Chemical Constituents of the Plants of the Genus *Calophyllum*

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1. Introduction. – The genus *Calophyllum* of the Guttiferae family, a large group of tropical trees consisting of *ca.* 180–200 different species [1], is well-known as a rich and valuable source of bioactive xanthones and coumarins, especially since the isolation of the calanolides (= benzo-tripyranones), a unique subclass within the HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs), has been reported [2][3]. Chromanones are also distinctive compounds of this genus. A number of plants of this genus are used as traditional herbal medicines, such as being a diuretic [4], for the treatment of malaria, venereal diseases, and for blood pressure [5], rheumatism, varicose, haemorrhoids, and chronic ulcers [6], as well as skin infections, wounds,
leprous nephritis, pain, eye diseases, and inflammations [7]. The modern pharmacology research of genus *Calophyllum* has further revealed many activities, such as antiviral, antitumor-promoting, antimalarial, antibacterial, as well as cytotoxic activity.

To facilitate further research work, in this article, we review the structures and biological properties of the known constituents from *Calophyllum*.

2. Chemical Constituents. – The compounds of *Calophyllum* species were classified into four groups: coumarins, 1–84, xanthones, 85–166, chromanones, 167–211, steroids and triterpenoids, 212–238, and some other compounds, 239–243 (see the Table).

2.1. Coumarins. Natural coumarins isolated from the *Calophyllum* genus belong, from a biogenetic point of view, to a homogeneous group of naturally occurring heterocycles with a biosynthetic scheme related to that of neoflavonoids [76]. The known coumarins of the genus *Calophyllum* isolated over the past few decades include pyranocoumarins, 1–47, furocoumarins, 48–65, furo-pyranocoumarins, 66–69, simple coumarins, 70–80, and others, 81–84. Individual members of the groups vary with respect to the substituent at C(4) of the lactone ring of the coumarins, where Me, Pr, or Ph groups may be encountered. In 1996, McKee *et al.* concluded three basic structural types of pyranocoumarins which are the most frequent coumarins (Fig. 1): i) tetracyclic dipyrano-coumarins A, in which the C rings have a geminal dimethyl moiety, e.g., compounds 1–18; ii) tricyclic pyranocoumarins B, e.g., compounds 19–32; and iii) tetracyclic dipyrano-coumarins C with reversed C and D pyran rings, i.e., the geminal dimethyl groups are in the D ring, e.g., as in compounds 33–35 [19].

![Fig. 1. Three basic structural types of pyranocoumarins](image)

