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Chemical compounds and antibacterial activity of *Garcinia dulcis* (Roxb)kurz.

Hady Anshory Tamhid*[1]

[1]Department of Pharmacy, Faculty of Mathematics and Natural Sciences, Universitas Islam Indonesia, Yogyakarta, Indonesia

Article Review

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***Corresponding author:**
hadyanshory@uii.ac.id

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ABSTRACT

Garcinia dulcis is a medicinal plant used traditionally to treat various diseases including infections of wounds and ulcers. The antibacterial activity of this plant has also been widely reported, but the most potent compounds as an antibacterial agent are not widely reported, even though the compounds contained in this plant is well known. This paper reviews the compounds contained in G. dulcis plants and their potential as antibacterial agents. Each part of this plant, such as leaves, fruits, flowers, seeds, stems, and roots, contains secondary metabolites which are potential antibacterial agents. Here are described the compounds contained in each part of the plant, such as xanthones, the most dominant compounds, then flavonoids, benzophenones, chromones, and triterpenoid. Their antibacterial activity is also described, especially those that have strong activity against bacteria. The molecular structure and the possibilities of how the antibacterial mechanism are also discussed. Eleven compounds that have the potential to be used as antibacterial agents for the treatment of infectious diseases. Garcigerin A (27) and α-mangostin (54) are compounds that have the most vigorous activity against S. aureus and MRSA compared to the other compounds. The Compounds that have strong activity can be used as antibacterial agents for anti-infective therapy, although they must go through various further studies.

Garcinia dulcis merupakan tanaman obat yang digunakan secara tradisional untuk mengobati berbagai macam penyakit termasuk infeksi luka dan bisul. Aktivitas antibakteri dari tanaman ini juga sudah banyak dilaporkan. Namun senyawa aktif dari tanaman ini yang paling bertanggung jawab memberikan efek antibakteri belum pernah dilaporkan, padahal kandungan senyawa dalam tanaman ini sudah banyak diketahui. Paper ini mereview senyawa-senyawa yang terkandung dalam tanaman G.dulcis serta potensinya sebagai agen antibakteri. Setiap bagian dari tanaman ini, seperti daun, buah, bunga, biji, batang dan akar mengandung senyawa metabolit sekunder yang berpotensi sebagai agen antibakteri. Hasil review menunjukkan senyawa yang paling banyak terdapat dalam tiap bagian tanaman ini adalah golongan santon, kemudian golongan flavonoid, benzofenon, kromon, dan triterpenoid. Aktivitas antibakteri dari senyawa-senyawa ini juga diuraikan, terutama yang memiliki aktivitas antibakteri yang kuat. Struktur senyawa dan mekanisme aksinya sebagai antibakteri juga dibahas. Terdapat sebelas senyawa yang dengan aktivitas yang kuat dan berpotensi sebagai agen antibakteri untuk mengobati penyakit infeksi. Senyawa garcigerin (27) dan α-mangostana (54) adalah dua senyawa yang memiliki aktivitas antibakteri yang paling kuat terhadap S.aureus dan MRSA dibanding dengan senyawa-senyawa lain yang diperoleh dari tanaman ini. Kedua senyawa ini sangat berpotensi digunakan sebagai agen antibakteri untuk terapi penyakit infeksi, namun perlu dilakukan penelitian lanjut secara invivo maupun klinis untuk melihat efektivitas, farmakokinetk, dan farmakodinamiknya.

INTRODUCTION

The use of medicinal plants as an alternative therapy is now overgrowing, starting from the use of fresh plants, dry plants, extract, and active compound isolates. In Asian, including Indonesia, the use of plants as traditional medicine is so high that almost every country has clear regulations regarding the use of medicinal plants as herbal therapy.[1] The use of medicinal plants as a therapy for diseases is extensive, including infectious diseases, especially those caused by bacteria. It has been reported that 69% of antibiotics currently are from a natural product.[2] But only a few are sourced from plants, even though it is known that the potential of medicinal plants as an anti-infective agent is enormous. A chemical compound of plantssuch as phenolic groups, flavonoids, terpenoids, and alkaloids have been shown to have vigorous antibacterial activity.[3] On the other hand, infectious diseases (especially by bacteria) are one of the highest causes of death in Indonesia.[4] One more fact that bacterial resistance to antibiotics used today is increasing.[5] Based on these, the study of antibacterial compounds from medicinal plants needs to be improved so that it is not impossible that the active compounds can be used as an alternative drug which more effective and safer to common drugs used today.

