



Garcinia subelliptica Merr. (Fukugi): A multipurpose coastal tree with promising medicinal properties

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ABSTRACT

In this short review, the current knowledge on the botany, ecology, uses, and medicinal properties of the multipurpose *Garcinia subelliptica* (Fukugi) is updated. As yet, there are no reviews on this indigenous and heritage coastal tree species of the Ryukyu Islands in Japan, which has ethnocultural, ecological, and pharmacological significance. Planted by the Okinawan people some 300 years ago, Fukugi trees serve as windbreaks and accord protection against the destructive typhoons. The species has become a popular ornamental tree, and its bark has been used for dyeing fabrics. It forms part of the food chain for mammals and insects and serves as nesting sites for birds. Endowed with bioactive compounds of benzophenones, xanthenes, biflavonoids, and triterpenoids, *G. subelliptica* possesses anticancer, anti-inflammatory, anti-tyrosinase, trypanocidal, antibacterial, DNA topoisomerase inhibitory, DNA strand scission, choline acetyltransferase enhancing, hypoxia-inducible factor-1 inhibitory, and antiandrogenic activities. Fukugetin and fukugiside are two novel biflavonoids named after the species. The chemical constituents of Fukugi fruits when compared with those of mangosteen yielded interesting contrasts.

KEY WORDS: Anticancer, anti-inflammatory, chemical constituents, Fukugi, *Garcinia subelliptica*

INTRODUCTION

The genus *Garcinia* consists of ~450 species, distributed in Africa, Madagascar, Asia, Australia, Polynesia, and Central America [1]. China has 20 species, of which 13 are endemic and one is introduced [1] while 35 species occur in India [2]. The plant list of 2013 has listed a total of 396 species of *Garcinia* with accepted names [3]. Southeast Asia has about 30 species that produce edible fruits, of which most of them are sour because they contain citric acid [4]. *Garcinia mangostana* L. (mangosteen) is the most popular as it produces the sweetest fruits.

Garcinia species are known to contain a wide variety of chemical constituents, notably, benzophenones and xanthenes. Benzophenones have a wide range of biological and pharmacological properties, for example, antioxidant, antimicrobial, anti-inflammatory, anti-HIV, cytotoxic, hepatoprotective, antiparasitic, and antidiabetic properties [5-7]. Antioxidant, anti-inflammatory, antimicrobial, cytotoxic, and antiplasmodial activities have been reported in xanthenes [8,9].

In this short review, the current knowledge on the botany, ecology, uses, and medicinal properties of *Garcinia subelliptica* is updated. It is an indigenous and heritage coastal tree species of the Ryukyu Islands in Japan. To date, there are no reviews on *G. subelliptica*, and there is adequate information in literature on the ethnocultural, ecological, and pharmacological significance of the species to warrant this update.

BOTANY AND USES

G. subelliptica Merr. of the family Clusiaceae (previously Guttiferae) is native to the Ryukyu Islands of Japan, China, Taiwan, India, Sri Lanka, and the Philippines [1,2]. Locally known as Fukugi (Japanese mangosteen), the tree can grow up to 15-20 m tall [10]. Young trees have a compact conical crown with alternating pairs of erect branches sprouting from a main trunk. Older trees have broader crowns and a thick trunk with grayish bark. Characteristic features of the tree are the upward-pointing branches and leaves, cone-shaped crown, and yellowish latex.

Leaves of *G. subelliptica* are simple, spirally arranged in opposite pairs, ovate-oblong in shape, thickly leathery, and rounded at the apex [10]. Twigs are 4-6 angled. The undersurface is yellow-green, and the uppersurface glossy and dark green. The midrib is prominent while the side veins are not visible. Leaves are reddish-bronze when young, turning yellow-green, and dark green when mature. Sun leaves of *G. subelliptica* are smaller, thicker, and more elliptic than shade leaves [11]. Having more and larger stomata, sun leaves also have higher chlorophyll content than shade leaves.