Compound 10 was firstly named as (−)-calanolide B [3]. Fuller *et al.* named compound 11 as costatolide [18]. But, Spino *et al.* recognized that (−)-calanolide B and costatolide were the same compound, i.e., 10 [9]. Calanolide E (26) was first isolated from *C. lanigerum* [3]. McKee *et al.* isolated this compound and its diastereoisomer calanolide E2 (27) from the stem bark of the same plant. So, they renamed calanolide E as calanolide E1, but the configurations of the two diastereoisomers were not defined [19]. Recedesolide (31) was isolated from *C. recedens* and *C. blancoi* with different structures [26][27]. Compounds 34 and 35 were first identified as shown in Fig. 2, with the names as calanolides C and D, respectively [3], but later, their structures were revised, and they were renamed as pseudocalanolides C and D (Table) [77][78]. Calophyllic acid (36) and isocalophyllic acid (37) belong to the pyranocoumarins of type A, but the lactone ring is cleaved.
| Compound | Name | Plant | Part | Ref. |
|----------|------|-------|------|------|
| 1        | Inophyllum C | *C. inophyllum* | leaf | [2][8] |
|          |       |       | seed | [9]  |
|          |       |       | nut  | [10] |
|          |       | *C. brasiliense* | stem bark | [11] |
|          |       | *C. teysmannii var. inophyloide* | bark | [12][13] |
| 2        | Inophyllum E | *C. inophyllum* | leaf | [2][8] |
|          |       |       | seed | [9]  |
|          |       |       | nut  | [10] |
|          |       | *C. brasiliense* | stem bark | [11] |
|          |       | *C. teysmannii var. inophyloide* | bark | [12] |
| 3        | Soullattroloide | *C. teysmannii var. inophyloide* | latex | [14][15] |
| 4        | Cordatolide A | *C. lanigerum var. austrocoriaceum* | latex | [15] |
|          |       | *C. cordato-oblongum* | leaf | [16] |
|          |       |       | twig, bud | [17] |
| 5        | Cordatolide B | *C. cordato-oblongum* | leaf | [16] |
|          |       |       | twig, bud | [17] |
| 6        | 12-Methoxycordatolide B | *C. cordato-oblongum* | twig, bud | [17] |
| 7        | (+)-Calanolide A | *C. lanigerum* | fruit, twig | [3] |
| 8        | 12-Acetoxygalanolide A | *C. lanigerum* | fruit, twig | [3] |
| 9        | 12-Methoxygalanolide A | *C. lanigerum* | fruit, twig | [3] |
| 10       | (−)-Calanolide B | *C. teysmannii var. inophyloide* | latex | [18] |
| 11       | Costatolide | *C. teysmannii var. inophyloide* | latex | [18] |
|          |       | *C. cerasiferum* | seed | [9]  |
| 12       | 12-Methoxycalanolide B | *C. lanigerum* | fruit, twig | [3] |
| 13       | Calanolide F | *C. teysmannii var. inophyloide* | leaf, twig | [19] |
| 14       | Inophyllum A | *C. inophyllum* | leaf | [2]  |
|          |       | *C. brasiliense* | stem bark | [11] |
|          |       | *C. moonii* | leaf | [20] |
| 15       | Soullattroloide | *C. teysmannii var. inophyloide* | latex | [14][15][18] |
|          |       | *C. moonii* | leaf | [20] |
|          |       | *C. teysmannii* | latex | [21] |
| 16       | Inophyllum B | *C. inophyllum* | leaf | [2]  |
|          |       |       | seed | [9]  |
| 17       | Inophyllum P | *C. inophyllum* | leaf | [2]  |
| 18       | Inophyllum D | *C. inophyllum* | leaf | [2]  |
|          |       | *C. brasiliense* | stem bark | [11] |
| Compound Name | Plant Part | Plant Species | Ref. |
|----------------|------------|---------------|------|
| Calophyllolide  | nut, seed | C. inophyllum | [10] |
| Brasimarin A    | stem bark  | C. brasiliense | [11] |
| Calanone        | stem bark  | C. brasiliense | [11] |
|                 | bark       | C. teysmannii var. inophylloide | [12][13] |
