The Genus *Calophyllum*: Review of Ethnomedicinal Uses, Phytochemistry and Pharmacology

5

Shiv Gupta and Pawan Gupta

Abstract

The species of genus *Calophyllum* have been reported for several ethnomedicinal uses in the traditional systems of medicine. The scientific study of the genus *Calophyllum* revealed that it is a rich source of bioactive secondary metabolites. These phytochemicals have shown a wide range of biological activities. Some of these have reached to the clinical developmental stage. The *Calophyllum inophyllum* seed oil has been proved to be an acceptable sustainable source of biodiesel. Few species of the genus are endangered and have been included in the red list of threatened species by the IUCN Red List. Owing to the importance of the genus a review of its ethnomedicinal uses, phytochemistry, and pharmacology has been carried out. It will further help to explore the molecular mechanism of phytochemicals for health benefits.

Keywords

Coumarins · Xanthones · Antiviral activity · Anti-proliferative activity · HIV-inhibitors

5.1 Introduction

Plant-based natural products have been a potential source of lead compounds for the discovery and development of drugs. Antimalarial drugs such as artemisinin and quinine and anticancer drugs such as paclitaxel and vinblastine are some of the well-known natural products which are used for the effective treatment of the disease. The major problem associated with the natural products is poor bioavailability and limited yield. These problems are being overcome by medicinal chemists by

S. Gupta · P. Gupta (✉)
School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab, India
e-mail: pawan.20270@lpu.co.in

J. Singh et al. (eds.), *Bioactive Natural Products in Drug Discovery*,
https://doi.org/10.1007/978-981-15-1394-7_5

synthesizing the natural products in good yield and by preparing their analogues with good bioavailability. The genus *Calophyllum* has also proved to be a potential source of lead compounds for the drug discovery and development. Calanolide A, a non-nucleoside reverse transcriptase inhibitor isolated from the genus, is being evaluated under clinical trial. The genus is a rich source of several medicinally active compounds falling under various chemical classes. The genus includes 190 species and is classified under Calophyllaceae family. The species of the genus are identified with various distinguishing characters like red-coloured outer bark and drupe fruit. The species of the genus such as *Calophyllum inophyllum* is also known to be used traditionally to alleviate disease and is used in the management of leprosy. Owing to the medicinal importance of the genus *Calophyllum*, this chapter presents a review of its ethnomedicinal uses, phytochemistry and pharmacology.

5.2 Morphology and Taxonomy

The genus *Calophyllum* was previously included in the Guttiferae family (Group AP 2009). Now, the APG III (Angiosperm Phylogeny Group) system of flowering plant classification classifies it under Calophyllaceae family. There are 190 species in the genus, of which 179 were identified in the Old World (Africa, Asia and Europe) and only 10 species in the New World (the Americas and Oceania) (Eckenwalder 1980). These species are distributed mainly from eastern Africa to the Pacific in the Old World (Stevens 1980). The multivariate analysis by Diaz et al. showed that other American species of the genus *Calophyllum* are originated from this taxon (Díaz 2013). The species in genus *Calophyllum* are difficult to classify due to the challenge of establishing distinct boundaries (Watt 2014).

The species under the *Calophyllum* genus range from very high trees to shrubs. However, most of the species are medium-sized trees. The habitat of the species ranges from wet tropical rainforest of the lowlands to drier areas at higher altitudes. Some of the species are also found in flooded areas. The genus has several distinguishing taxonomical characteristics like red-coloured outer bark with diamond-shaped fissures and presence of opposite leaves with closely and alternating parallel veins. Other characteristics of the species include axillary, terminal and raceme inflorescences. The fruits of the genus *Calophyllum* are drupe possessing very thin layers of flesh along with a large seed. The sepals and petals in the genus are arranged in hermaphrodite flowers. These also secrete latex which is yellow or white in colour (Eckenwalder 1980). Several species of the genus such as *C. apetalum*, *C. bracteatum*, *C. caudatum*, *C. cordato-oblongum* and *C. mooni* have been included in the red list of threatened species by the IUCN RedList. Furthermore, 18 species are categorized as vulnerable (viz. *C. apetalum*, *C. caudatum*, *C. cordato-oblongum*), 5 species as endangered (viz. *C. insularum*, *C. morobense*, *C. nubicola*, *C. trapezifolium* and *C. waliense*) and 3 species as critically endangered (viz. *C. acutiputamen*, *C. africanum* and *C. cuneifolium*) (Stevens 1980).

5.3 Ethnomedicinal Uses

A number of plants of the genus *Calophyllum* are used as traditional medicine for the treatment of chronic diseases such as ulcer, eye infections, haemorrhoids, hypertension, infections, inflammation, leprosy, malaria, nephritis, pain, rheumatism, skin infection, tumours, varicose, venereal diseases, wound and peptic ulcers (Table 5.1). The seed oil of *C. apetalum* is used by traditional practitioners for the treatment of leprosy (Watt 2014). The latex of the seed of *C. inophyllum* has also been used for the management of leprosy. The seed oil of *C. apetalum* and *C. soulattri* was used in the treatment of skin infections (Stevens 1980; Watt 2014). The infusion of *C. apetalum* mixed with the honey is used for treating scabies (Watt 2014). *C. apetalum*, *C. tacamahaca* and *C. inophyllum* are reported to be used in the treatment of rheumatism (Dorla et al. 2019; Lavergne 2001; Watt 2014). Trunk

Table 5.1 Traditional uses of few species of the genus *Calophyllum*

Species	Traditional use	References
C. apetalum	Treatment of leprosy and cutaneous infections, infusion mixed with honey used in scabies and rheumatism	Watt (2014)
C. blancoi	Latex used to treat wounds, boils, tumours, swellings and also to alleviate asthma	Stevens (1980)
C. brasiliense	Trunk-bark decoction with the root bark of *Coutarea hexandra* used as an antidiabetic and vermifuge, also used in diarrhoea and intestinal worms	Grenand et al. (1987), Yasunaka et al. (2005)
C. caledonicum	Diuretic, highly resistant towards fungi and termites	Hay et al. (2003), Morel et al. (2002)
C. inophyllum	Root decoction is used to treat ulcers, boils and ophthalmia, the bark used to treat orchitis, the latex rubbed on the skin against rheumatism and psoriasis, and a leaf decoction to treat eye infections	
C. lucidum	Dressing of sores, and for a headache remedy	Abraham (1912)
C. membranaceum	Used to reduce inflammation around bruises and to kill pain, relieve rheumatic joint pain, lumbago and wound pain	Stevens (1980)
C. soulattri	Infusion of the root is rubbed on to affected areas in order to alleviate rheumatic pain, fresh bark from the shoots is used as medicine for women who have just given birth, oil obtained from the seed is used externally in the treatment of rheumatism and skin infections, injected into the muscles, the refined oil relieves the pain in leprosy	
C. tacamahaca	Eye diseases, rheumatism, headache, gout, arthritis, dermic problems, skin disorders, memory troubles, blood circulation	Lavergne (2001)
C. tomentosum	Oil extracted from the seed, known as 'kenna tal', is used in the treatment of skin diseases	Stevens (1980)

bark decoction of *C. brasiliense* along with the root bark of *Coutarea hexandra* is used for the treatment of diabetes (Yasunaka et al. 2005). Root decoction of *C. inophyllum* is used locally in the treatment of ulcers and the leaf decoction is used in the treatment of eye infections (**10**). Furthermore, infusion of the roots of *C. soulattri* is rubbed on the skin to alleviate rheumatic pain. The oil extracted from the seeds of *C. tomentosum* is used in the treatment of skin disease (Stevens 1980).

5.4 Phytochemistry

The genus *Calophyllum* is a rich source of bioactive compounds such as xanthones and coumarins. The first phytochemical analysis of the genus was carried out in 1950 by Polonsky and Ormancey-Potier (Ormancey-Potier et al. 1951; Polonsky 1957). Since then several species of the genus have been explored for their phytochemical content. The phytochemical investigation has revealed the presence of various classes of secondary metabolites among which coumarins, xanthones, chromanones, triterpenes, steroid and glycosides are the predominant classes of phytoconstituents present in the genus (Subramanian and Nair 1971; Kashman et al. 1992; McKee et al. 1996; Dharmaratne and Wijesinghe 1997).

5.4.1 Coumarins

Coumarins are commonly found in the genus *Calophyllum*. Most of these coumarins are biosynthesized in the leaves. The coumarins have heterocyclic structure and their biosynthesis is related to the biosynthetic scheme for neo-flavonoids. Coumarins isolated from *Calophyllum* exhibit various pharmacological activities and can be used as a biomarker. The coumarins of the genus are further subclassified as simple coumarins, furanocoumarins, pyranocoumarins and furo-pyranocoumarins. Calanolide A (**1**), costatolide (**2**) (also known as calanolide B), calanolide C (**3**) and calanolide D (**4**) were isolated from the fruits and twigs of *C. lanigerum.* Calanolide E1 (**5**) and calanolide E2 (**6**) (diastereoisomer of calanolide E1) were isolated from the stem bark of *C. lanigerum* (Kashman et al. 1992; McKee et al. 1996). Patil et al. (1993) isolated two tetracyclic dipyranocoumarins, i.e. calophyllic acid (**7**) and isocalophyllic acid (**8**), from the leaves of *C. inophyllum.* Similarly, recedesolide (**9**), a tricyclic pyranocoumarin, was isolated from *C. blancoi* (Shen et al. 2004). Shen et al. (2003) isolated inocalophyllin A (**10**) and B (**12**) along with their methyl esters (**11**and **13**, respectively) from the seeds of *C. inophyllum*. Furthermore, Yasunaka et al. (2005), Gomez-Verjan et al. (2014) and Pires et al. (2014) isolated mammea-type coumarins [A/BA (**14**), A/BB (**15**) and B/BB (**16**)] from the leaves of *C. brasiliense.* Tomentolide A (**17**) and B (**18**) were isolated from the nut kernels of *C. tomentosum* (Nigam and Mitra 1968). Recently, a new coumarin Wallimarin T (**19**) was isolated from the stem bark of *C. wallichianum* (Fig. 5.1; Table 5.2).

