Chemical Constituents and Important Applications of *Garcinia Indica* - A Review

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Abstract: *Traditional medicines play an important role in the current scenario and more than 50% of the world's population depends on the constituents extracted from plants for short term and long term disorders and diseases. Different parts of the plants namely, leaves, fruits, seeds, bark and roots possess diverse medicinal properties. A small to moderate size plant Garcinia indica, belonging to the Clusiaceae family is one of the most important, widely used, medicinal plant. In the old classification it belongs to Guttiferae family, and has 1350 species approximately. Chemical constituents extracted from different parts of this plant possess anticancer, antiulcer, antioxidative, antiglycation, antitumor activity, etc.,. Garcinol, anthocyanins and hydroxycitric acid are the important chemical constituents of this plant and identified as responsible for the most of its medicinal properties. The main aim of this review is to bring out the basic information like geographical distribution, physiochemical parameters, phytoconstituents and pharmacological properties about Garcinia indica known so far and also the new field yet to be explored.*

Key words: Garcinia indica; garcinol; anticancer; Neuroprotective;

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Introduction

Garcinia indica also known as kokum is a tropical fruit native to India. The fruit is reported to be rich in polysaccharides. Its fruit possess pleasant, tangy-sweet taste. One of the important chemical compounds present in the plant is Garcinol with the molecular formula $C_{38}H_{50}O_6$. Studies have confirmed the anti-oxidative activity of garcinol. Garcinol possess chelating ability and shows anticancer, anti-ulcer, anti-inflammatory and free radical scavenging activities. The oil extracted from *Garcinia indica* fruits can be freezed and used as butter which is non-greasy and found application in many creams, cosmetics, soaps and conditioners. It is used in chocolate and confectionary industry as well as pharmaceutical and cosmetic industry as surfactant. It is an Indian spice used in many parts of the country for making several vegetarian and non-vegetarian 'curry' preparations like chutneys, pickles, etc.,. Aqueous Kokum extract also has 4% sugar which can be fermented to make excellent quality wine. Amrut kokum is sugary syrup of kokum fruit, which is a strong soft drink to reduce thirst that is very popular throughout the summer season. The control of blood pressure and heart rate usually attained by using Kokum which is rich in B complex, minerals and vitamins. Garcinia indica is a versatile golden fruit helps to recover from constipation, flatulence and acidity. It possesses cardio protective activity also. The fruit of *Garcinia indica* is used to treat diarrhea, dysentery through Ayurvedic medicine. Further, it is being used to facilitate digestion and to treat sores, dermatitis and ear infection.

Geographical distribution:

Kokum (*Garcinia indica*) is also known as wild mangosteen or red mango. The following names Bindin, Biran, Bhirand, Bhinda, Katambi, Punarpuli, Ratamba or Amsool are also represent *Garcinia indica* in India.[1] *Garcinia indica* belongs to the botanical family of Clusiaceae and 1350 species are known. The genus Garcinia contains 200 species out of

which over 20 are found in India.[2] The tropical humid rainforests of Western Ghats in South India is the predominant place for growth of *Garcinia indica* with elevation of around 800 meters. It is a slender tree with drooping branches. The canopy is dense with green leaves. *Garcinia indica* is an androdioecious tree producing male and bisexual flowers on separate plants. It is also used in traditional fish curries. November to February gokum is flowering and from April to May ripening occurs. About 30 to 50 kg of fruit can be obtained after 15 years properly cared single plant. The ripe Kokum fruit is red or dark purple colored containing 3-8 large seeds. The diameter of the spherical gokum fruit is 2.5 to 3.0 cm. Seeds are usually connected to the rind by tissue which is surrounded by red acidic pulp. High content of malic acid and little amounts of tartaric and citric acids give pleasant tart taste to the fruit.