The species is monoecious with male and female flowers occurring on the same trees [10]. Fruits are oval, green when young and yellowish-orange when mature, and very sour in taste. Photos of male flowers, young fruits, and mature fruits are shown in Figure 1. Fukugi trees begin to flower in early May and fruits mature in late August each year [12]. Fallen ripe fruits emit a strong and unpleasant odor [13].

Fukugi trees have been planted on the Ryukyu Islands by the Okinawan people some 300 years ago, embracing the concept of Feng Shui [14,15]. Dominating the rural landscape, the trees provide shade, serve as windbreaks, and accord protection against the destructive typhoons. The species is planted as forest belts or groves along the coast and the boundaries of villages, and as hedges in the gardens of houses. On the island of Ishigaki, a survey of 12 villages showed that 30% of the houses have Fukugi trees [14].

Fukugi trees lining the stone walls of traditional houses with red roof tiles and a pair of guardian lions are very much of the Okinawan cultural landscape. The walls of 1.2-1.5 m in height protect the lower parts of buildings while the crown foliage of Fukugi shelters the upper parts, particularly the roofs and eaves [16]. On the Ryukyu Islands, the esthetics of Fukugi trees forming the landscape of such villages embodies traditional wisdom and the Satoyama concept of man living in harmony with nature.

In Okinawa, *G. subelliptica* also forms the landscape of shrines and other sacred sites [15]. Out of 683 trees enumerated and measured, data on the average tree height, trunk diameter, and tree age were 10 m, 35 cm, and 140 years. Fukugi trees reaching almost 80 cm in trunk diameter and more than 300 years old have been recorded. These growth data suggest that Fukugi is a very slow growing tree.

In recent years, trees of *G. subelliptica* have become popular ornamentals along roadsides and in gardens. Ripe Fukugi

fruits are a food source for the Ryukyu flying foxes (*Pteropus dasymallus*) during the summer although their main food items are the fruit crops cultivated by the farmers [17]. The larvae of a new species of moth named *Heleanna fukugi* were found feeding on young leaves of *G. subelliptica* [18]. Adult moths of this species were found emerging from nests of the bull-headed shrike built on branches of Fukugi trees [19]. In the Ryukyu Islands, the yellow pigment from the bark of Fukugi trees has been used to dye traditional fabrics including the Okinawan Bingata [13,20]. On the occasion of the Shichi festival on Iriomote Island, we observed that Miruku (God of Harvest) wore a traditional yellow kimono dyed using the bark of Fukugi.

Elsewhere, trees of *G. subelliptica* have gained popularity as an ornamental and landscape plant in East and Southeast Asia. Although *G. subelliptica* is not known for its uses in folk medicine, there is now convincing *in vitro* scientific evidence that the species is rich in bioactive compounds with pharmacological properties of medicinal values.

CHEMICAL CONSTITUENTS

Major classes and the number of compounds of *G. subelliptica* are benzophenones (58), xanthenes (30), biflavonoids (15), and triterpenoids (7) [Table 1]. Benzophenones and xanthenes have been isolated from the fruit, seed, wood, bark, and root. Garcinielliptones are the dominant benzophenones while garcinia xanthenes and subelliptenones are the major xanthenes. Biflavonoids are found primarily in the leaf. *Garcinia* flavones are the dominant biflavonoids. Triterpenoids are found in the leaf and fruit. Fukugetin and fukugiside [Figure 2] were the first two biflavonoids isolated from the stem bark of *G. subelliptica* [21,22]. Other compounds that are novel to *G. subelliptica* are shown in Table 1.

Benzophenones or phloroglucins are a diverse class of phenolic compounds consisting of more than 300 members and characterized by having a common phenol-carbonyl-phenol skeleton [4,6]. The A ring generally contains up to two substituents while the B ring can undergo prenylation and cyclization producing a wide variety of structurally unique compounds with bi-, tri-, and tetra-cyclic ring systems. Benzophenones are major intermediates in the biosynthetic pathway of xanthenes and are typically found in *Garcinia* species. They are non-polar compounds that become increasingly hydrophobic with more prenyl groups attached.