Garcinia dulcis or mundu is one of the medicinal plants that is believed by the people to cure various diseases, such as ulcer and wound infections,[6] besides that it is traditionally also believed to treat struma, lymphangitis, and parotitis.[7] Scientifically, the flowers and seeds are known to have antibacterial and antioxidant activity,[8,9] the barks have an antimalarial effect,[10] and the leaves and fruits are effective as antibacterial, antioxidant, and anticholesterol.[11–13] Its fruit extract is effective as an anti-cancer in liver cells,[14] besides it can also reduce LDL levels and increase HDL cholesterol in mice,[15] and can provide vasorelaxant effects in hypertensive rats.[16] Indonesian people recognise this plant with the name 'mundu' and include it from the garcinia family. This plant grows in primary forests, lowland forests or on the riverside in the areas of Java, Sulawesi and Maluku.[17] *Garcinia dulcis* is known to contain various kinds of secondary metabolites including benzophenones, flavonoids, bioflavonoids, chromones, xanthones and triterpenoids. In this article, we will discuss the compounds that have been successfully isolated from *Garcinia dulcis* along with chemical structure and their antibacterial activity.

Classification and Botanical

Garcinia dulcis is also known as *Garcinia elliptica* Choisy, *Garcinia longifolia* Blume, *Stalagmites dulcis*, *Xanthochymus dulcis* Roxb, and *Xanthochymus javanensis*, Blume. Some regions in Indonesia recognise this plant with the name mundu, Malaysia also calls this plant the name mundu, while Thailand calls it the name *Ma Phut*.[18] This species originated from Java, Malaysia, Thailand, Borneo and Philippines. The taxonomic classification of this plant is shown below:[18]

Kingdom	: Plant
Division	: Spermatophyte
Subdivision	: Magnoliophyta
Class	: Magnoliopsida
Order	: Theales
Family	: Clusiaceae
Genus	: *Garcinia*
Species	: *Garcinia dulcis* (Roxb.) Kurz.

These plants have a height of about 10-13 meters, the stem is brown or dark grey, and the branches are green. The leaves are green to dark green, ovoid, oval, rounded with a length of 10-30 cm and a width of 3-15 cm. Flowers are small and dense with yellowish green or yellowish white petals. The fruit is slightly oval-shaped round with a diameter of 5-8 cm, the surface of the fruit is smooth green, and when ripe it will be yellow to dark yellow. The fruit flesh is slightly fibrous but soft with a sweet-sour taste. The seeds are brown with a length of about 2.5 cm.[17,18] This plant produces one period in a year in July-September,[19] and flowering in April-May.[20] The shape of the tree, leaves, fruit, flowers, and the stems shown in Figure 1.

Figure 1. Morphology of *Garcinia dulcis*. (A) Tree, (B) flowers that haven't bloomed yet, (C) branch, (D) fruit and seed appearance, (E) leaves, (F) freshly grown fruit, and (G) stem. (These images are author collection pictures)

Phytochemical Compound

Secondary metabolites contained in a plant are very numerous, as well as those found in the plant *G.dulcis*. Based on table 1, 68 types of compounds reported have been successfully isolated and identified from *G. dulcis*. These compounds are grouped into five types of groups, that is benzophenones, chromones, flavonoids, xanthones, and triterpenoids. The xanthone group was the major compound in this plant with 46 compounds, followed by 16 compounds of the flavonoid group. While the benzophenone, chromone and triterpenoid groups are three, two and one compound respectively. Every part of the plant is known to contain various kinds of compounds. *Garcinia dulcis* leaves contain flavonoids, chromones, xanthones and triterpenoids. The primary compound of its leaves is flavonoid, whereas xanthones are found predominantly in the stem, roots, fruit, seeds, and flowers. Even in its roots, only xanthone was found, it is 16 compounds. Triterpenoid is only found in one compound, that is in the leaves and stems. The most common compound group is xanthones, then flavonoids, benzophenone, chromone and triterpenoids respectively. The subsection below will discuss each compound and their structure based on the class of compounds we have categorised.