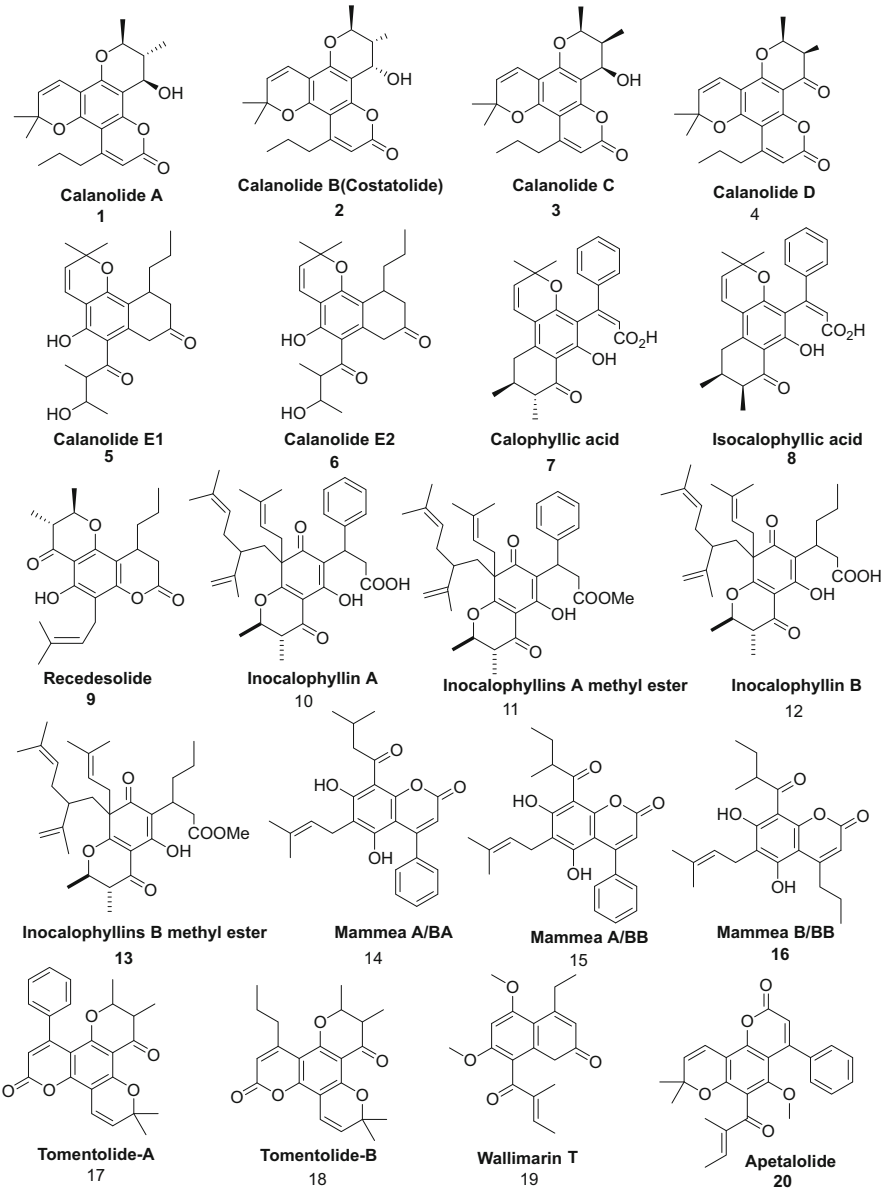

Fig. 5.1 Molecular structures (1–132) of bioactive molecules isolated from various species of the genus *Calophyllum* (1–38: coumarins, 39–79: xanthones, 80–110: chromanones, 111–123: triterpenes and steroids, 124: glycosides, 125–132: miscellaneous compounds)

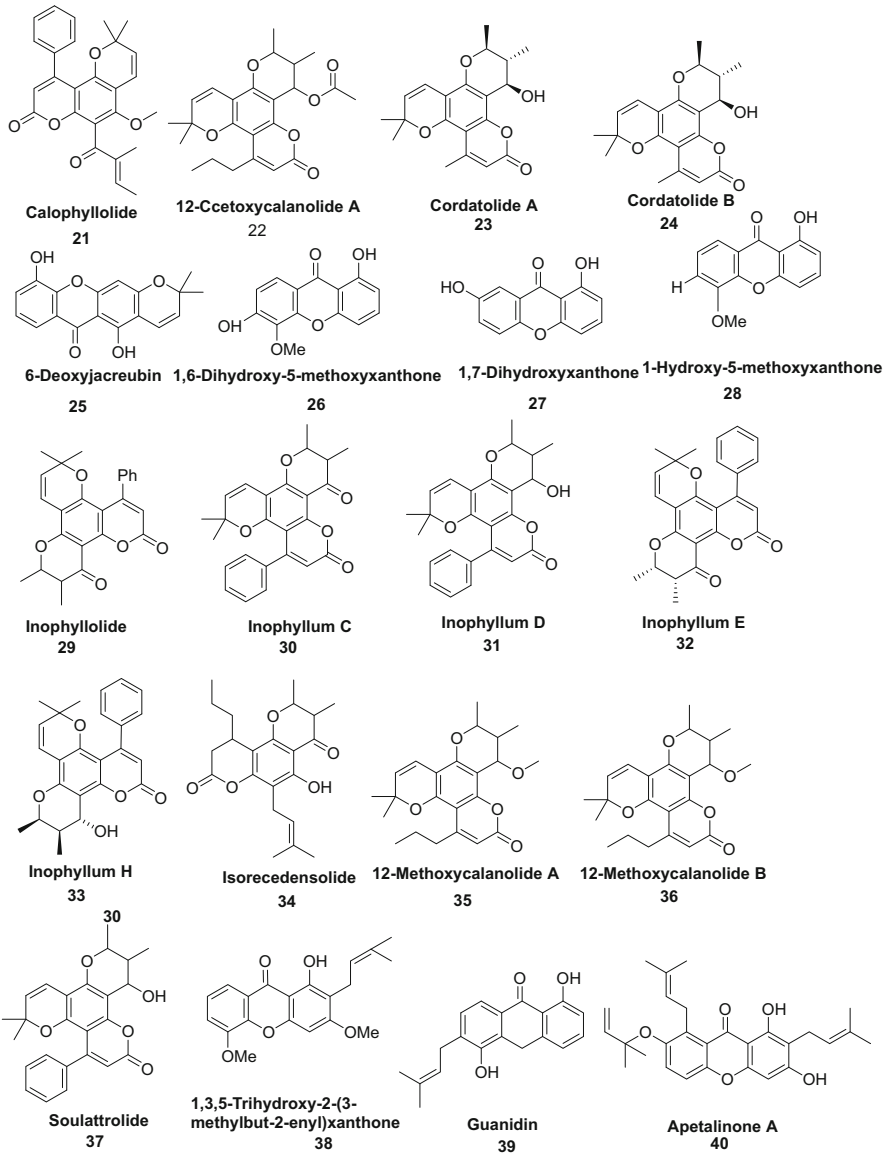

Fig. 5.1 (continued)

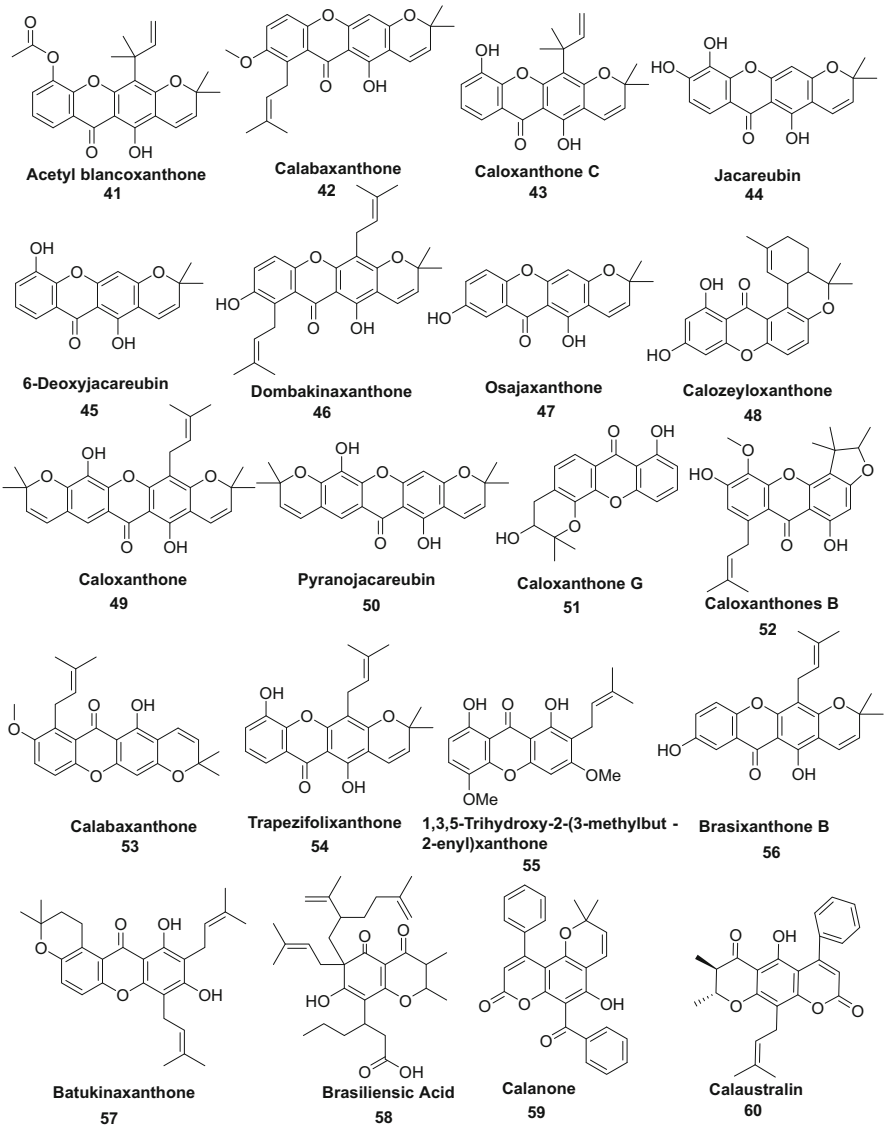

Fig. 5.1 (continued)

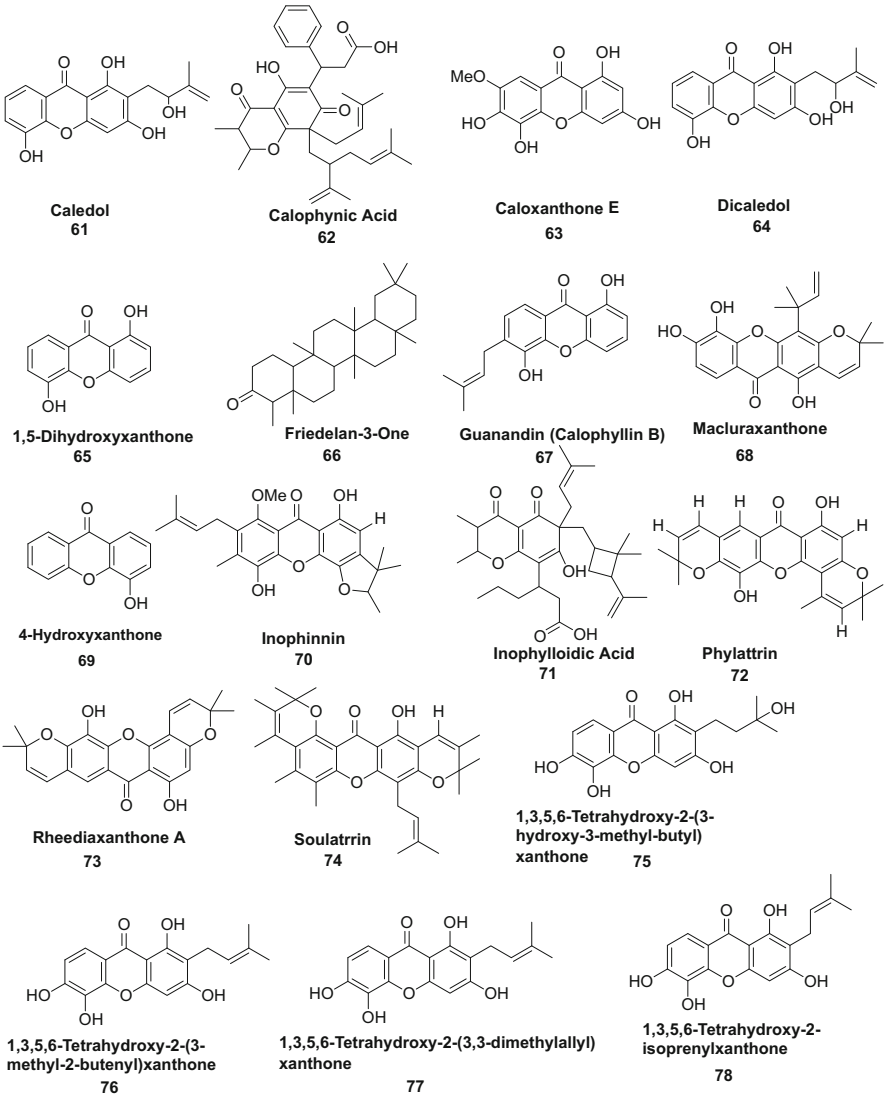

Fig. 5.1 (continued)