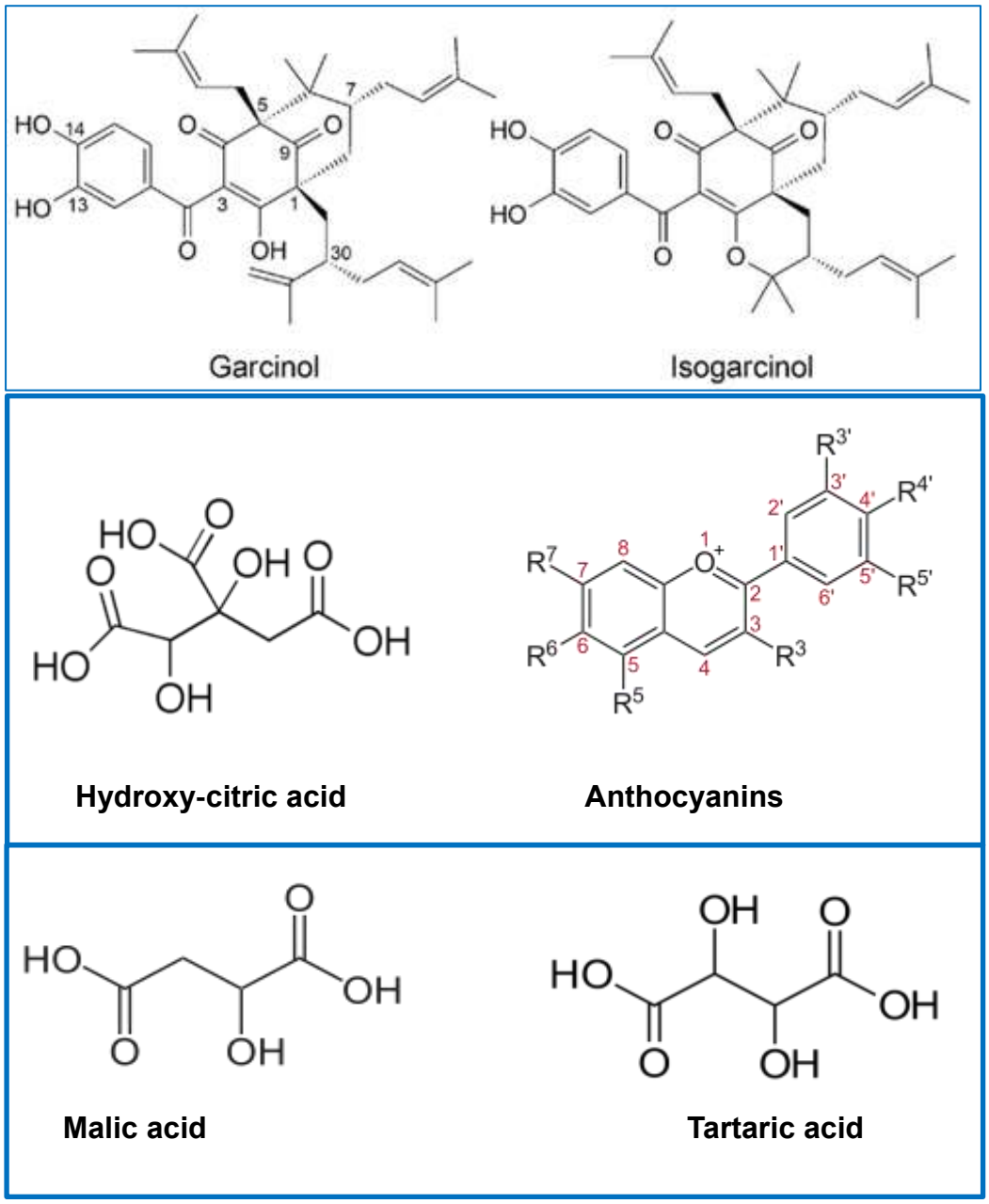
Chemical constituents

Garcinia indica available all over india, possess numerous chemical compounds and the important members are polyisoprenylated benzophenone derivatives such as Garcinol and isogarcinol which is the structural isomer of garcinol. Garcinol is a yellow coloured fat soluble pigment while isogarcinol is an colourless isomer. The fruit also contains hydroxycitric acid lactones, citric acid and oxalic acid. It also contains malic acid in larger quantity and little amounts of tartaric and citric acids give pleasant tart test to the fruit.