Figure 1: A wasp visiting male flowers (left), young green fruits (middle), and mature orange fruits of *Garcinia subelliptica*

Table 1: Classes and names of compounds isolated from *Garcinia subelliptica*

Compound class and name	Plant part	Reference
Benzophenones		
Cycloxanthochymol*	Fruit	[23-25]
4',6-Dihydroxy-2,3',4-trimethoxybenzophenone*	Wood	[26]
Garcinialiptones A–D*	Fruit	[25]
Garcinielliptones A–S*	Fruit, seed	[27-32]
Garcinielliptones FA–FE*	Fruit	[24,33-35]
Garcinielliptones HA–HF*	Fruit, wood	[34,36]
Garcinielliptin oxide	Seed	[28]
Garcinol	Fruit	[23]
Garsubellins A–E*	Seed, wood	[28,32,37,38]
Isogarcinol	Fruit	[23]
Isoxanthochymol	Fruit	[23-25]
Subellinone*	Wood	[39]
2',3',6-Trihydroxy-2,4-dimethoxybenzophenone*	Wood	[40]
Xanthochymol	Fruit, seed	[13,23-25]
Xanthones		
1,2-Dihydroxy-5,6-dimethoxyxanthone*	Wood	[26]
1,5-Dihydroxy-3-methoxyxanthone	Root bark	[41]
2,5-Dihydroxy-1-methoxyxanthone*	Wood	[42]
2,6-Dihydroxy-1,5-dimethoxyxanthone*	Wood	[26]
1,7-Dihydroxyxanthone	Fruit	[33]
1,6-O-Dimethylsymphoxanthone*	Wood	[40]
Garciniaxanthones A–E*	Wood, root, root bark, stem bark	[20,26,42-44]
Globuxanthone	Root bark	[45]
4-Hydroxybrasilixanthone B*	Stem bark	[20]
12 β -Hydroxy-des-d-garcigerin	Root bark	[45]
Isogarciniaxanthone E*	Stem bark	[20]
1-O-Methylsymphoxanthone*	Wood	[42]
Subelliptenones A–I*	Wood, root bark, stem bark	[20,41,42,45-47]
Symphoxanthone	Wood	[42]
1,3,6,7-Tetrahydroxyxanthone	Fruit	[24]
1,4,5-Trihydroxy-2-(1,1-dimethyl-2-propenyl) xanthone	Stem bark	[20]
1,2,5-Trihydroxyxanthone*	Wood	[26]
1,4,5-Trihydroxyxanthone*	Root	[43]
Biflavonoids		
Amentoflavone	Leaf	[48]
17, 114'-Dimethylamentoflavone	Fruit	[33]
Garciniaflavones A–F*	Leaf	[48]
3'''-O-Methylfukugetin	Fruit	[13]
4'''-O-Methylfukugetin*	Seed	[13]
4'''-O-Methylmorelloflavone	Leaf	[48]
Morelloflavone (fukugetin)*	Leaf, fruit, seed, stem bark	[13,20,21,48]
Morelloflavone-7''-O- β -glucopyranoside (fukugiside)*	Leaf, stem bark	[22,48]
Podocarpusflavone A	Leaf	[48]
Volkensiflavone	Seed	[13]
Triterpenoids		
β -Amyrin	Leaf, fruit	[31]
Canophyllic acid	Fruit	[33]
Canophyllol	Fruit	[33]
Cycloart-25-ene-3 β ,24-diol	Leaf	[48]
Cycloartenol	Leaf	[48]
5-Hydroxymethylfurfural	Fruit	[33]
Oleanan-3-one	Leaf	[48]

Compounds with an asterisk are novel.

Xanthones are secondary metabolites that have a unique tricyclic C6-C3-C6 aromatic structure [49]. The substitution of isoprene, methoxyl, and hydroxyl groups at various locations of the A and B rings can result in a diverse array of xanthone compounds.