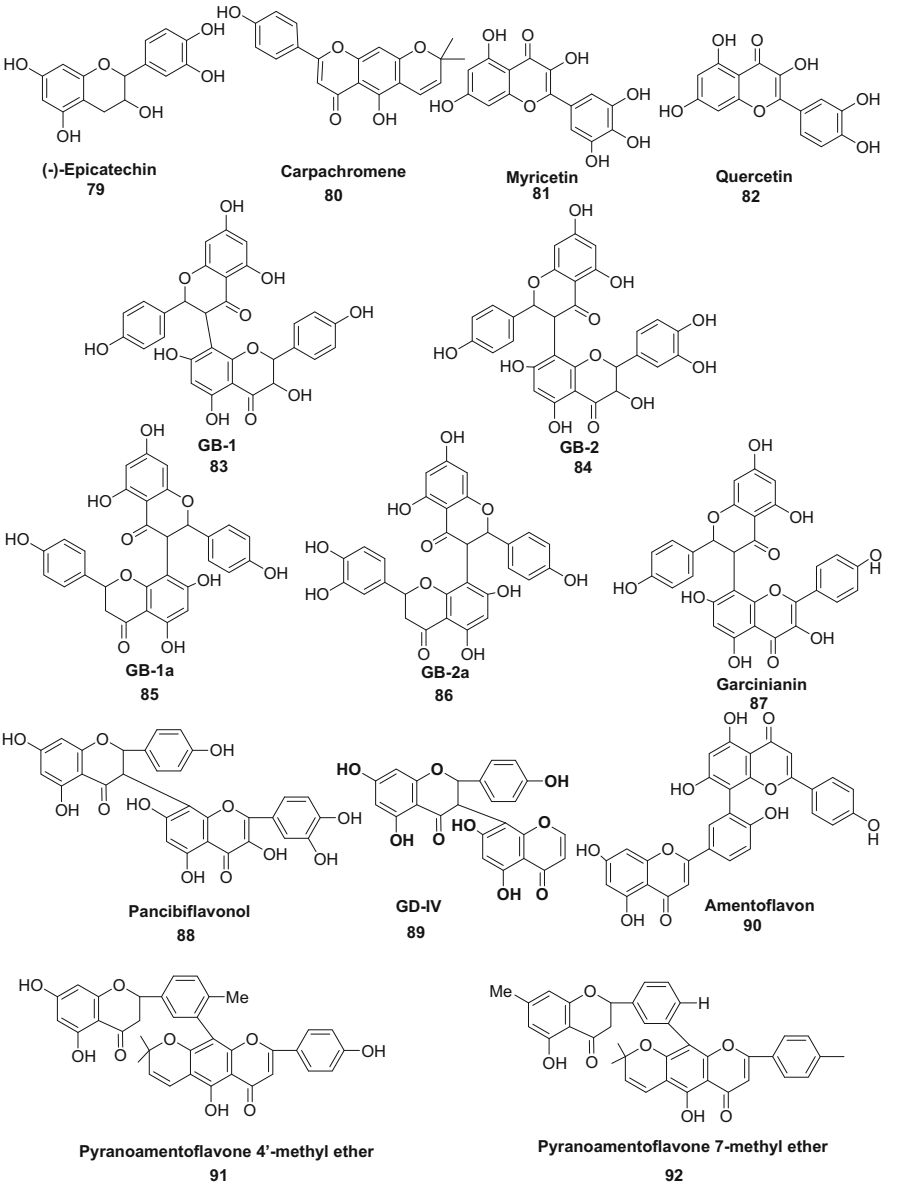

Fig. 5.1 (continued)

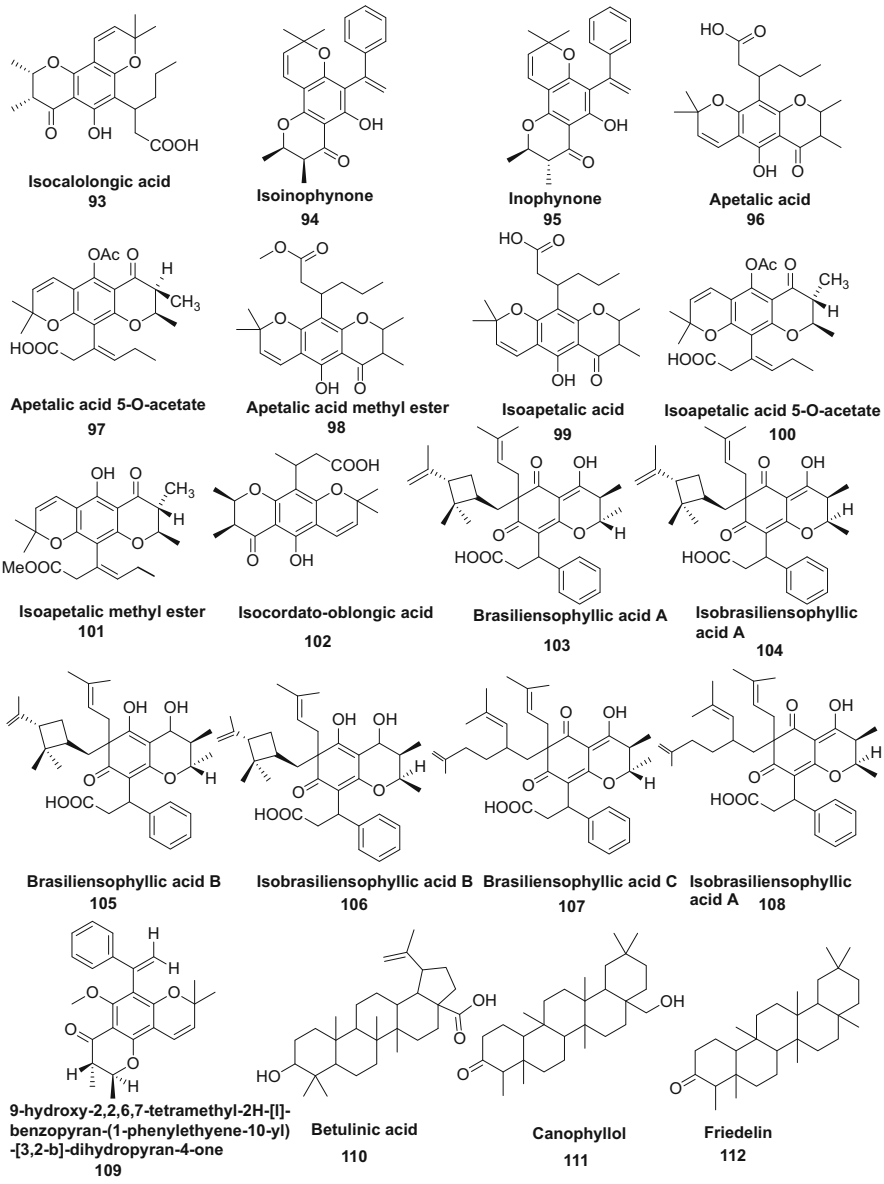

Fig. 5.1 (continued)

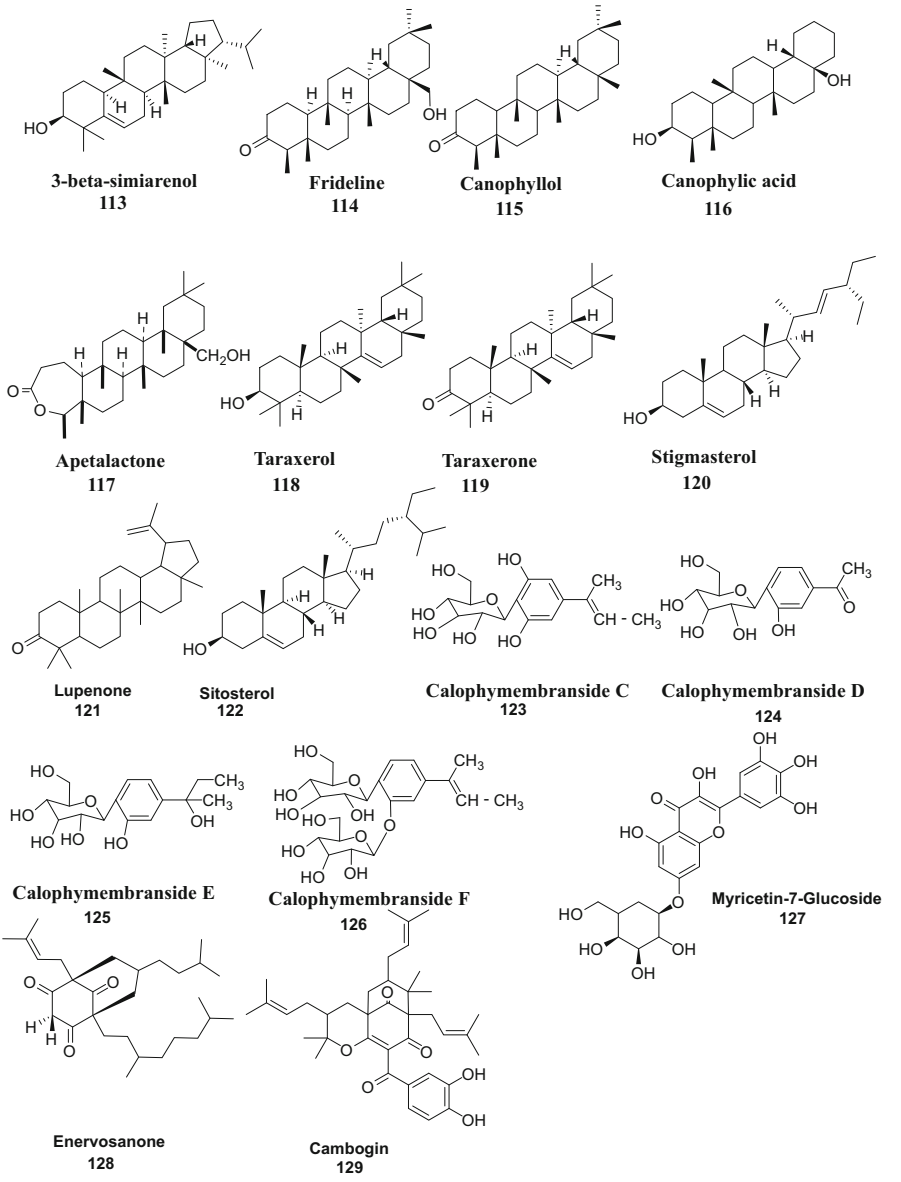

Fig. 5.1 (continued)