Composition of fruit Garcinia is a rich source of active compounds including garcinol, xanthochymol, isoxanthochymol and Hydroxycitric acid. These are flavonoids, benzophenones, xanthones, lactones and phenolic acids [3]. The fruits contain garcinol, hydroxycitric acid, citric acid, acetic acid, malic acid and ascorbic acid. The major constituent of Kokum rind is garcinol $C_{38}H_{50}O_6$, a polyisoprenylated benzophenones, isogarcinol and camboginol. Garcim-1, Garcim-2 and cambogin are the chief oxidative

products of garcinol, along with macurin, mangostin, isogarcinol, gambogic acid, clusianone, , oblongifolin (A, B, C), guttiferone (I, J, K, M, N). The pH of the Kokum fruit is between 1.5 to 2.0, imparting the higher acidity naturally. Hydroxyacetic acid and hydroxycitric acid are the main constituents of the rind of ripe Kokum fruits. It also contains 2.4% pigment as a mixture of two anthocyanins namely, cyanidin-3-sambubioside and cyanidin3-glucoside in the ratio 4:1. Studies have shown that the fresh rind of Kokum contains 80% moisture, 2% protein, 2.8% tannin, 5% pectin, 14% crude fiber, 4.1% total sugars, 1.4% fat, 2.4% pigment, 22% hydroxycitric acid, 0.06% ascorbic acid [4]. Kokum leaves are reported to contain L-leucine, 75% moisture, protein 2.3g, fat 0.5g, fiber 1.24g, carbohydrates 17.2g, iron 15.14mg, calcium 250mg, ascorbic acid 10mg and oxalic acid 18.10mg per 100g. Hydroxycitric acid lactone and citric acid are present in leaves and rinds in minor quantities [4]. Kokum seeds are rich in glycerides of stearic acid (55%), oleic acid (40%), palmitic acid (3%), linoleic acid (1.5%), hydroxyl capric acid (10%) and myristic acid (0.5%). Kokum seed contains about 25% edible fat commonly known as Kokum butter. It is extracted mostly by crushing seeds, boiling them in water and removing fat from top orby churning the seeds in water or by solvent extraction method. The yellowish crude kokum butter is used as edible fat or adulterant of ghee. Refined Kokum butter, which is white in colour, is comparable with high quality hydrogenated fats. Free fatty acids are present up to 7.2% of total Kokum butter [5]. In the cosmetic industry for preparations of lotions, creams, lip-balms and soaps, Kokum butter is being used. The relative high melting point of Kokum butter makes it one of the most stable exotic butter which does not need any refrigeration. Many reports confirm the presence chemical constituents and their role in preventing the diseases.

Figure 1. The Molecular structures of the important chemical constituents of *Garcinia indica*



New perspective

The cocaine memory reconsolidation can be disrupted by garcinol which is reported by Monsey *et al* (2016). Garcinol was systemically administered to rats at the putative time of cocaine memory reconsolidation, 30 min after exposure to the previously cocaine-paired conditioned stimuli (CS). Remarkably, garcinol completely inhibited subsequent CS-induced cocaine-seeking behavior and the acquisition of a new CS-reinforced response in the absence of cocaine reinforcement.

Garcinol and isogarcinol are already reported to be active in the treatment of cancer cells. The inhibition of histone acetyl transferases (HATs) by garcinol and isogarcinol is key property against various tumor models, NF-κB signaling, and STAT-signaling. The promising results about anticancer activity of garcinol and isogarcinol are presented in **Table 1**, published by Rainer Schobert, Bernhard Biersack [6]. Recently discovered effects of garcinol and isogarcinol on inflammation and neurodegenerative diseases are listed in ***Table 2,*** published by Rainer Schobert, Bernhard Biersack.

The effect of chemical constituents present in *Garcinia indica,* on the study of Alzheimer disease is an important area of research. Since the antioxidant and anti-inflammetary effects of Garcinol is well documented, the possible neuroprotective role of garcinol can be expected and elaborated. The regulation of memory and cognition has been achieved through the use of Garcinol which influence the neuronal growth and survival. Garcinol also alter the neurochemical status in brain. The observed neuro-rescue property of garcinol can be use it as an effective compound in Parkinson's disease (PD) therapeutics since it is capable of ameliorating the related pathophysiological changes. The usage of garcinol as a novel anti-Parkinsonian agent and as a bridge between histone acetylation defects and the pathological aspects of PD can be studied effectively at molecular level.