Biflavonoids are flavonoid-flavonoid dimers of varying structures due to the different dimer combinations such as flavanone-flavone, flavone-flavone, and flavone-flavonol [50]. Linking the flavonoids, there are two general types of bond connections: C-C and C-O-C. Structural diversity arises when the connecting

bond and many hydroxyl and/or methoxyl substituents groups can occur in different positions.

An interesting study on the chemical constituents of green and ripe fruits and seeds of Fukugi in Okinawa reported that the yield of xanthochymol content of ripe fruits is about six times that of green fruits [13]. The content of fukugetin of ripe seeds is about 10 times more than that of green seeds. The isolation of volkensiflavone from ripe seeds of *G. subelliptica* was reported for the first time.

Among the 110 compounds isolated from *G. subelliptica* [Table 1], 85 compounds (77%) are novel, of which 53 are benzophenones, 23 are xanthenes, and 9 are biflavonoids. Major novel compounds are garcinielliptones A-S, FA-FE, and HA-HF (29), subelliptenones A-I (9), *Garciniaflavones* A-F (6), garsubellins A-E (5), *Garciniaxanthenes* A-E (5), and garcinialiptones A-D (4).

When the chemical constituents of fruits of *G. subelliptica* are compared with those of *G. mangostana* (mangosteen), some interesting contrasts become evident. Only two xanthenes (1,3,6,7-tetrahydroxyxanthone and 1,7-dihydroxyxanthone) have been isolated from the fruit of *G. subelliptica* [Table 1]. In contrast, phytochemical and pharmacological reviews on mangosteen have listed 48-50 xanthenes from the fruits, notably those of mangostins, garcinones, mangostenones, and garcimangosones [51,52]. Two reviews on the benzophenones of *Garcinia* species have included *G. subelliptica* but not *G. mangostana* [4,6]. The fruit of *G. mangostana* contains low contents of guttiferone A and xanthochymol [53]. In contrast, a total of 48 benzophenones have been isolated from *G. subelliptica* [Table 1].

PHARMACOLOGICAL ACTIVITIES

Anticancer

Xanthenes isolated from the stem bark of *G. subelliptica* were the first compounds reported to be cytotoxic to cancer cell lines [20]. Against HeLa cells, the growth inhibition of 50% (GI₅₀) values of garciniaxanthone A, garciniaxanthone E, and 1,4,5-trihydroxy-2-(1,1-dimethyl-2-propenyl) xanthone were 17, 10, and 14 μ M, respectively. 4-Hydroxybrasili-xanthone B and isogarciniaxanthone E had GI₅₀ values of 17 and 16 μ M, respectively. Interestingly, fukugetin showed no inhibitory activity against HeLa cells.

Benzophenonoids of *G. subelliptica* also possess cytotoxic activity. Isolated from the fruits of *G. subelliptica*, garcinielliptone FB displayed marginal cytotoxicity against MCF-7, Hep 3B, and HT-29 human cancer cell lines [33]. An initial study on benzophenonoids isolated from the fruit of *G. subelliptica* reported that xanthochymol was moderately cytotoxic to MCF-7, Hep2, HeLa, and KB human cancer cells [24]. A follow-up study by the same group of scientists [25] reported that all benzophenonoids from the fruit of *G. subelliptica* displayed cytotoxicity against A549, DU145, KB, and vincristine-resistant KB human tumor cell lines with inhibitory concentration 50% (IC₅₀) values ranging from 3.3 to 7.3 μ g/ml. They included garcinialiptones A-D, xanthochymol, isoxanthochymol, and cycloxanthochymol. Another compound (GP-1) from the fruit of *G. subelliptica*-induced apoptosis and autophagy of HT-29 human colorectal cancer cells through caspase- and mitochondria-related pathways [54].