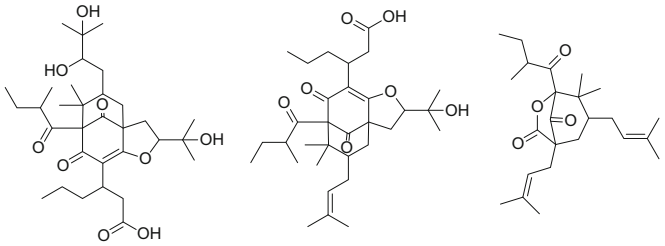

Fig. 5.1 (continued)

5.4.2 Xanthones

Xanthones have been isolated from the bark and wood of several species of the genus. These xanthones differ in structure by oxygenation pattern and position of isoprenyl group in the xanthone nucleus. Xanthones are also substituted with various other functionalities like OH, OMe, OCOMe, 3-carboxybutyl, 1,1-dimethylprop-2-enyloxy, 2,3-dihydroxy-3-methylbutyl, 4-hydroxy-3-methylbutyl and 4-hydroxy-3-methylbut-2-enyl and 4-hydroxy-3-methylbut-2-enyl. Guanidine (**39**), a 1,5-dihydroxy-6-(3,3-dimethylbut-2-enyl)-1,5-dihydroxy xanthone, was isolated from the timber of *C. walker* (Dahanayake et al. 1974). Apetalinone A **(40)** was isolated from *C. apetalum.* Apetalinone A bears 1,1-dimethylprop-2-enyloxy ether substitution which suggested that its biosynthesis involves Claisen rearrangement and Diels–Alder reaction (Iinuma et al. 1997). Acetylblancoxanthone (**41**), caloxanthone A (**42**), caloxanthone C (**43**), jacareubin (**44**), 6-deoxyjacareubin (**45**), dombakinaxanthone (**46**) and osajaxanthone (**47**) are pyranoxanthones possessing a pyran ring at C5-C6, C6-C7 or C7-C8 isolated from the *Calophyllum* spp. (Dharmaratne and Wijesinghe 1997; Yimdjo et al. 2004; Shen et al. 2005; Taher et al. 2005; Mah et al. 2015). Dombakinaxanthone (**46**), a trioxygenated diprenylated chromen-xanthone, and calozeyloxanthone (**48**) were also isolated from *C. moonii*. (Dharmaratne and Wijesinghe 1997). Furthermore, caloxanthone (**49**) and pyranojacaeubin (**50**) possess two pyran rings. Caloxanthone G (**51**) possesses 2,2-dimethyl-3,4-dihydropyrane ring while caloxanthone B (**52**) possesses a furan ring. Gunasekera et al. (1977) isolated three xanthones calabaxanthone **(53)**, trapezifolixanthone (**54**) and 1,3,5-trihydroxy-2-(3-methylbut-2-enyl)xanthone (**55**) from the bark of *C. cuneifolium*. Similarly, brasixanthone B (**56**) was isolated from the stem bark of *C. inophyllum* (Mah et al. 2015) (Fig. 5.1; Table 5.2).

5.4.3 Chromanones

Secondary metabolites having chromanone nucleus, viz. flavonoids, biflavonoids and pyranochromanones, have also been isolated from the genus *Calophyllum*.

Table 5.2 Phytochemicals isolated from the species of the genus *Calophyllum*

Compound name	Species	Part used	Reference
Coumarins			
Calanolide A	*C. lanigerum*	Fruits and twigs	Kashman et al. (1992)
Calanolide B (Costatolide)	*C. lanigerum*	Fruits and twigs	
Calanolide C	*C. lanigerum*	Fruits and twigs	
Calanolide D	*C. lanigerum*	Fruits and twigs	
Calanolide E1	*C. lanigerum*	Stem bark	McKee et al. (1996)
Calanolide E2	*C. lanigerum*	Stem bark	
Calophyllic acid	*C. inophyllum*	Leaves	Patil et al. (1993)
Isocalophyllic acid	*C. inophyllum*	Leaves	
Recedesolide	*C. blancoi*	Leaves	Shen et al. (2004)
Inocalophyllin A	*C. inophyllum*	Seeds	Shen et al. (2003)
Inocalophyllin A methyl ester	*C. inophyllum*	Seeds	
Inocalophyllin B	*C. inophyllum*	Seeds	
Inocalophyllin B methyl ester	*C. inophyllum*	Seeds	
Mammea A/BA	*C. brasiliense*	Leaves	Yasunaka et al. (2005)
Mammea A/BB	*C. brasiliense*	Leaves	Gomez-Verjan et al. (2014)
Mammea B/BB	*C. brasiliense*	Leaves	Pires et al. (2014)
Tomentolide A	*C. tomentosum*	Nut kernels	Nigam and Mitra (1968)
Tomentolide B	*C. tomentosum*	Nut kernels	
Wallimarin T	*C. wallichianum*	Stem bark	Tee et al. (2018)
Apetalolide	*C. apetalum*	Nut kernels	Nigam and Mitra (1968)
Calophyllolide	*C. inophyllum*	Kernels	Ormancey-Potier et al. (1951)
12-Cetoxycalanolide A	*C. lanigerum*	Fruits and twigs	Kashman et al. 1992
Cordatolide A	*C. cordato-oblongum*	Leaves	Dharmaratne et al. (1998a, b)
Cordatolide B	*C. cordato-oblongum*	Leaves	
6-Deoxyjacreubin	*C. soulattri*	Timber	Gunasekera et al. (1977)
1,6-Dihydroxy-5-methoxyxanthone	*C. soulattri*	Timber	
1,7-Dihydroxyxanthone	*C. soulattri*	Timber	
1-Hydroxy-5-methoxyxanthone	*C. soulattri*	Timber	
Inophyllolide	*C. inophyllum*	Nuts	Kawazu et al. (1968)
Inophyllum C	*C. inophyllum*	Nuts	Yimdjo et al. (2004)
Inophyllum D	*C. symingtonianum*	Bark and leaves	Aminudin et al. (2015)

(continued)

Table 5.2 (continued)

Compound name	Species	Part used	Reference
Inophyllum E	*C. inophyllum*	Nuts	Yimdjo et al. (2004)
Inophyllum H	*C. symingtonianum*	Bark and leaves	Aminudin et al. (2015)
Isorecedensolide	*C. blancoi*	Roots	Shen et al. (2005)
12-Methoxycalanolide A	*C. lanigerum*	Fruits and twigs	Kashman et al. (1992)
12-Methoxycalanolide B	*C. lanigerum*	Fruits and twigs	
Soulattrolide	*C. soulattri*	Bark	Gunasekera et al. (1977)
1,3,5-Trihydroxy-2-(3-methylbut-2-enyl)xanthone	*C. soulattri*	Timber	
Xanthones			
Guanidine	*C. walker*		Dahanayake et al. (1974)
Apetalinone A	*C. apetalum*		Iinuma et al. (1997)
Acetyl blancoxanthone	*C. blancoi*	Root	Shen et al. (2005)
Caloxanthone A	*C. inophyllum*	Root bark	Yimdjo et al. (2004)
Caloxanthone C (inoxanthone, blancoxanthone)	*C. inophyllum*	Stem bark	Mah et al. (2015)
Jacareubin	*C. brasiliense*	Heartwood	Abe et al. (2004)
6-Deoxyjacareubin	*C. brasiliense*	Heartwood	
Dombakinaxanthone	*C. moonii*	Root bark	Dharmaratne and Wijesinghe (1997)
Osajaxanthone	*C. enervosum*	Stem bark	Taher et al. (2005)
Calozeyloxanthone	*C. moonii*	Root bark	Dharmaratne and Wijesinghe 1997
Caloxanthone	*C. blancoi*	Roots	Shen et al. (2005)
Pyranojacareubin	*C. blancoi*	Roots	
Caloxanthone G	*C. austroindicum*	Wood	Iinuma et al. (1996)
Caloxanthone B	*C. inophyllum*	Root bark	Yimdjo et al. (2004)
Calabaxanthone	*C. cuneifolium*	Bark	Gunasekera et al. (1977)
Trapezifolixanthone	*C. cuneifolium*	Bark	Gunasekera et al. (1977)
1,3,5-Trihydroxy-2-(3-methylbut −2-enyl) xanthone	*C. cuneifolium*	Timber	
Brasixanthone B	*C. inophyllum*	Stem bark	Mah et al. (2015)
Batukinaxanthone	*C. moonii*	Root bark	Dharmaratne and Wijesinghe (1997)
Brasiliensic acid	*C. inophyllum*	Root bark	Yimdjo et al. (2004)
Calanone	*C. symingtonianum*	Bark & leaves	Aminudin et al. (2015)
Calaustralin	*C. inophyllum*	Nuts	Yimdjo et al. (2004)
Caledol	*C. caledonicum*	Leaves	Oger et al. (2003)
Calophynic acid	*C. inophyllum*	Root bark	Yimdjo et al. (2004)
Caloxanthone E	*C. inophyllum*	Root bark	Iinuma et al. (1995)

(continued)

Table 5.2 (continued)