Table 1. Anticancer activity of chemical constituents present in *Garcinia indica*

Cancer type	Effects	Mechanisms	*In vivo* activity
Lung cancer	Sensitization to cisplatin and erlotinib (garcinol), **[7]** suppression of cancer stem cells (garcinol),**[8, 9]** increased TRAIL-based apoptosis (garcinol) **[10]**	Upregulation of let-7c and miR-200c (garcinol), **[7]** suppression of Wnt/*β*-catenin/STAT3 and ALDH1 A1 (garcinol), **[8]** activation of DDIT3, induction of DR5 (garcinol), **[9]** suppression of c-FLIP (garcinol) **[10]**	Inhibition of H441 LCSC mouse xenograft tumor growth (garcinol)29
Colorectal cancer	Increased apoptosis and cell growth inhibition (garcinol), **[11]** inhibition of angiogenesis and invasion (garcinol), **[11]** inhibition of DNA repair (garcinol) **[12]**	Suppression of mPGES1, HIF-1*α*, VEGF, MMP (garcinol), **[11]**inhibition of base excision repair *via* HAT inhibition (garcinol) **[12]**	–
Breast cancer	Sensitization to taxol (garcinol),**[13]** increased apoptosis (garcinol) **[14]**	Suppression of caspase-3/iPLA2 and NF-*κ*B/Twist1 signaling (garcinol), **[13]** p53 dependent induction of Bax (garcinol), **[14]** suppression of Bcl-XL (garcinol),	Sensitization to taxol in orthotopic 4T1 mammary carcinoma (garcinol)36

		[14] proteasome-based degradation of ADA3 (garcinol) **[15]**	
Prostate cancer	Increased apoptosis, inhibition of autophagy (garcinol) **[16]**	Induction of Bax, suppression of Bcl-2 and mTOR (garcinol) **[16]**	Inhibition of PC-3 mouse xenograft tumor growth (garcinol) **[16]**
Pancreatic cancer	Suppression of cancer stem cell character (garcinol), **[17]** tumor growth inhibition (garcinol) **[18]**	Suppression of Mcl-1, EZH2, ABCG2, Gli-1, and Notch-1, induction of miR-200c (garcinol) **[17]**	Inhibition of tumor growth in KPC mice: K-ras and p53 conditional mutant mice (garcinol) **[18]**
Oral squamous cell carcinoma	Inhibition of tumor cell growth, induction of apoptosis, inhibition of angiogenesis and colony formation (garcinol) **[19]**	Inhibition of NF-κB and COX-2, suppression of VEGF (garcinol) **[19]**	–
Cervical cancer	Inhibition of tumor cell growth (garcinol), **[20]**, suppression of tumorigenesis (garcinol),	Activation of PI3 K/AKT signaling (garcinol), **[20]** suppression of HIF-1α (garcinol) **[21]**	Induction of T-cadherin in vivo (garcinol)48

	[20] sensitization to radiotherapy (garcinol) **[21]**		
Miscellaneous cancers	Tumor cell growth inhibition [gallbladder carcinoma (garcinol), **[23]** neuroblastoma (garcinol), **[24]** melanoma (GAR-NPs), **[22]** hepatoma (GAR-NPs), **[22]** leukemia (isogarcinol)],**19** synergism with STAT5-SH2 domain inhibitor AC-4-130 (leukemia, garcinol), **[25]** induction of apoptosis and G2/M arrest (leukemia, isogarcinol), induction of autophagy (osteosarcoma, garcinol) **[27]**	Suppression MMP2 and MMP9 (gallbladder carcinoma) (garcinol), **[23]** synergism with STAT5 inhibition *via* HAT inhibition (leukemia, garcinol), **[25]** increased TRAIL-based apoptosis by induction of DR5 and suppression of c-FLIP (hepatoma, renal cancer, garcinol), **[26]** LC-3 shift (osteosarcoma, garcinol) **[27]**	Moderate accumulation of garcinol nanoparticles in tumors of B16-F10 tumor bearing mice (GAR-NPs) **[22]**

Table 2. Effect of chemical constituents present in *Garcinia indicaon* inflammation and neurodegenerative diseases.