From the seed of *G. subelliptica*, β -amyryn and garcinielliptone FC caused NTUB1 human bladder cancer cell death in a concentration-dependent manner after exposure for 24 and

72 h [31,32]. Cell death was by apoptosis through a ROS-dependent mechanism. Three benzophenones, garcinol, isogarcinol, and xanthochymol isolated from the fruit of *Garcinia purpurea* displayed potent cytotoxic activity against four leukemia cell lines in the order of isogarcinol > xanthochymol > garcinol [55]. As shown in Table 1, all these three compounds have also been isolated from the fruit of *G. subelliptica* [23]. A recent publication has reported that garcinielliptone FC from the fruit of *G. subelliptica*-induced apoptosis in HT-29 cells involving both caspase-dependent and caspase-independent pathways [35]. In addition, garcinielliptone FC also effectively suppressed the activity of nuclear factor- κ B, a key inflammation-related molecule.

Anti-inflammatory

Fukugi has been reported to possess anti-inflammatory activity. The ethanol leaf extract of *G. subelliptica* reduced nitric oxide production in lipopolysaccharide (LPS) stimulated RAW 264.7 macrophages. Expression of cyclooxygenase-2 was notably reduced and production of proinflammatory cytokines was inhibited [56]. From the seed of *G. subelliptica*, garcinielliptones (garsubellin A, garcinielliptin oxide, and garcinielliptone F) had potent inhibitory effects on the release of β -glucuronidase and lysozyme, and on superoxide formation from neutrophils stimulated with fMLP/CB [28,29]. Garcinielliptones L and M showed potent inhibitory effects on the release of β -glucuronidase from peritoneal mast cells stimulated with *p*-methoxy-*N*-methyl phenethylamine and on nitric oxide production in RAW 264.7 cells in response to LPS [30].

Anti-tyrosinase

Using L-dihydroxyphenylalanine as substrate, leaves of 39 coastal plant species found in Iriomote, Japan, were screened for tyrosinase inhibition [57]. Leaves of *G. subelliptica* with 57% inhibition ranked third. Fukugetin was one of the two biflavonoids isolated from the leaves of *G. subelliptica*. The compound exhibited much stronger inhibition (IC₅₀ of 2.5 μ g/ml) than kojic acid (IC₅₀ of 9.1 μ g/ml) and arbutin (IC₅₀ of 62 μ g/ml) when tested using L-tyrosine as substrate. This suggested that biflavonoids, such as fukugetin, may be developed into agents for skin lightening and/or for prevention of food browning. However, the acetone fruit extract of *G. subelliptica* displayed very weak anti-tyrosinase activity [58].

Other Bioactivities

Other pharmacological properties of *G. subelliptica* include trypanocidal, antibacterial, DNA topoisomerase inhibitory, DNA strand scission, choline acetyltransferase (ChAT) enhancing, hypoxia-inducible factor-1 (HIF-1) inhibitory, and anti-androgenic activities. They are briefly described as follows:

From the stem bark of *G. subelliptica*, xanthenes exhibited trypanocidal properties when tested against epimastigotes and trypomastigotes of *Trypanosoma cruzi* [20]. The parasitic

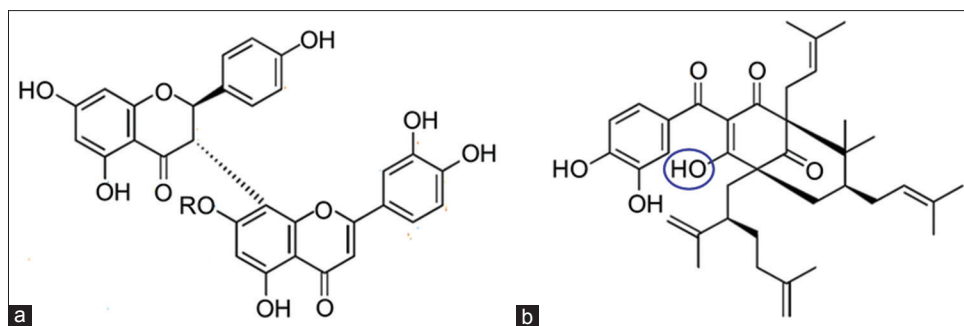


Figure 2: Molecular structures of fukugetin, fukugiside, and xanthochymol. (a) Biflavonoids: Fukugetin (R = H) and fukugiside (R = β -D-gluc), (b) Benzophenone: (+)-xanthochymol

protozoan *T. cruzi* is the etiologic agent of Chagas' disease, which is transmitted to humans and animals by insect vectors. Among the nine xanthenes isolated, subelliptenone B had the strongest activity against epimastigotes with IC_{100} value of $51 \mu\text{M}$ while garciniaxanthone B was most effective against trypomastigotes with IC_{100} value of $8 \mu\text{M}$.