a) Benzophenone

The type of benzophenone group obtained from the plant is a benzophenone-isoprenylation, where this compound belongs to the phenol group. Benzophenone-isoprenylation is a compound that is widely distributed in Garcinia sp, including *G. dulcis*.[21] There are three types of benzophenone-isoprenylation which have been reported to be successfully isolated from this plant, namely garcinol (1), cambogin (2) and xantochymol (3). These three compounds have also been reported in other Garcinia genus.[22–25] Compounds 1 and 2 were isolated from the fruits while compound 3 was isolated from the flowers.[8,12]

b) Flavonoid

Flavonoids are a type of secondary metabolite that is very common in all kinds of plants. Sixteen flavonoid compounds that have been reported to have been successfully isolated from *G.dulcis*. Flavonoid compounds of 6 and 7 are flavon and flavan respectively, compound 8-9 is isoflavone, compounds 4, 5, and 10-14 are biflavonoid, and compounds 15 - 17 are chalcon types. More than half of the types of flavonoids found are biflavonoids. According to Iwashina (2000), biflavonoid is indeed most commonly found in the family plants of Guttiferae (Clusiaceae), especially the genus Garcinia.[26] Therefore it is reasonable if biflavonoids are very dominant in *Garcinia dulcis*.biflavonoid compounds were 10 - 14 obtained from leaves, while compounds 4 and 5 were obtained from the stems. There are five new compounds that have been reported to be successfully isolated from the plants, namely dulcisflavan (7) and dulcisisoflavon (8) isolated from the fruits,[12] Dulcisbiflavonoid A (14) which are isolated from the leaves,[27] and Dulcisbiflavonoid B (15) and C (16) which are isolated from green stems or twigs.[28] While other flavonoid compounds reported from this plant have been previously known.

c) Chromone

There are two types of chromone compounds which are reported to have been isolated from *G.dulcis*. The first is the dulcinone (20), a new compound isolated from the flowers of *G.dulcis* [8], and the other is the Penta (Ome) flavonone (I-3, II-8) -chromon (21) obtained from the leaves.[29] Dulcinon (20) is a hydroxycromones type of cromones that has anti-inflammatory effect, preventive effect of myocardial ischemia, and effect of increasing melanin synthesis.[30]

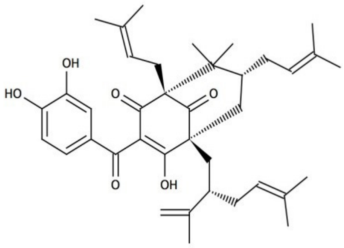
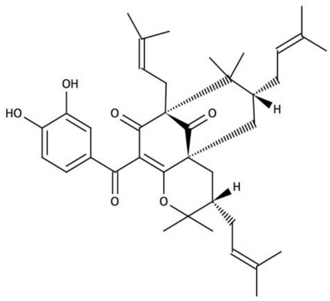
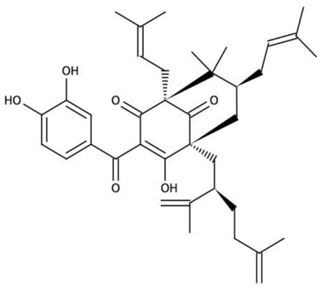
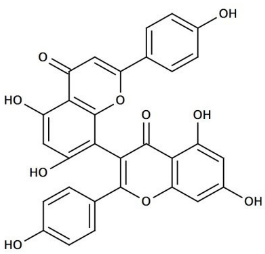
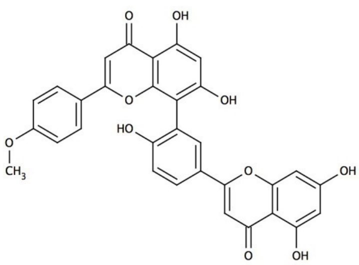
d) Xanthone