Compound name	Species	Part used	Reference
Dicaledol	*C. caledonicum*	Leaves	Oger et al. (2003)
1,5-Dihydroxyxanthone	*C. inophyllum*	Root bark	Yimdjo et al. (2004)
Friedelan-3-one	*C. inophyllum*	Root bark	
Guanidine (calophyllin B)	*C. walkeri*	Timber	Dahanayake et al. (1974)
3-Hydroxyblancoxanthone (macluraxanthone)	*C. blancoi*	Roots	Shen et al. (2005)
4-Hydroxyxanthone	*C. inophyllum*	Stem bark	Mah et al. (2015)
Inophinnin	*C. inophyllum*	Stem bark	
Inophylloidic acid	*C. inophyllum*	Root bark	Yimdjo et al. (2004)
Phylattrin	*C. inophyllum*	Stem bark	Mah et al. (2015)
Rheediaxanthone A	*C. inophyllum*	Stem bark	
Soulatrin	*C. inophyllum*	Stem bark	
1,3,5,6-Tetrahydroxy-2-(3-hydroxy-3-methyl-butyl) xanthone	*C. brasiliense*	Heartwood	Abe et al. (2004)
1,3,5,6-Tetrahydroxy-2-(3-methyl-2-butenyl) xanthone	*C. brasiliense*	Heartwood	
1,3,5,6-Tetrahydroxy-2-(3,3-dimethylallyl) xanthone	*C. brasiliense*	Heartwood	Yasunaka et al. (2005)
1,3,5,6-Tetrahydroxy-2-isoprenylxanthone	*C. austroindicum*	Trunk	Iinuma et al. (1996)
Flavonoid			
(−)-Epicatechin	*C. enervosum*	Stem bark	Taher et al. (2005)
Carpachromene	*C. symingtonianum*	Bark & leaves	Aminudin et al. (2015)
Myricetin	*C. inophyllum*	Androecium	Subramanian and Nair (1971)
Quercetin	*C. inophyllum*	Androecium	
GB-1	*C. pauciflorum*	Stem bark	Ito et al. (1999)
GB-2	*C. pauciflorum*	Stem bark	
GB-1a	*C. pauciflorum*	Stem bark	
GB-2a	*C. pauciflorum*	Stem bark	
Garcinianin	*C. pauciflorum*	Stem bark	
Pancibiflavonol	*C. pauciflorum*	Stem bark	
GD-IV	*C. pauciflorum*	Stem bark	
Amentoflavone	*C. brasiliense*	Leaves	Reyes-Chilpa et al. (2004)
Pyranoamentoflavone 4′-methyl ether	*C. venulosum*	Leaves	Cao et al. (2001)
Pyranoamentoflavone 7-methyl ether	*C. venulosum*	Leaves	
Pyranochromanone			
Isocalolongic acid	*C. recedens*	Bark	Guerreiro et al. (1973)
Isoinophynone	*C. inophyllum*	Leaves	Khan et al. (1996)

(continued)

Table 5.2 (continued)

Compound name	Species	Part used	Reference
Inophynone	*C. inophyllum*	Leaves	Ali et al. (1999)
Apetalic acid	*C. blancoi*	Seeds	Shen et al. (2004)
Apetalic acid 5-O-acetate	*C. blancoi*	Seeds	
Apetalic acid methyl ester	*C. blancoi*	Seeds	
Isoapetalic acid	*C. blancoi*	Seeds	
Isoapetalic acid 5-O-acetate	*C. blancoi*	Seeds	
Isoapetalic methyl ester	*C. blancoi*	Seeds	
Isocordato-oblongic acid	*C. symingtonianum*	Bark & leaves	Aminudin et al. (2015)
Brasiliensophyllic acid A	*C. brasiliense*		Cottiglia et al. (2004)
Isobrasiliensophyllic acid A	*C. brasiliense*		
Brasiliensophyllic acid B	*C. brasiliense*		
Isobrasiliensophyllic acid B	*C. brasiliense*		
Brasiliensophyllic acid C	*C. brasiliense*		
Isobrasiliensophyllic acid A	*C. brasiliense*		
9-Hydroxy-2,2,6,7-tetramethyl-2H-[l]-benzopyran-(1-phenylethyene-10-yl)-[3,2-b]-dihydropyran-4-one	*C. tomentosum*	Leaves	Babu et al. (1994)
Triterpenes and steroids			
Betulinic acid	*C. tomentosum*	Bark	Karunanayake et al. (1981)
Canophyllol	*C. brasiliense*	Leaves	Reyes-Chilpa et al. (2004)
Friedelin	*C. brasiliense*	Leaves	Yasunaka et al. (2005)
3β-Simiarenol	*C. walkeri*		Dahanayake et al. (1974)
Frideline	*C. apetalum*		Joshi et al. (2013)
Canophyllol	*C. apetalum*		
Canophyllic acid	*C. inophyllum*		Govindachari et al. (1968), Govindachari et al. (1967)
Apetalactone	*C. apetalum*		
Taraxerol	*C. walkeri*		Dahanayake et al. (1974)
Taraxerone	*C. moonii*		Dharmaratne and Wijesinghe (1997)
Stigmasterol	*C. wallichianum*	Stem bark	Tee et al. (2018)
Lupenone	*C. symingtonianum*	Bark & leaves	Aminudin et al. (2015)
Sitosterol	*C. apetalum*	Bark	Nigam and Mitra (1969)
Glycoside			
Calophymembranside C	*C. membranaceum*	Stem	Ming et al. (2016)

(continued)

Table 5.2 (continued)

Compound name	Species	Part used	Reference
Calophymembranside D	*C. membranaceum*	Stem	Zhu et al. (2018)
Calophymembranside E	*C. membranaceum*	Stem	
Calophymembranside F	*C. membranaceum*	Stem	
Myricetin-7-glucoside	*C. inophyllum*	Androecium	Subramanian and Nair (1971)
Miscellaneous compounds			
Enervosanone	*C. enervosum*	Stem bark	Taher et al. (2005)
Cambogin	*C. enervosum*	Stem bark	
Sundaicumone A	*C. sundaicum*	Leaves	Cao et al. (2006a, b)
Sundaicumone B	*C. sundaicum*	Leaves	
Soulattrone A	*C. soulattri*	Bark	Nigam et al. (1988)

Epicatechin (**80**), carpachromene (**81**) and myricetin (**82**) flavonoids have been isolated from the stem bark, leaves and androecium of flowers, from *C. enervosum*, *C. symingtonianum* and *C. inophyllum*, respectively (Table 5.2) (Subramanian and Nair 1971; Taher et al. 2005; Aminudin et al. 2015). Quercetin (**83**) was also isolated from the androecium of flowers of *C. inophyllum* (Subramanian and Nair 1971).

The biflavonoids of type flavanone-flavonol [GB-1 (**84**) and GB-2 (**85**)], flavanone-flavanone [GB-1a (**86**) and GB-2a (**87**)], flavanone-flavonol [garcinianin (**88**) and pancibiflavonol (**89**)], flavanone-flavone [GD-IV (**90**)] and flavone-flavone [amentoflavone (**91**)] have also been isolated from the species of genus *Calophyllum* (Table 5.2) (Ito et al. 1999; Reyes-Chilpa et al. 2004). Pyranoamentoflavone 4′-methyl ether (**92**) and pyranoamentoflavone 7-methyl ether (**93**) were also isolated from the leaves of *C. venulosum* (Cao et al. 2001).

Isocalolongic acid (**94**), isoinophynone (**95**) and inophynone (**96**) are 1-benzopyran-4-one class of compounds possessing an additional pyran ring which is fused at C7-C8 bond. Inophynone (**96**) and isoinophynone (**95**) which are a pair of epimers were isolated from the ethanolic extract of the fresh leaves of *C. inophyllum* (Ali et al. 1999). Compounds **97**–**103** are pyranochromanone derivatives, isolated from various species of the genus *Calophyllum* (Table 5.2) (Shen et al. 2004; Aminudin et al. 2015).

Brasiliensophyllic acid A **(104),** isobrasiliensophyllic acid A **(105),** brasiliensophyllic acid B **(106),** isobrasiliensophyllic acid B **(107),** brasiliensophyllic acid C **(108)** and isobrasiliensophyllic acid A **(109)** are novel chromanone acids which were isolated from the bark of *C. brasiliense* (Cottiglia et al. 2004) (Fig. 5.1; Table 5.2).

5.4.4 Triterpenes and Steroid

Betulinic acid (**111**), canophyllol (**112**) and friedelin (**113**) are the most common triterpenes found in the genus *Calophyllum* (Table 5.2) (Karunanayake et al. 1981;

Reyes-Chilpa et al. 2004; Yasunaka et al. 2005). Genus *Calophyllum* is a rich source of various triterpenes, which belong to various groups like adianane [3β-simiarenol (**114**)], fridelane [frideline (**115**) and canophyllol (**116**)], lupane [betulinic acid (**111**)], oleanane [canophyllicacid (**117**) and apetalactone (**118**)] and taraxerane [taraxerol (**119**) and taraxerone (**120**)]. Furthermore, stigmasterol (**121**) was also isolated from the stem bark of *C. wallichianum* (Tee et al. 2018) (Fig. 5.1; Table 5.2).

5.4.5 Glycosides

Flavonoid glycoside, myricetin-7-glucoside (**128**), was isolated from the androecium of flowers of *C. inophyllum* (Subramanian and Nair 1971). Similarly, Ming et al. (2016) isolated a new C-glycoside calophymembranside C (**124**) from the stem of *C. membranaceum*. Further, Zhu et al. (2018) isolated three C-glycosides calophymembranside D(**125**), calophymembranside E (**126**) and calophymembranside F (**127**), from the stem of *C. membranaceum* (Fig. 5.1).

5.4.6 Miscellaneous

Secondary metabolites belonging to other chemical classes apart from the above-mentioned ones have also been isolated from the genus *Calophyllum*. A C_{24} terpenoid, *s*oulattrone A, was isolated from the bark of *C. soulattri* (Nigam et al. 1988). Enervosanone (**129**) and cambogin (**130**), two phloroglucinols, were isolated from the stem bark of *C. enervosum* (Taher et al. 2005). Similarly, two 3-propylpropanoic acid moiety-bearing phloroglucinols, i.e. sundaicumone A (**131**) and sundaicumone B (**132**), were isolated in bioassay-guided fractionation using glucocorticoid receptor assay from the leaves of *C. sundaicum* (Cao et al. 2006a, b) (Fig. 5.1; Table 5.2).

5.5 Bioactivities of Genus *Calophyllum*

The genus *Calophyllum* exhibited several biological activities such as antiviral, antimalarial, chemopreventive, antisecretory, antibacterial, cytoprotective, analgesic, antitumour-promoting and cytotoxic activity.

5.5.1 Antiviral Activity

The dipyrano-tetracyclic coumarins such as calanolides, inophyllums and cordatolides isolated from the genus have exhibited potential anti-HIV activity (Kashman et al. 1992; Patil et al. 1993; Dharmaratne et al. 1998a, b). Studies on its mechanism of action showed that these compounds inhibit reverse transcriptase enzyme and are classified as non-nucleoside reverse transcriptase inhibitors (Creagh

et al. 2001). Researchers from the National Cancer Institute studied anticancer potential of Malaysian trees in Sarawak's forest. Unfortunately, they did not get any anticancer compound; instead they found an anti-HIV compound calanolide A from leaves and twigs of *C. lanigerum*. The isolated compound calanolide A showed complete protection against HIV-1 replication, with an IC_{50} of 5.9 ± 1.9 μM. The relocation efforts of the tree were failed and percentage of calanolide A was very less in other species of the genus *Calophyllum*. Further research showed that calanolide B, an isomer of calanolide A, is slightly less active. Calanolide B has the advantage of being readily available from the latex without causing any harm to the trees (Kashman et al. 1992). The development of calanolides was licensed by NCI/NIH to MediChem Research, Inc. (now Advanced Life Sciences) which negotiated an agreement with the Sarawak State Government for the development of calanolides as an anti-HIV drug. A joint venture company named Sarawak Medichem Pharmaceuticals was incorporated for the development of the lead molecule. After the joint venture arrangement proved unworkable, the lead role in the development was transferred to a Sarawakian company named Craun Research Sendirian Berhad. MediChem Research successfully synthesized (+)-calanolide A which is in early clinical trials, while (−)-calanolide B is in preclinical development. 11-Demethyl-12-oxo, an analogue of calanolide A, possesses comparable in vitro anti-HIV-1 activity and is used as a template to study structure–activity relationship of other congeners (Hanna 1999).