Xanthochymol from the fruit of *G. subelliptica* inhibited the growth of methicillin-resistant *Staphylococcus aureus* with minimum IC (MIC) of $3.1 \mu\text{g/ml}$, which was superior to that of vancomycin ($6.3 \mu\text{g/ml}$) used as positive control [23]. Against methicillin-sensitive resistant *S. aureus*, the MIC of xanthochymol was $3.1 \mu\text{g/ml}$ similar to that of vancomycin ($6.3 \mu\text{g/ml}$). It was postulated that the chelated OH group at C-1 of xanthochymol [Figure 2b] may be involved in the inhibitory activity.

Subelliptenone F from *G. subelliptica* has been reported to inhibit DNA topoisomerases I and II with IC_{50} values of 30 and $<1.0 \mu\text{g/ml}$, respectively [59]. Topoisomerases are the key enzymes of cells that regulate the topological structure of DNA and cells die when these enzymes are inhibited [60]. Topoisomerase inhibitors are therefore among the most active anticancer agents.

Benzophenones (garcinielliptones FC, HC, and HF) from the heartwood and fruit of *G. subelliptica* exhibited DNA strand scission activity [34,36]. In the presence of Cu(II), all three garcinielliptones caused significant breakage of the supercoiled plasmid pBR322 DNA. Compounds with the ability to induce DNA breakage and degradation, for example, bleomycin, have been used as anticancer drugs [36].

Garsubellin A isolated from the wood of *G. subelliptica* was found to enhance the activity of ChAT at $10 \mu\text{M}$ in P10 rat septal neuron cultures [37]. Deficiency in ChAT is a key enzyme involved in the synthesis of neurotransmitter acetylcholine and its deficiency is believed to be implicated in the development of the dementia of Alzheimer's disease.

From the leaf of *G. subelliptica*, amentoflavone strongly inhibited HIF-1 in human embryonic kidney 293 cells under hypoxic conditions [48]. Overexpression of HIF-1 is associated with increased tumor growth and angiogenesis, and HIF-1 inhibitors are known to be anticancer agents [61].

Hydroxyxanthenes from the root bark of *G. subelliptica*, notably subelliptenone F, displayed strong antiandrogenic activity in LNCaP prostate cancer cells [62]. Androgens are primary regulators of prostate cancer cell growth and proliferation in human males [63]. As activation of the androgen receptor is crucial for prostate cancer growth, current therapies are adopting androgen depletion and antiandrogen approaches [64].

CONCLUSION

As heritage trees of the Ryukyu Islands in Japan, the multipurpose *G. subelliptica* has ethnocultural, ecological, and pharmacological significance. Planted some 300 years ago, Fukugi trees dominate the rural landscape, providing shade, and protection of villages during the typhoons. The species has gained popularity as an ornamental tree for landscaping roadsides and gardens, and its bark is still being used as a natural dye for fabrics. It is an important food source for mammals and insects, and serves as nesting sites for birds. Endowed with bioactive compounds of benzophenones, xanthenes, biflavonoids, and triterpenoids, Fukugi possesses anticancer, anti-inflammatory, anti-tyrosinase, trypanocidal, antibacterial, DNA topoisomerase inhibitory, DNA strand scission, ChAT enhancing, HIF-1 inhibitory, and antiandrogenic activities. Fukugetin and fukugiside are two novel biflavonoids named after the species. Not known for its uses in folk medicine, there is now convincing *in vitro* scientific evidence that *G. subelliptica* is rich in bioactive compounds with pharmacological properties of medicinal values. *In vivo* and toxicity studies would be the next phase of research, and the prospects for clinical trials are far from the horizon.

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