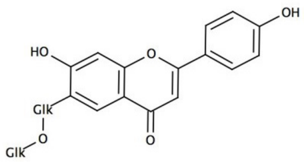
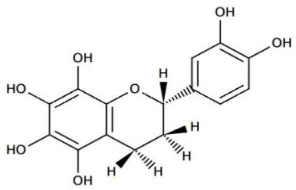
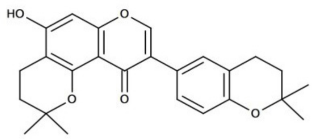
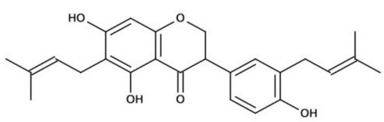
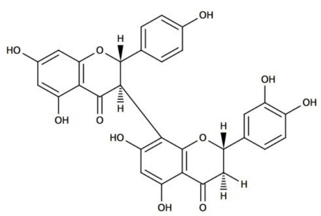
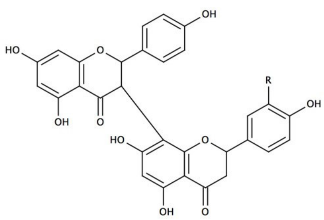
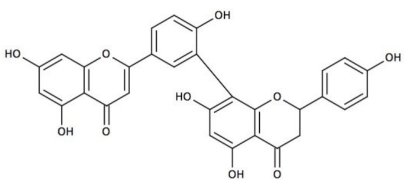
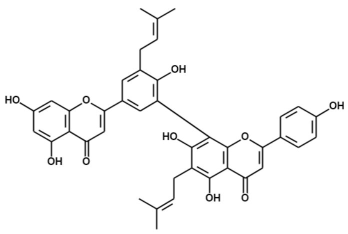
Xanthones are the most abundant group of compounds found in Garcinia plants.[31–33] The xanthone compounds are also known to have many biological activities, such as antioxidants, antimicrobials, anti-inflammatory, anti-cancer and antihyperlipid.[34–37] In this review, there are 46 types of xanthone compounds which have been reported to have been isolated from the plant and more than half of them are prenylated xanthones. This is in accordance with a previous study which stated that the primary type of xanthone compounds in the Guttiferae family (*G. dulcis*) is prenylated xanthones.[34] Twenty-five of these compounds are new xanthone that was found in this plant, namely dulciol A-E (22-26), dulcisxanthone A-L (39 - 50), and dulxanthone A-H (55 - 62). Chromatographic profiles of xanthones are similar to that of flavonoids and their structure is also related. Flavonoids are frequently found in plants. Meanwhile, xanthone is obtained in a limited number of families.[34]

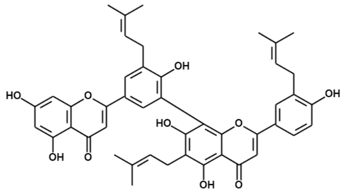
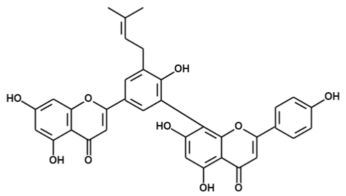
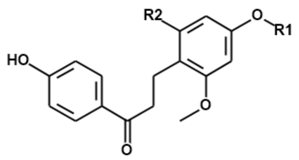
e) The triterpenoid

Triterpenoid compounds that were obtained from this plant are friedelin (68). This compound is not only present in *G.dulcis* plants but is widely distributed in various other plants.[38–40] Compound 68 was found in the stems and leaves of *G. dulcis*.[29,41] Friedelin has an antibacterial effect on Gram-positive bacteria. However, its activity is not strong with a MIC value of more than 128 μg/mL.[42] Friedelin also has antioxidant and liver protective effects,[43] hypolipidemic effect,[44] and anti-diarrheal activity.[45]