Inophyllums such as inophyllum B and P, isolated from *C. inophyllum*, displayed activity against HIV with an IC_{50} value of 38 nM and 130 nM, respectively (Patil et al. 1993). Similarly, cordatolides A and B isolated from *C. cordato-oblongum* showed anti-HIV activity with an IC_{50} value of 12.3 nM and 19 μM, respectively. Five pyranoxanthones isolated from *C. blancoi* also showed activity against the coronavirus with EC_{50} of 3–15 μg/ml (Shen et al. 2005) (Table 5.3).

5.5.2 Antimicrobial Activity

Undi oil (*C. inophyllum*) showed antibacterial activity against several Gram-positive bacteria. The activity of ethanol extract was 14 times of the original oil (Bhat et al. 1954). Novel chromanone acids, brasiliensophyllic acid A–C and isobrasiliensophyllic acid A–C, isolated from the bark of *C. brasiliense* exhibited antibacterial activity against *Bacillus cereus* and *Staphylococcus epidermidis* (Cottiglia et al. 2004). In addition, different parts of *C. soulattri* plant (methyl alcohol extracts of root, stem bark and leaf barks) exhibited a wide range of antibacterial activities (Khan et al. 2002) (Table 5.3).

5.5.3 Inhibition of the Multidrug Transporter P-glycoprotein

The coumarins of genus *Calophyllum* as well as their synthetic analogues inhibited the multidrug transporter P-glycoprotein. Structure–activity relationship study of

Table 5.3 Bioactive compounds isolated from *Calophyllum* spp.

Compound	Property/active against	Reference(s)
Antiviral compounds		
Calanolide F	Anti-HIV	McKee et al. (1996)
(−)-Calanolide B	Anti-HIV	McKee et al. (1996)
Calanolide A	Anti-HIV	Kashman et al. (1992)
Calophyllolide	Anticoagulant	Arora et al. (1962)
Inophyllum B, P	HIV-RT inhibition	Patil et al. (1993)
Soulattrolide	HIV-RT inhibition	Pengsuparp et al. (1996)
Cordatolide A, B	HIV-RT inhibition	Dharmaratne et al. (1998a, b)
Inophyllum B, P, D, C	HIV-RT inhibition	Patil et al. (1993)
Inophyllum B acetate	HIV-RT inhibition	Patil et al. (1993)
11,12-Anhydroinophyllum P	HIV-RT inhibition	Patil et al. (1993)
Antimicrobial compounds		
Dicaledol	*A. fumigatus*	Morel et al. (2002); Oger et al. (2003)
Caledonixanthone E	*A. fumigatus*	Morel et al. (2002)
Caloxanthone F	*A. fumigatus*	Morel et al. (2002)
7-Hydroxy-1,8-dimethoxyxanthone	*A. fumigatus*	Morel et al. (2002)
Calolongic acid	*A. fumigatus*	Hay et al. (2003)
Isocalolongic acid	*A. fumigatus*	Hay et al. (2003)
Calanolide E	*B. cereus*	Tee et al. (2018)
Brasiliensophyllic acid A, B	*B. cereus*	Cottiglia et al. (2004)
Isobrasiliensophyllic acid A, B	*B. cereus*	Cottiglia et al. (2004)
Calanolide E	*B. subtilis, B. megaterium, B. pumilus*	Tee et al. (2018)
Blancoxanthone	Coronavirus	Shen et al. (2005)
Cambogin	*B. subtilis, E. coli, P. aeruginosa, S. aureus*	Taher et al. (2005)
Enervosanone	*B. subtilis, E. coli, S. aureus, P. aeruginosa*	Taher et al. (2005)
Calozeyloxanthone	*E. faecalis, E. faecium* (VR)	Sakagami et al. (2002)
Mammea A/BB	*M. tuberculosis* H37Rv	Pires et al. (2014)
(−)Mammea B/BB	*M. tuberculosis* H37Rv	Pires et al. (2014)
Mammea A/BA	*S. aureus*	Yasunaka et al. (2005)
Jacareubin	*S. aureus*	Yasunaka et al. (2005)
1,3,5,6-Tetrahydroxy-2-(3,3-dimethylallyl)xanthone	*S. aureus*	Yasunaka et al. (2005)
Calophyllolide	*S. aureus*	Bhat et al. (1954); Yimdjo et al. (2004)
Caloxanthone A	*S. aureus*	Yimdjo et al. (2004)
Calophynic acid	*S. aureus*	Yimdjo et al. (2004)
Brasiliensic acid	*S. aureus*	Yimdjo et al. (2004)
Inophylloidic acid	*S. aureus*	Yimdjo et al. (2004)

(continued)

Table 5.3 (continued)

Compound	Property/active against	Reference(s)
Calaustralin	*S. aureus*	Yimdjo et al. (2004)
Inophyllum C	*S. aureus*	Yimdjo et al. (2004)
Calozeloxanthone	*S. aureus* (MR)	Dharmaratne et al. (1999)
Calozeloxanthone	*S. aureus* (MR)	Yasunaka et al. (2005)
Anticancer compounds *TPA-induced EBV-EA activation inhibitory activity*		
Brasixanthone B	–	Ito et al. (2002)
Brasixanthone C	–	Ito et al. (2002)
Brasixanthone D	–	Ito et al. (2002)
8-Desoxygartanin	–	Ito et al. (2002)
Calanolide A	–	Ito et al. (2003)
Brasimarin A	–	Ito et al. (2003)
Brasimarin B	–	Ito et al. (2003)
Brasimarin C	–	Ito et al. (2003)
Calanolide C	–	Ito et al. (2003)
Calanone	–	Ito et al. (2003)
Garcinianin	–	Ito et al. (1999)
Mammea B/BB	–	Ito et al. (2003)
Talbotaflavone	–	Ito et al. (1999)
Calocoumarin A	–	Itoigawa et al. (2001)
Isocalophyllic acid	–	Itoigawa et al. (2001)
Calophyllolide	–	Itoigawa et al. (2001)
Apetatolide	–	Itoigawa et al. (2001)
Cytotoxic compounds		
Hexane extract of *C. mucigerum* stem bark	CEM-SS	Ee et al. (2004)
Apetalic acid methyl ester	Hela, KB, Med	Shen et al. (2004)
Apetalic acid 5-O-acetate	Hela, KB, Med	Shen et al. (2004)
Isopetalic acid methyl ester	Hela, KB, Med	Shen et al. (2004)
Isorecedensolide	Hela, KB, Med	Shen et al. (2004)
Recedensolide	Hela, KB, Med	Shen et al. (2004)
Mammea A/BA	k562, pc3, u251	Reyes-Chilpa et al. (2004)
Mammea C/OA + C/OB	k562, pc3, u251	Reyes-Chilpa et al. (2004)
Mammea A/AA cyclo F	KB	Guilet et al. (2001)
Mammea A/AB cyclo F	KB	Guilet et al. (2001)
Mammea A/AC cyclo F	KB	Guilet et al. (2001)
Caloxanthone A	KB	Ito et al. (2002)
Calophynic acid	KB	Ito et al. (2002)
Brasiliensic acid	KB	Ito et al. (2002)
Inophylloidic acid	KB	Ito et al. (2002)
Calophyllolide	KB	Ito et al. (2002)
Pyranojacareubin	KB	Ito et al. (2002)

VR vancomycin resistant, *MR* methicillin resistant

these compounds showed a favourable region of electrostatic and steric volume. The study also revealed the importance of hydrophobic and neutral-charge group for the activity (Raad et al. 2006).

5.5.4 Anticancer Activity

Mammea-type coumarins (A/BA, A/BB, B/BB and B/BA) showed anticancer activity against various cancer cell lines including BV173, HL60, HTC116, K562, MALM6, PC3, SEM, U251 and a P-glycoprotein overexpressing cell line. Study of their mechanism of action suggested that these anticancer activities are due to the induction of caspase-mediated cell death (Kimura et al. 2005). Brasixanthones A–D displayed significant anti-proliferative activity against TPA-induced Epstein-Barr virus early antigen (EBV-EA) activation in Raji cells lines (Ito et al. 2002). Similarly, 8-desoxygartanin, calanolide A, brasimarin A, brasimarin B, brasimarin C, calanolide C, calanone and mammea B/BB also showed inhibition of TPA-induced EBV-EA activation in Raji cell lines (Ito et al. 2003) (Table 5.3).

5.5.5 Antimalarial Activity

Hay et al. (2004) isolated and tested seven xanthone compounds against chloroquino-resistant strain of *Plasmodium falciparum.* The IC_{50} values of tested compounds range from 0.8 to 4.4 μg/ml. SAR study showed that the OH group position is critical for the activity and the presence of 1,1-dimethylallyl, an additional pyran ring, two isopentenyl chains or one isopentenyl chain with a pyranic ring is favourable for the activity. It was also concluded that the hydroxylation of the prenyl side chain is not required for higher activity. The resin of *C. antillanum* showed potent activity against *P. falciparum* with an IC_{50} value of 0.3 μg/ml (Cuesta-Rubio et al. 2015).

5.5.6 Anti-parasite Activity

Mammea-type coumarins (A/BA, A/BB and B/BB) showed anti-parasitic activity against *Trypanosoma cruzi* and *Leishmania amazonensis.* The observed anti-parasitic activity was due to disruption of mitochondrial swelling, which in turn loses normal ultrastructure (Reyes-Chilpa et al. 2004). Similarly, three xanthones (jacareubin, 6-deoxyjacareubin, and 1,3,5,6-tetrahydroxy-2-(3-methyl-2-butenyl) xanthone) isolated from the heartwood of *C. brasiliense* showed in vitro trypanocidal activity against epimastigotes and trypomastigotes of *T. cruzi*. Further, xanthones isolated from *C. brasiliense* showed potential against Chagas disease with IC_{100} value of 153–213 μM against trypomastigotes (Abe et al. 2004).

5.5.7 Sulphotransferase Inhibitor

Xanthones isolated from the heartwood of *C. brasiliense* showed reversible inhibition of sulphotransferases 1A1 (SULT1A1) with IC_{50} value ranging from 1.6 to 7.4 μM. Similarly, coumarins isolated from *C. brasiliense* showed inhibition of SULT1A1 with IC_{50} value ranging from 47 to 185 μM and SULT2A1 with IC_{50} value ranging from 16 to 31 μM (Mesía-Vela et al. 2001).

5.5.8 Anti-dyslipidaemic Activity

The canophyllic acid, amentoflavone and a mixture of calophyllic acid and isocalophyllic acid isolated from *C. inophyllum* showed dose-dependent lipid-lowering activity under in vivo condition in triton-induced hyperlipidaemia model (Prasad et al. 2012).

