as a weight loss agent in humans were controversial, especially regarding the long term benefits and when the randomized, placebo-controlled clinical trials were counted (Heymsfield *et al.*, 1998; Marquez *et al.*, 2012). Also, some clinical studies reported various toxic effects such as toxicity towards spermatogenesis and hepatotoxicity (Kim *et al.*, 2013). However, scientific evidence based on structure, mechanism of action and long history of the use of *Garcinia* had shown 'no observed adverse effect level' (NOAEL) at levels up to 2800 mg/day and suggests that HCA is safe for use (Chuah *et al.*, 2012, 2013).

3.3: Biological activities of garcinol: Garcinol, the major polyisoprenylated benzophenone isolated from *G. indica* exhibits potential antioxidant activity by scavenging DPPH radicals, hydroxyl radicals, suppressing superoxide anion, effective against peroxynitrite-induced lipid peroxidation and inhibiting xanthine oxidase activity. The strong antioxidant activity of garcinol is attributed to the presence of both the phenolic hydroxy groups and β -diketone moiety that shows keto enol tautomerism as in the case of curcumin (Padhye *et al.*, 2009). Garcinol plays an important role in the treatment of gastric ulcers caused by the hydroxyl radical or by a chronic infection with *Helicobacter pylori* as evident from its antiulcer activity in rats induced by indomethacin and acts as a good antioxidant when administered orally (Yamaguchi *et al.*, 2000; Kolodziejczyk *et al.*, 2009). It shows antibiotic activity against methicillin-resistant *Staphylococcus aureus* comparable to that of vancomycin and also proven to exhibit several anticancer activities. Garcinol is also able to suppress colonic aberrant crypt foci (ACF) formation in rats and inhibits topoisomerases I and II at concentrations comparable to that of etoposide. Garcinol decreases the cell viability, increases cell death and apoptosis in human leukemia HL-60 cells, HT-29 cells, HeLa cells and colon cancer cells (Pan *et al.*, 2001; Balasubramanyam *et al.*, 2004). 4-NQO induced oral carcinogenesis in rats and Nic-induced human breast cancer (MDA-MB-231) cell proliferation were suppressed by garcinol (Yoshida *et al.*, 2005; Chen *et al.*, 2011). Earlier studies showed that garcinol acts as a neuroprotective agent by inhibiting the expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) in lipopolysaccharide activated macrophages (LPS) and blocks activation of eukaryotic transcription factor NF- κ B induced by LPS (Liao *et al.*, 2004). It has been established that the phenolic hydroxyl groups as well as β -diketone moiety, that shows keto-enoltautomerism as in the case of curcumin, is

important for the biological activities of garcinol. The isoprenyl chain consists of hydrophobic sites, is also important for binding to biological targets (Padhye *et al.*, 2009).

In addition, other secondary metabolites isolated from *G. gummi-gutta* also showed various biological activities. Xanthenes reported from *G. gummi-gutta* shows activities such as vasodilatory, antimalarial, antiviral activity, human leukemia, cytotoxic activity, α -glucosidase activity, CNS activity and platelet activating factor (PAF). Guttiferones and polyisoprenylated benzophenones reported from *G. gummi-gutta* have shown interesting biological properties such as leishmanicidal, anticancer, antifungal, antiproteolytic, cytotoxicity, apoptotic, cytoprotection against HIV-1 *in vitro* and inhibited the binding activity of a-liver X receptor (LXR α) but is less effective against b-receptor (LXR β).

Conclusions

G. gummi-gutta is a common fruit plant of the Western Ghats, attributed with a wide range of applications ranging from food, medicines and nutraceuticals. The fruit rind of *G. gummi-gutta* is the major source of (-)-hydroxycitric acid (HCA). In addition, secondary metabolites such as xanthenes, benzophenones, organic and amino acids were also reported from this plant. The potential beneficial effects include antioxidant, antihelmenthic, antidiabetic, antimicrobial, antiobesity and hyperlipidaemic properties. Reports on the toxicity and observations during clinical trials suggest that *G. gummi-gutta* is safe for human consumption.

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