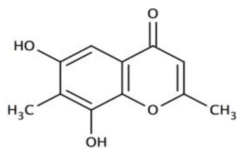
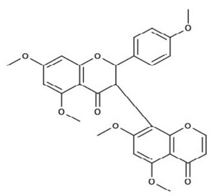
Table 1. Chemical compounds of *Garcinia dulcis* (Group, Structure, and Plant parts)

Group Structure	Compound name (code)	Plant parts (sources)
Benzophenone		
	Garcinol (1)	Fruit[12]
	Cambogin (2)	Fruit[12]
	Xanthochymol (3)	Fruit[8]
Flavonoid		
	Biapigenin (4)	Stem[41]
	Podocarpusflavone (5)	Stem,[41] Flower[8]

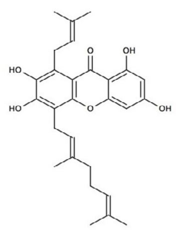
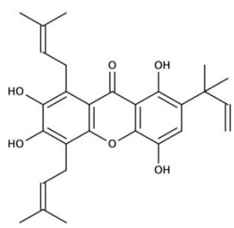
	Dulcinosida (6)	Fruit[12]
	Dulcisflavan (7)	Fruit[12]
	Dulcisisoflavon (8)	Fruit[12]
	Lupalbigenin (9)	Fruit[12]
	GB-2a (10)	Leaves,[27] Flower,[8] Stem[28]
	R=H : Volkensiflavon (11)	Leaves,[27] Flower,[8] Stem[28]
	R=OH : Morelloflavon (12)	Leaves,[27] Seed,[9] Flower,[8] Stem[28]
	Amentoflavone (13)	Leaves,[27] Stem[28]
	Dulcisbiflavonoid A (14)	Leaves[27]

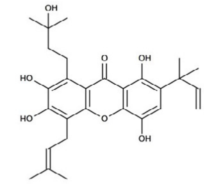
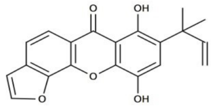
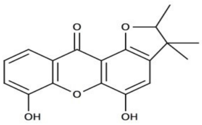
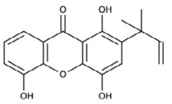
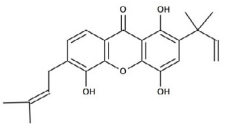
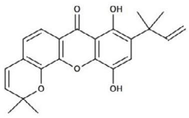
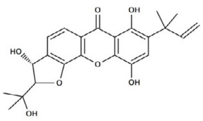
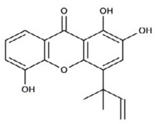
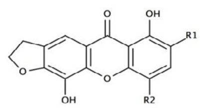
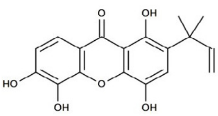
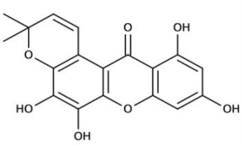
	Dulcisbiflavonoid B (15)	Branch[28]
	Dulcisbiflavonoid C (16)	Branch[28]
	R1=Me, R2 = H : Loureirin A (17)	Seed[9]
	R1=Me, R2=OMe : Loureirin B (18)	Seed[9]
	R1 dan R2=H : Loureirin C (19)	Seed[9]