5.5.9 Antioxidant Activity and Anti-inflammatory Activity

Oil obtained from the nuts of *C. inophyllum* showed antioxidant activity by inhibiting lipid peroxidation. The antioxidant activity of the oil helps to protect skin cells from damage by reactive oxygen species (Mahmud et al. 1998). Xanthones isolated form *C. inophyllum* exhibited in vivo anti-inflammatory activity when administered through intraperitoneal or oral routes in rats (Gopalakrishnan et al. 1980).

5.5.10 Hypotensive Activity

Oku et al. (2005) studied inhibitory effects of 22 xanthones on exogenous platelet-activating factor (PAF)-induced hypotension in in vivo assay. The result of the study showed that caloxanthone E, 1,3,5,6-tetrahydroxy-2-isoprenylxanthone, 6-deoxyjacareubin and guanidine showed 60% inhibition in PAF-induced hypotension (Oku et al. 2005).

5.5.11 α-Glucosidase Activity

Two flavonoids amentoflavone and carpachromene along with two coumarins, inophyllum D and inophyllum H, isolated from the crude extracts of the bark and leaves of *C. symingtonianum* showed promising α-glucosidase activity with IC_{50} ranging from 6.4 to 62.3 μM, which was better than the synthetic drug acarbose (IC_{50} 456.4 μM) (Aminudin et al. 2015).

5.5.12 Other Activities

Coumarin named inophyllolide isolated by bioassay-guided fractionation from the nuts of *C. inophyllum* showed anti-piscicidal activity (Kawazu et al. 1968). Calofloride isolated from the seeds of *C. verticillatum* showed significant molluscicidal activity (Ravelonjato et al. 1992). Calophyllolide, a coumarin isolated from the *C. inophyllum*, showed anticoagulant action in in vivo experiments. The coagulation activity was in between the dicoumarol (slow and long acting) and ethyl biscoumacetate (very fast and short acting) (Arora et al. 1962). Amentoflavone isolated from the bark and leaves of *C. symingtonianum* showed potential 15-LOX inhibitory activity with an IC_{50} value of 0.04 μM (Aminudin et al. 2015).

5.6 Conclusions

Genus *Calophyllum* is a rich source of bioactive secondary metabolites of class xanthones, coumarins and chromanone. Other classes of secondary metabolites like triterpenoid and glycoside found in the genus *Calophyllum* have shown a wide range of biological activities like antiviral, anticancer, antimalarial, antibacterial and anti-proliferative and inhibition of P-glycoprotein (involved in the multidrug transport process) and inhibition of sulphotransferases. Calanolide A, isolated from the genus *Calophyllum*, has shown potential anti-HIV activity and continues to be in the clinical developmental stage. The dependence of calanolide A availability on isolation from the natural source has posed a problem in its further development. Various synthetic routes and alternative sources of the compounds with better yields are being explored to overcome this problem. Further studies to explore the molecular mechanism of the phytochemicals need to be done to exploit it for health benefits.

Conflict of Interest Authors declare no conflict of interest.

References

Abe F, Nagafuji S, Okabe H, Akahane H, Estrada-Muñiz E, Huerta-Reyes M, Reyes-Chilpa R (2004) Trypanocidal constituents in plants 3. Leaves of Garcinia intermedia and heartwood of *Calophyllum* brasiliense. Biol Pharm Bull 27(1):141–143

Abraham E. Materia Medica Guian. Britt. *Timehri, 3rd ser.* 1912;2

Ali MS, Mahmud S, Perveen S, Ahmad VU, Rizwani GH (1999) Epimers from the leaves of *Calophyllum* inophyllum. Phytochemistry 50(8):1385–1389

Aminudin NI, Ahmad F, Taher M, Zulkifli RM (2015) α-Glucosidase and 15-lipoxygenase inhibitory activities of phytochemicals from *Calophyllum* symingtonianum. Nat Prod Commun 10 (9):1585–1587

Arora R, Mathur C, Seth S (1962) Calophyllolide, a complex coumarin anticoagulant from *Calophyllum* inophyllum Linn. J Pharm Pharmacol 14(1):534–535

Babu V, Arya R, Ilyas M, Nasim K (1994) 9-Hydroxy-2, 2, 6, 7-tetramethyl-2H-[1]-benzopyran-(1-phenylethylene-10-yl)-[3, 2-b]-dihydropyran-4-one from *Calophyllum* tomentosum. Phytochemistry 35(2):507–510

Bhat SG, Kane JG, Sreenivasan A (1954) The in vitro evaluation of the antibacterial activity of Undi oil (*Calophyllum inophyllum* Linn.). J Am Pharm Assoc 43(9):543–546

Cao S, Low K-N, Glover RP, Crasta SC, Ng S, Buss AD, Butler MS (2006a) Sundaicumones a and B, Polyprenylated Acylphloroglucinol derivatives from *Calophyllum* sundaicum with weak activity against the glucocorticoid receptor. J Nat Prod 69(4):707–709

Cao S-G, Sim KY, Goh S (2001) Minor methylated pyranoamentoflavones from *Calophyllum* venulosum. Nat Prod Lett 15(5):291–297

Cao S-G, Sim KY, Goh SH (2006b) Minor methylated Pyranoamentoflavones from *Calophyllum* venulosum. Nat Prod Lett 15(5):291–297

Cottiglia F, Dhanapal B, Sticher O, Heilmann J (2004) New chromanone acids with antibacterial activity from *Calophyllum* brasiliense. J Nat Prod 67(4):537–541

Creagh T, Ruckle JL, Tolbert DT, Giltner J, Eiznhamer DA, Dutta B, Flavin MT, Xu Z-Q (2001) Safety and pharmacokinetics of single doses of (+)-Calanolide a, a novel, naturally occurring nonnucleoside reverse transcriptase inhibitor, in healthy, human immunodeficiency virus-negative human subjects. Antimicrob Agents Chemother 45(5):1379–1386

Cuesta-Rubio O, Oubada A, Bello A, Maes L, Cos P, Monzote L (2015) Antimicrobial assessment of resins from *Calophyllum* antillanum and *Calophyllum* inophyllum. Phytother Res 29 (12):1991–1994

Dahanayake M, Kitagawa I, Somanathan R, Sultanbawa MUS (1974) Chemical investigation of ceylonese plants. Part VII. Extractives of *Calophyllum* thwaitesii planch and Triana and *Calophyllum* walkeri Wight (Guttiferae). J Chem Soc, Perkin Trans 1:2510–2514

Dharmaratne HRW, Sajeevani JRDM, Marasinghe GPK, Ekanayake EMHGS (1998a) Distribution of pyranocoumarins in *Calophyllum* cordato-oblongum. Phytochemistry 49(4):995–998

Dharmaratne HRW, Wanigasekera WMAP, Mata-Greenwood E, Pezzuto JM (1998b) Inhibition of human immunodeficiency virus type 1 reverse transcriptase activity by Cordatolides isolated from *Calophyllum* cordato-oblongum. Planta Med 64(05):460–461

Dharmaratne HRW, Wijesinghe WMNM, Thevanasem V (1999) Antimicrobial activity of xanthones from *Calophyllum* species, against methicillin-resistant *Staphylococcus aureus* (MRSA). J Ethnopharmacol 66(3):339–342

Dharmaratne HRW, Wijesinghe WNM (1997) A trioxygenated diprenylated chromenxanthone from *Calophyllum* moonii. Phytochemistry 46(7):1293–1295

Díaz DMV (2013) Multivariate analysis of morphological and anatomical characters of *Calophyllum* (Calophyllaceae) in South America. Bot J Linn Soc 171(3):587–626

Dorla E, Grondin I, Hue T, Clerc P, Dumas S, Gauvin-Bialecki A, Laurent P (2019) Traditional uses, antimicrobial and acaricidal activities of 20 plants selected among Reunion Island's flora. S Afr J Bot 122:447–456

Eckenwalder JE (1980) Taxonomy of the West Indian cycads. J Arnold Arbor 61(4):701–722

Ee GCL, Ng KN, Taufiq-Yap YH, Rahmani M, Ali AM, Muse R (2004) Mucigerin, a new coumarin from *Calophyllum* mucigerum (Guttiferae). Nat Prod Res 18(2):123–128

Gomez-Verjan JC, Estrella-Parra EA, González-Sánchez I, Vázquez-Martínez ER, Vergara-Castañeda E, Cerbón MA, Reyes-Chilpa R (2014) Molecular mechanisms involved in the cytotoxicity induced by coumarins from C alophyllum brasiliense in K 562 leukaemia cells. J Pharm Pharmacol 66(8):1189–1195

Gopalakrishnan C, Shankaranarayanan D, Nazimudeen S, Viswanathan S, Kameswaran L (1980) Anti-inflammatory and CNS depressant activities of xanthones from *Calophyllum* inophyllum and Mesua ferrea. Indian J Pharmacol 12(3):181

Govindachari T, Prakash D, Viswanathan N (1968) Apetalactone, a new triterpene lactone from *Calophyllum* species. J Chem Soc C: Organic:1323–1324

Govindachari TR, Viswanathan N, Pai BR, Rao UR, Srinivasan M (1967) Triterpenes of *Calophyllum* inophyllum Linn. Tetrahedron 23(4):1901–1910

Grenand P, Moretti C, Jacquemin H. Pharmacopées Traditionnelles en Guyane, Créoles, Palikur. *Wayapi. Edit. ORSTOM, Paris.* 1987

