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

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
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).

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. calophylllic acid (7) and isocalophylllic 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)
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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 pyranojacareubin (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.
| Compound name             | Species          | Part used          | Reference                  |
|--------------------------|------------------|--------------------|----------------------------|
| 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        | (1968)                    |
| 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-Cetoxyocalanolide A   | C. lanigerum     | Fruits and twigs   | Kashman et al. 1992       |
| Cordatolide A            | C. cordatoolongum| Leaves             | Dharmaratne et al. (1998a, b) |
| Cordatolide B            | C. cordatoolongum| Leaves             |                            |
| 6-Deoxyjaecrubin         | 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)
| 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-Methoxyacalanolate A             | *C. lanigerum* | Fruits and twigs        | Kashman et al. (1992)            |
| 12-Methoxyacalanolate B             | *C. lanigerum* | Fruits and twigs        |                                   |
| Soulattrolide                       | *C. souattri* | Bark                    | Gunasekera et al. (1977)         |
| 1,3,5-Trihydroxy-2-(3-methylbut-2-enyl)xanthone | *C. souattri* | Timber                  |                                   |

**Xanthones**

| Compound name                        | Species      | Part used               | Reference                        |
|-------------------------------------|--------------|-------------------------|----------------------------------|
| 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)              |
| Caloxeyloxanthone                   | *C. moonii*  | Root bark               | Dharmaratne and Wijesinghe 1997  |
| Caloxanthone                         | *C. blancoi* | Roots                   | Shen et al. (2005)               |
| Pyrojacareubin                      | *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)         |
| Trazepizofolixanthone               | *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)           |
| Calaustraline                       | *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)             |
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      | Dahayanayake 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   |                            |
| Soulattrin                                        | C. inophyllum      | Stem bark   |                            |
| 1,3,5,6-Tetrahydroxy-2-(3-hydroxy-3-methyl-butyl) | C. brasiliense     | Heartwood   | Abe et al. (2004)          |
| xanthone                                          |                    |             |                            |
| 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       | Inuma et al. (1996)        |

**Flavonoid**

| Compound name       | Species             | Part used | Reference                  |
|---------------------|---------------------|-----------|----------------------------|
| (−)-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) |
| Pyranocamentoflavone 4’-methyl ether              | C. venulosum        | Leaves    | Cao et al. (2001)          |
| Pyranocamentoflavone 7-methyl ether               | C. venulosum        | Leaves    |                            |

**Pyranochromanone**

| Compound name       | Species   | Part used | Reference                  |
|---------------------|-----------|-----------|----------------------------|
| Isocalolongic acid  | C. recedens | Bark    | Guerreiro et al. (1973)    |
| Isoinophynone       | C. inophyllum | Leaves | Khan et al. (1996)         |
| Compound name                        | Species                | Part used         | Reference                      |
|-------------------------------------|------------------------|-------------------|--------------------------------|
| Inophynone                          | *C. inophyllum*        | Leaves            | Ali et al. (1999)              |
| Apetalic acid                       | *C. blancoi*           | Seeds             |                                |
| Apetalic acid 5-O-acetate           | *C. blancoi*           | Seeds             | Shen et al. (2004)             |
| 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             |                                |
| Isoapetalic acid                    | *C. blancoi*           | Seeds             |                                |
| Isoapetalic acid 5-O-acetate        | *C. blancoi*           | Seeds             |                                |
| Isoapetalic 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-[1]-benzopyran-(1-phenylethylene-10-yl)-[3,2-b]-dihydropyran-4-one | *C. tomentosum* | Leaves | Babu et al. (1994) |

**Triterpenes and steroids**

| Compound name                        | Species                | Part used         | Reference                      |
|-------------------------------------|------------------------|-------------------|--------------------------------|
| 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              | Nigum and Mitra (1969)         |

**Glycoside**

| Compound name                        | Species                | Part used         | Reference                      |
|-------------------------------------|------------------------|-------------------|--------------------------------|
| Calophymembranside C                | *C. membranaceum*      | Stem              | Ming et al. (2016)             |

(continued)
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 [garcinin (88) and panciblfavonol (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). Pyranoamento flavone 4'-methyl ether (92) and pyranoamento flavone 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 [canophyllic acid (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 calophyembranside C (124) from the stem of *C. membranaceum*. Further, Zhu et al. (2018) isolated three C-glycosides calophyembranside D (125), calophyembranside E (126) and calophyembranside 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*. AC 24 terpeneoid, soulattrone 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 dipyrrano-tetracyclic coumarins such as calanolides, inophyllums and cordatololides 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
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) |
| Soulattrolid | HIV-RT inhibition | Pengsuparp et al. (1996) |
| Cordatolide A, B | HIV-RT inhibition | Dharmararane 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** | | |
| Dicaleolid | *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) |
| Calophylinic acid | *S. aureus* | Yimdjo et al. (2004) |
| Brasiliensis acid | *S. aureus* | Yimdjo et al. (2004) |
| Inophylloidic acid | *S. aureus* | Yimdjo et al. (2004) |

(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

| Compound                  | Property/active against | Reference(s)                      |
|---------------------------|-------------------------|-----------------------------------|
| 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)            |
| Isolocalophyllic acid     | –                       | Itoigawa et al. (2001)            |
| Calophyllolide            | –                       | Itoigawa et al. (2001)            |
| Apetatalolide             | –                       | Itoigawa et al. (2001)            |

**Cytotoxic compounds**

| Hexane extract of *C. mucigerum* stem bark | Property/active against | Reference(s)                      |
|-------------------------------------------|-------------------------|-----------------------------------|
| 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)                 |
| Calophylic acid                           | KB                      | Ito et al. (2002)                 |
| Brasiliensic acid                         | KB                      | Ito et al. (2002)                 |
| Inophyllloidalic 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 chloroquine-resistant strain of Plasmodium falciparum. The IC50 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 IC50 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 IC100 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 from *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 molluscidal 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.

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