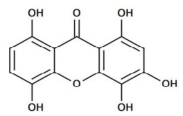
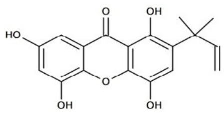
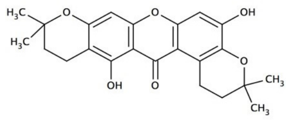
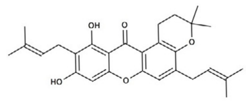
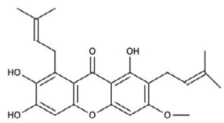
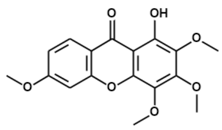
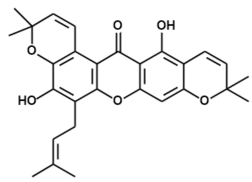
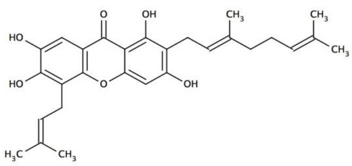
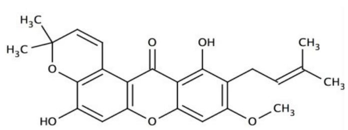
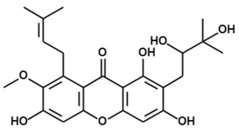
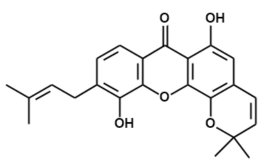
Chromone

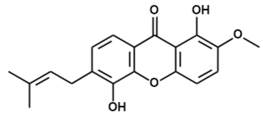
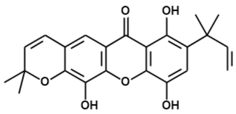
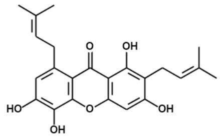
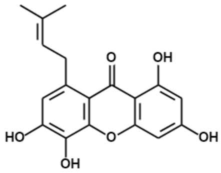
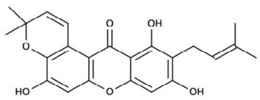
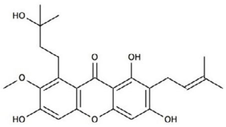
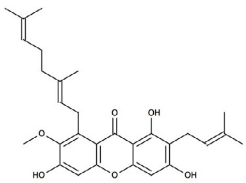
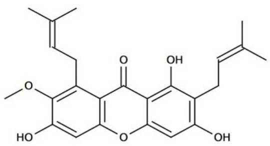
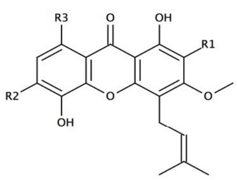
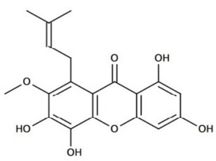
	Dulcinone (20)	Flower[8]
	Penta (Ome) flavanon (I-3, II-8)-kromon (21)	Leaves[29]

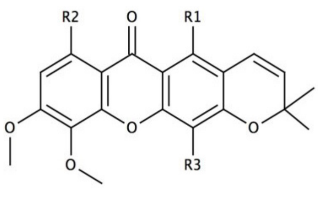
Xanthone

	Biapigenin (4)	Stem[41]
	Podocarpusflavone (5)	Stem[41], Flower [8]

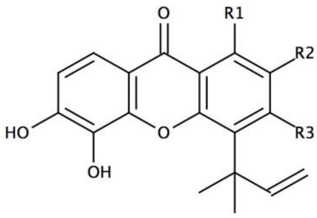
	Dulciol C (24)	Root[46]
	Dulciol D (25)	Root[46]
	Dulciol E (26)	Root[46]
	Garcigerrin A (27)	Root bark[10], Stem bark[47]
	Garciniaxanthone A (28)	Root[46]
	Garciniaxanthone B (29)	Root[46]
	Garciniaxanthone D (30)	Root[46]
	Globuxanthone (31)	Root[46]
	R1 = R2 =OH : Subelliptenone C (32)	Root[46]
	R2 = R1 =OH : Subelliptenone D (33)	Root[46]
	Subelliptenone F (34)	Root[46]
	Toxyloxanthone B (35)	Root bark[46]

	1,3,4,5,8-pentahydroxy xanthone (36)	Root bark[46]
	1,4,5,7-tetrahydroxy-2-(1,1-dimetilalil) xanthone (37)	Root bark[46]
	BR-xanthone (38)	Fruit[12] ,Flower[8]
	Dulcisxanthone A (39)	Fruit[12]
	Dulcisxanthone B (40)	Fruit[12]
	Dulcisxanthone C (41)	Flower[8]
	Dulcisxanthone D (42)	Flower[8]
	Dulcisxanthone E (43)	Flower[8]
	Dulcisxanthone F (44)	Flower[8]
	Dulcisxanthone G (45)	Seed[9]
	Dulcisxanthone H (46)	Branch[48]