Group AP (2009) An update of the angiosperm phylogeny group classification for the orders and families of flowering plants: APG III. Bot J Linn Soc 161(2):105–121
Guerreiro E, Kunesch G, Polonsky J (1973) Chromanones de l'écorce de *Calophyllum* recedens. Phytochemistry 12(1):185–189
Guilet D, Seraphin D, Rondeau D, Richomme P, Bruneton J (Oct 2001) Cytotoxic coumarins from *Calophyllum* dispar. Phytochemistry 58(4):571–575
Gunasekera SP, Jayatilake GS, Selliah SS, Sultanbawa MUS (1977) Chemical investigation of ceylonese plants. Part 27. Extractives of *Calophyllum* cuneifolium Thw. And *Calophyllum* soulattri Burm. F.(Guttiferae). J Chem Soc, Perkin Trans 1 13:1505–1511
Hanna L (1999) Calanolide A: a natural non-nucleoside reverse transcriptase inhibitor. BETA 12 (2):8
Hay AE, Guilet D, Morel C, Larcher G, Macherel D, Le Ray AM, Litaudon M, Richomme P (2003) Antifungal Chromans inhibiting the mitochondrial respiratory chain of pea seeds and new Xanthones from *Calophyllum* caledonicum. Planta Med 69(12):1130–1135
Hay A-E, Hélesbeux J-J, Duval O, Labaïed M, Grellier P, Richomme P (2004) Antimalarial xanthones from *Calophyllum* caledonicum and Garcinia vieillardii. Life Sci 75(25):3077–3085
Iinuma M, Ito T, Tosa H, Tanaka T, Miyake R, Chelladurai V (1997) Prenylated xanthonoids from *Calophyllum* apetalum. Phytochemistry 46(8):1423–1429
Iinuma M, Tosa H, Tanaka T, Yonemori S (1995) Two xanthones from roots of *Calophyllum* inophyllum. Phytochemistry 38(3):725–728
Iinuma M, Tosa H, Toriyama N, Tanaka T, Ito T, Chelladurai V (1996) Six xanthones from *Calophyllum* austroindicum. Phytochemistry 43(3):681–685
Ito C, Itoigawa M, Mishina Y, Filho VC, Enjo F, Tokuda H, Nishino H, Furukawa H (2003) Chemical constituents of *Calophyllum* brasiliense. 2. Structure of three new coumarins and cancer chemopreventive activity of 4-substituted coumarins. J Nat Prod 66(3):368–371
Ito C, Itoigawa M, Mishina Y, Filho VC, Mukainaka T, Tokuda H, Nishino H, Furukawa H (2002) Chemical constituents of *Calophyllum* brasiliensis: structure elucidation of seven new Xanthones and their cancer Chemopreventive activity. J Nat Prod 65(3):267–272
Ito C, Itoigawa M, Miyamoto Y, Rao KS, Takayasu J, Okuda Y, Mukainaka T et al (1999) A new Biflavonoid from *Calophyllum* panciflorum with antitumor-promoting activity. J Nat Prod 62 (12):1668–1671
Itoigawa M, Ito C, Tan HT-W, Kuchide M, Tokuda H, Nishino H, Furukawa H (2001) Cancer chemopreventive agents, 4-phenylcoumarins from *Calophyllum* inophyllum. Cancer Lett 169 (1):15–19
Joshi SP, Kulkarni SR, Phalgune UD, Puranik VG (2013) New dipyranocoumarin from the leaves of *Calophyllum* apetalum Willd. Nat Prod Res 27(20):1896–1901
Karunanayake S, Sotheeswaran S, Uvais M, Sultanbawa S, Balasubramaniam S (1981) Xanthones and triterpenes of *Calophyllum* tomentosum. Phytochemistry 20(6):1303–1304
Kashman Y, Gustafson KR, Fuller RW, Cardellina JH, McMahon JB, Currens MJ, Buckheit RW et al (1992) The calanolides, a novel HIV-inhibitory class of coumarin derivatives from the tropical rainforest tree, *Calophyllum* lanigerum. J Med Chem 35(15):2735–2743
Kawazu K, Ohigashi H, Mitsui T (1968) The piscicidal constituents of *Calophyllum* inophyllum Linn. Tetrahedron Lett 9(19):2383–2385
Khan M, Kihara M, Omoloso A (2002) Antimicrobial activity of *Calophyllum* soulattri. Fitoterapia 73(7–8):741–743
Khan NU-D, Parveen N, Singh MP, Singh R, Achari B, Dastidar PP, Dutta PK (1996) Two isomeric benzodipyranone derivatives from *Calophyllum* inophyllum. Phytochemistry 42(4):1181–1183
Kimura S, Ito C, Jyoko N, Segawa H, Kuroda J, Okada M, Adachi S et al (2005) Inhibition of leukemic cell growth by a novel anti-cancer drug (GUT-70) from *Calophyllum* brasiliense that acts by induction of apoptosis. Int J Cancer 113(1):158–165
Lavergne R. *Tisaneurs et plantes médicinales indigènes: l'île de La Réunion*: Éd. Orphie; 2001
Mah SH, Cheng Lian Ee G, Teh SS, Sukari MA (2015) Antiproliferative xanthone derivatives from *Calophyllum* inophyllum and *Calophyllum* soulattri. Pak J Pharm Sci 28(2):425–429

Mahmud S, Rizwani G, Ahmad M, Ali S, Perveen S, Ahmad V (1998) Antimicrobial studies on fractions and pure compounds of *Calophyllum* inophyllum Linn. Pak J Pharmacol 15(2):13–25

McKee TC, Fuller RW, Covington CD, Cardellina JH, Gulakowski RJ, Krepps BL, McMahon JB, Boyd MR (1996) New pyranocoumarins isolated from *Calophyllum* lanigerum and *Calophyllum* teysmannii. J Nat Prod 59(8):754–758

Mesía-Vela S, Sańchez R, Estrada-Muniz E, Alavez-Solano D, Torres-Sosa C, Jiménez-Estrada M, Reyes-Chilpa R, Kauffman F (2001) Natural products isolated from Mexican medicinal plants: novel inhibitors of sulfotransferases, SULT1A1 and SULT2A1. Phytomedicine 8(6):481–488

Ming M, Zhang X, Chen H-F, Zhu L-J, Zeng D-Q, Yang J, Wu G-X, Wu Y-Z, Yao X-S (2016) RXRα transcriptional inhibitors from the stems of *Calophyllum* membranaceum. Fitoterapia 108:66–72

Morel C, Séraphin D, Teyrouz A, Larcher G, Bouchara J-P, Litaudon M, Richomme P, Bruneton J (2002) New and antifungal xanthones from *Calophyllum* caledonicum. Planta Med 68 (01):41–44

Nigam S, Mitra C (1968) Constituents of *Calophyllum* tomentosum and C. apetalum nuts. Planta Med 16(04):450–457

Nigam S, Mitra C (1969) Constituents of *Calophyllum* apetalum and *Calophyllum* tomentosum trunk bark. Phytochemistry 8(01):223–224

Nigam SK, Banerji R, Rebuffat S, Pascard C, Bodo B (1988) Soulattrone a, a C24 terpenoid from *Calophyllum* soulattri. Phytochemistry 27(2):527–530

Oger J-M, Morel C, Helesbeux J-J, Litaudon M, Séraphin D, Dartiguelongue C, Larcher G, Richomme P, Duval O (2003) First 2-hydroxy-3-methylbut-3-enyl substituted xanthones isolated from plants: structure elucidation, synthesis and antifungal activity. Nat Prod Res 17 (3):195–199

Oku H, Ueda Y, Iinuma M, Ishiguro K (2005) Inhibitory effects of xanthones from Guttiferae plants on PAF-induced hypotension in mice. Planta Med 71(01):90–92

Ormancey-Potier A, Buzas A, Lederer E (1951) Sur le calophyllolide et 1′ acide calophyllique isolés des graines de *Calophyllum* inophyllum. *Bulletin de la Société Chimique de France*. 577

Patil AD, Freyer AJ, Eggleston DS, Haltiwanger RC, Bean MF, Taylor PB, Caranfa MJ, Breen AL, Bartus HR (1993) The inophyllums, novel inhibitors of HIV-1 reverse transcriptase isolated from the Malaysian tree, *Calophyllum* inophyllum Linn. J Med Chem 36(26):4131–4138

Pengsuparp T, Serit M, Hughes SH, Soejarto DD, Pezzuto JM (1996) Specific inhibition of human immunodeficiency virus type 1 reverse transcriptase mediated by soulattrolide, a coumarin isolated from the latex of *Calophyllum* teysmannii. J Nat Prod 59(9):839–842

Pires CTA, Brenzan MA, Scodro RB, DAG C, LDG L, VLD S, Cardoso RF (2014) Anti-mycobacterium tuberculosis activity and cytotoxicity of *Calophyllum* brasiliense Cambess (Clusiaceae). Mem Inst Oswaldo Cruz 109(3):324–329

Polonsky J (1957) Structure Chimique Du Calophyllolide, De Linophyllolide Et De Lacide Calophyllique, Constituants Des Noix De *Calophyllum* inophyllum. Bull Soc Chim Fr 7:1079–1087

Prasad J, Shrivastava A, Khanna A, Bhatia G, Awasthi S, Narender T (2012) Antidyslipidemic and antioxidant activity of the constituents isolated from the leaves of *Calophyllum* inophyllum. Phytomedicine 19(14):1245–1249

Raad I, Terreux R, Richomme P, Matera E-L, Dumontet C, Raynaud J, Guilet D (2006) Structure–activity relationship of natural and synthetic coumarins inhibiting the multidrug transporter P-glycoprotein. Bioorg Med Chem 14(20):6979–6987

Ravelonjato B, Libot F, Ramiandrasoa F, Kunesch N, Gayral P, Poisson J (1992) Molluscicidal constituents of Calophyllum from Madagascar: activity of some natural and synthetic neoflavonoids and khellactones. Planta Med 58(01):51–55

Reyes-Chilpa R, Estrada-Muñiz E, Apan TR, Amekraz B, Aumelas A, Jankowski CK, Vázquez-Torres M (2004) Cytotoxic effects of mammea type coumarins from *Calophyllum* brasiliense. Life Sci 75(13):1635–1647

Sakagami Y, Kajimura K, Wijesinghe W, Dharmaratne H (2002) Antibacterial activity of calozeyloxanthone isolated from *Calophyllum* species against vancomycin-resistant enterococci (VRE) and synergism with antibiotics. Planta Med 68(06):541–543

Shen Y-C, Hung M-C, Wang L-T, Chen C-Y (2003) Inocalophyllins A, B and their methyl esters from the seeds of *Calophyllum* inophyllum. Chem Pharm Bull 51(7):802–806

Shen Y-C, Wang L-T, Khalil AT, Chiang LC, Cheng P-W (2005) Bioactive pyranoxanthones from the roots of *Calophyllum* blancoi. Chem Pharm Bull 53(2):244–247

Shen Y-C, Wang L-T, Khalil AT, Kuo Y-H (2004) Chromanones and dihydrocoumarins from *Calophyllum* blancoi. Chem Pharm Bull 52(4):402–405

Stevens PF (1980) A revision of the Old World species of *Calophyllum* (Guttiferae). J Arnold Arbor 61(2):117–424

Subramanian SS, Nair A (1971) Myricetin-7-Glucoside from the androecium of the flowers of *Calophyllum* inophyllum. Phytochemistry 10(7):1679–1680

Taher M, Idris MS, Ahmad F, Arbain D (2005) A polyisoprenylated ketone from *Calophyllum* enervosum. Phytochemistry 66(6):723–726

Tee KH, Ee GCL, Ismail IS, Karunakaran T, Teh SS, Jong VYM, Mohd Nor SM (2018) A new coumarin from stem bark of *Calophyllum* wallichianum. Nat Prod Res 32(21):2565–2570

Watt G (2014) Dictionary of the economic products of India volume II (Cabbage to Cyperus). Cambridge University Press, Cambridge, pp 29–32

Yasunaka K, Abe F, Nagayama A, Okabe H, Lozada-Pérez L, López-Villafranco E, Muñiz EE, Aguilar A, Reyes-Chilpa R (2005) Antibacterial activity of crude extracts from Mexican medicinal plants and purified coumarins and xanthones. J Ethnopharmacol 97(2):293–299

Yimdjo MC, Azebaze AG, Nkengfack AE, Meyer AM, Bodo B, Fomum ZT (2004) Antimicrobial and cytotoxic agents from *Calophyllum* inophyllum. Phytochemistry 65(20):2789–2795

Zhu L-J, Yi S, Li X, Chen H-F, Ming M, Zhang X, Yao X-S (2018) C-glycosides from the stems of *Calophyllum* membranaceum. J Asian Nat Prod Res 20(1):49–54