Disease	Effects	Mechanisms
Skin inflammation	Inhibition of 12-O-tetradecanoylphorbol induced inflammation process and tumorigenesis in vitro and in vivo [28]	Suppression of NF-κB, ERK, JNK, p38 MAPK, PI3 K, and Akt [28]
Intimal hyperplasia	Suppression of leukocyte and vascular smooth muscle cell inflammation process in vitro, reduced arterial adherence and infiltration by leukocytes and macrophages in vivo [29]	Suppression of CCL2 and TNF-α [29]
LPS-induced inflammation	Increase of LPS-induced inflammation process in vitro and in vivo [30]	Increased expression of TNF-α and IL-6 [30]
Collagen-induced arthritis (CIA)	Suppression of CIA and ear edema, reduced bone and cartilage damage and low concentrations of inflammatory cytokines in vivo [31]	Suppression of NF-κB, iNOS, COX-2, NFAT and IL-2 [31]
Systemic lupus erythematosus (SLE) disease	Protection of kidneys in vivo, reduced renal histopathology and proteinuria, normalized serum biochemical indicator [32]	–

Psoriasis	Amendment of skin lesions induced by imiquimod, less toxic to liver and kidneys than cyclosporine A in vivo [33]	Suppression of IL-23/Th17 axis genes [33]
Macrophages	Beneficial effects on macrophages and peritoneal macrophages, reduced excretion of lysosomal enzymes in vivo [34]	Suppression of collagenase, elastase and hyaluronidase excretion [34]
Liver inflammation and acute liver failure	Prolonged survival of mice with acute liver failure [35]	Suppression of histone acetylation [35]
Endometriosis	Suppression of fibrosis in Klf11−/− animals [36]	Restoration of transcription factor KLF11 function, suppression of scar-tissue collagen (COL1 A1/Col1a1) [36]
Obesity-related inflammation	Inhibition of high fat diet (HFD)-induced obesity in vivo [37]	Increased levels of intestinal commensal bacteria Akkermansia, suppression of glutamate pyruvate transaminase, cholesterol and triacylglycerol [37]
Diabetes	Normalization of diabetic parameters in vivo [38]	

Osteolysis	Suppression of osteoclastogenesis in vitro and in vivo [39]	Suppression of PI3 K/Akt, MAPK and NF-κB signaling [39]
Multiple sclerosis, experimental autoimmune encephalomyelitis	Reduced intracranial lesions and demyelination of the spinal cord in vivo [40]	Targeting of JAK/STAT signaling pathway [40]
Neuropathic pain	Prolonged thermal withdrawal latency [41]	Suppression of acetyl-p65 [41]
Neuroinflammation of microglia	Suppression of inflammation factors in vitro and in vivo [42]	downregulation of NF-κB signaling, reduced expression of COX-2/PGE2, iNOS and interleukins (IL-1b, IL-6) [42]
Parkinson's disease	Neuroprotective effects, [43] reduction of dopamine side-effects/dyskinesia [44, 45]	MAO−B inhibition, [43] inhibition of catechol-*O*-methyltransferase [45]
Epilepsy	Decrease of mortality and of seizure scores in vivo [46]	Suppression of BDNF and TrkB and upregulation of GABAA and GAD65 [46]
Cocaine abuse	Support of drug abstinence [47, 48]	Inhibition of reinstatement by reconsolidation-based modes [45, 48]

Conclusion

The biochemistry of active chemical constituents present in the *Garcinia indica* is an emerging field of research. The understanding of the action of chemical constituents present in *Garcinia indica* towards various diseases at molecular level is still demanding. It is noteworthy that garcinol was found active against models of various neurological diseases such as EAE, Parkinson disease, epilepsy or drug addiction. The identification of new histone acetyl transferases as targets of garcinol or isogarcinol broadens the scope of application of these natural products including activities against viral and parasitic models. In addition, their distinct activities against cancer stem-like cells warrant studies against further tumor models. A promoting effect on LPS-induced inflammation processes by the chemical constituents of *Garcinia indica* is also reported. The anticancer activity of the natural compound present in *Garcinia indica*, Oblongifolin C has also confirmed which inhinbit HSPA8 and Cathepsin B *in vitro*. These discoveries underline once more the potential of chemical constituents of *Garcinia indica*, which merits further research. The availability of this useful plant which is rich in medicinally important compounds can be further explored with the modern scientific technology.

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