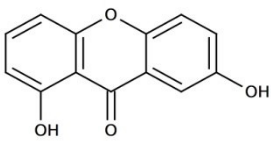
	Dulcisxanthone I (47)	Branch[48]
	Dulcisxanthone J (48)	Stem bark[47]
	Dulcisxanthone K (49)	Stem bark[47]
	Dulcisxanthone L (50)	Stem bark[47]
	Garcinone B (51)	Fruit[12], Flower[8]
	Garcinone D (52)	Fruit[12]
	Cowanin (53)	Fruit[12]
	α - Mangostin (54)	Fruit[12] Flower[8]
	R1= R3=OH, R2=H Dulxanthone A (55)	Stem bark[49]
	R1 = R2=OH, R3 = H : Dulxanthone B (56)	Stem bark[49]
	R1=H, R2=OMe, R3 = Dulxanthone C (57)	Stem bark[49]
	Dulxanthone D (58)	Stem bark[49]



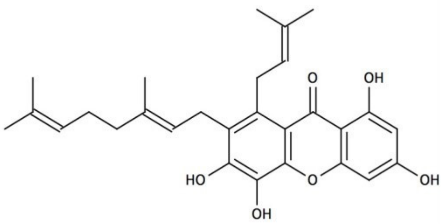
R1=R3=OMe, R2=H : Dulxanthone E (59)	Leaves[50,51]
R1=OH,R2=OMe,R3=H : Dulxanthone F (60)	Leaves[50,51]
R1=OH, R2=R3=OMe : Dulxanthone G (61)	Leaves[50,51]



R1=R3=OH, R2=H : Ugaxanthone (63)	Stem bark[49]
R1=R2=OH, R3=H : Symphoxanthone (64)	Stem bark[10]
R1=Ome,R2=OH,R3-H : 1-O-metylsympoxanthone (65)	Stem bark[10]

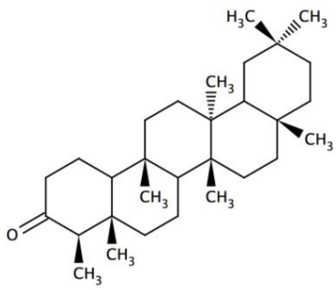


Euxanthone (66) — Stem bark[10], Seed[9]



Garciniaxanthone (67) — Stem bark[10]

Triterpen



Friedelin (68) — Stem[41], Leaves[29]

Antibacterial Activity

According to Redulovic et al. (2013), the antibacterial activity of a plant extract that categorised of high potent if the Minimum Inhibitory Concentration (MIC) value is less than 1000 µg/mL, while for plant isolates less than 100 µg/mL.[3] On the other hand, Rios and Recio (2005) said that experiments with quantities higher than 1 mg/ml for extracts or 0.1 mg/ml for isolated compounds should be avoided, whereas the presence of activity is exciting in the case of concentrations below 100 µg/ml for extracts and 10 µg/ml for isolated compounds.[52] Therefore we here focus on discussing about compounds that have antibacterial activity with MIC values less than 100 µg/mL. There are eleven compounds from all compounds of *G.dulcis* in this review which have strong antibacterial activity, namely garcinol (1), cambogin (2), xanthochymol (3), lupalbigenin (9) GB-2a (10), garcigerine A (27), dulcisxanthone J (48), garcinon B (51), garcinon D (52), cowanin (53), and α-mangostin (54) . All of eleven compounds that have antibacterial activity, only one type is really a new compound produced from its bark, namely dulcisxanthone J (48),[47] while the others are already known and found not only in *G.dulcis*.

Garcinol (1), cambogin (2), and xanthochymol (3) compounds are benzophenone compounds which have antibacterial activity against *Staphylococcus aureus* and Methicilin Resistant Staphylococcus aureus (MRSA) with MICs between 8-128 μg/mL.[8,12] These three compounds are prenylated benzophenone compounds which have phenol groups, so this class of compounds is also often categorized as phenol compounds. Compound 1 is also known to have antibacterial activity against MRSA bacteria with MIC 16 μg/mL, besides that it has also activities against *Helicobacter pylori* bacteria with higher activity than clarithromycin antibiotics.[53]

Other compounds that have antibacterial activity are lupalbigenin (9) and GB-2a (10), where both of these compounds belong to the flavonoid group. Antibacterial activity of compound 9 against bacteria *S. aureus* and MRSA is quite strong with MIC values 8 μg/mL,[12] whereas compound 10 is weaker with MIC 128 μg/mL against *S. aureus* and 64 μg/mL against MRSA bacteria. From other studies, it is known that compound 9 isolated from plants *Derris scandens* has weak antibacterial activity against *Bacillus subtilis*, *Bacillus sphaericus*, and *klebsiella aerugenes*.[54]

The compounds group of xanthones which strong antibacterial activity are Garcigerin A (27), dulcisxanthone J (48), garcinon B (51), garcinon D (52), cowanin (53), and α- mangostin (54). Compounds 27 and 52 are the two compounds that have the strongest antibacterial activity against *S.aureus* and MRSA compared to the other compounds in this plant. The MIC value of these two compounds is 4 μg / mL.[12,47] The α-mangostin (54) are known to have extensive antibacterial activity against various types of bacteria such as *S. aureus*, *Pseudomonas aeruginosa*, *Salmonella typhimurium*, *Bacillus subtilis*, *Klebsiella sp.*, *Proteus sp.*, and *Escherichia coli.*[55] Also, the compound 54 is active against Mycobacterium tuberculosis with MIC 6.25 μg / mL,[56] as well as against Vancomycin-Resistant Enterococci (VRE) with the same MIC value.[57]

There are at least five possible mechanisms for the secondary metabolites of plants to kill or inhibit bacterial growth, which disrupt the function and structure of bacterial cell membranes, interfere with the synthesis and function of DNA / RNA, disrupt cell metabolism, cause coagulation in the cell cytoplasm, and interfere with intercellular communication.[3] Benzophenone found in this plant are phenol compounds, where the antibacterial mechanism of this compound is strongly influenced by the existing phenol groups. The mechanism that might occur is to damage the cell membrane permeability. Besides that, the phenol group is also known to inhibit protein synthesis, inhibit ATP synthesis and interfere with cell metabolism.[3] The hydroxyl groups in the phenol compound can also bind to proteins or other molecules, such as lipoteikoic acid, on the cell wall, causing damage to the bacterial cell wall.[58]

Flavonoids are known to increase the permeability of bacterial cell membranes and interfere with bacterial DNA gyrase synthesis.[3] Compound 9 is an isoflavonoid compound which is known to interfere with DNA / RNA synthesis of *Vibrio Harvey*.[59] While santon compounds (α-mangostin) can cause damage to cell membranes by hydrophobic interactions with membrane lipids resulting in diffusion of water passing through the membrane and causing membrane deformation and ultimately bacterial death.[58,60]

Conclusion

A total of 68 types of compounds that have been successfully isolated and identified based on various literature that we reviewed from this review illustrate that the compound content in *G.dulcis* varies greatly. The benzophenones, flavonoids and xanthones show antibacterial activity with varying strengths. The presence of phenol groups in each compound plays an important role in its activity as an antibacterial, but the structural differences greatly affect its activity. There are eleven compounds that have the potential to be used as antibacterial agents for the treatment of infectious diseases. Garcigerin A (27) and α-mangostin (54) are compounds that have the most potent activity against *S.aureus* and MRSA compared to the other compounds, but it is possible to have different effects when used clinically, therefore further research on the active compounds of this plant, especially as an antibacterial agent to fight infectious diseases, needs to be carried out continuously.

CONFLICT OF INTEREST

The authors declare that there are no potential conflicts of interest.

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