| Mammea A/BA cyclo D | latex   | C. aff. biflorum | [14][15] |
| 5-Methoxy-2,2-dimethyl-6-(2-methyl-1-oxobut-2-enyl)-10-propyl-2H,8H-benzo|1,2-b:3,4-b'|dipyran-8-one | leaf | [24] |
| Cordatolide E   | stem bark  | C. lanigerum var. austrocoriaceum | [19] |
| Oblongulide     | twig, bud  | C. cordatoblongum | [17] |
| Calanolide E (calanolide E1) | fruit, twig | C. lanigerum var. austrocoriaceum | [3] |
| Calanolide E2   | stem bark  | C. lanigerum var. austrocoriaceum | [19] |
| (−)-6-Benzo|3.4-dihydro-3.4,5-trihydroxy-2,2-dimethyl-10-phenyl-2H,8H-benzo[1,2-b:3,4-b'|dipyran-8-one | seed  | [25] |
| Calopolyanolide C | seed      | C. polyanthum | [25] |
| Calopolyanolide D | seed      | C. polyanthum | [25] |
| Recedesolide    | bark       | C. recedens | [26] |
| Isorecedensolide | seed      | C. blancoi | [27] |
| Pseudocordatolide C | leaf    | C. lanigerum var. austrocoriaceum | [19] |
| Pseudocalanolide C (Calanolide C) | fruit, twig | C. lanigerum | [3] |
| Pseudocalanolide D (Calanolide D) | stem bark | C. brasiliense | [11] |
| Calophyllie acid | leaf      | C. inophyllum | [2] |
| Isocalophyllie acid | leaf   | C. inophyllum | [2] |
| Teysmanone A    | bark       | C. teysmannii var. inophylloide | [12] |
| Apetatolide     | aerial part| C. inophyllum | [22] |
| Calaustralin    | nut        | C. inophyllum | [10] |
| O-Methylisocalaustralin | bark     | C. australium | [28] |
| trans-7,8-Dihydro-5-methoxy-7,8-dimethyl-10-(3-methylbut-2-enyl)-4-phenyl-2H,6H-benzo[1,2-b:5,4-b']dipyran-2,6-dione | bark | C. teysmannii var. inophylloide | [13] |
| Compound | Name | Plant | Part | Ref. |
|----------|------|-------|------|------|
| 43 | Brasimarin C | *C. brasiliense* | stem bark | [11] |
| 44 | Calocoumarin A | *C. brasiliense* | stem bark | [11] |
| 45 | Teysmanone B | *C. teysmannii* var. inophylloide | bark | [12] |
| 46 | Isocalanone | *C. teysmannii* var. inophylloide | bark | [13] |
| 47 | Mammea A/AB cyclo E | *C. dispar* | stem bark | [29] |
| 48 | Calocoumarin B | *C. inophyllum* | aerial part | [22] |
| 49 | Mammea A/BA cyclo F | *C. dispar* | stem bark | [30] |
| 50 | Mammea A/BB cyclo F | *C. dispar* | stem bark | [30] |
| 51 | Mammea A/BC cyclo F | *C. dispar* | fruit | [30] |
| 52 | Mammea B/BA cyclo F | *C. brasiliense* | leaf | [24] |
| 53 | Mammea B/BB cyclo F | *C. brasiliense* | leaf | [24] |
| 54 | Isodisparfururan A | *C. dispar* | fruit | [30] |
| 55 | Brasimar B | *C. brasiliense* | stem bark | [11] |
| 56 | (−)-9-Benzoyl-2,3-dihydro-2-(1-hydroxy-1-methylethyl)-4-methoxy-5-phenyl-7H-furo[3,2-g][1]benzopyran-7-one | *C. teysmannii* var. inophylloide | bark | [13] |
| 57 | (−)-9-Benzoyl-2,3-dihydro-3-hydroxy-2-(1-hydroxy-1-methylethyl)-4-methoxy-5-phenyl-7H-furo[3,2-g][1]benzopyran-7-one | *C. teysmannii* var. inophylloide | bark | [13] |
| 58 | (−)-6-Benzoyl-8,9-dihydro-5-hydroxy-8-(1-hydroxy-1-methylethyl)-4-phenyl-2H-furo[2,3-h][1]benzopyran-2-one | *C. teysmannii* var. inophylloide | bark | [13] |
| 59 | Disparfururan B | *C. dispar* | stem bark | [30] |
| 60 | Disparacetylururan A | *C. dispar* | stem bark | [30] |
| 61 | Mammea A/AA deshydrocyclo F | *C. dispar* | stem bark | [30] |
| 62 | Mammea A/AA methoxy cyclo F | *C. dispar* | stem bark | [30] |
| 63 | Mammea A/AA cyclo F | *C. dispar* | stem bark | [30] |
| 64 | Mammea A/AB cyclo F | *C. dispar* | stem bark | [30] |
| 65 | Mammea A/AC cyclo F | *C. dispar* | fruit | [30] |
| 66 | Inophyllum G-1 | *C. inophyllum* | leaf | [2] |
| 67 | Inophyllum G-2 | *C. inophyllum* | leaf | [2] |
| 68 | Calocoumarin C | *C. inophyllum* | aerial part | [22] |
| 69 | Mammea A/AB dioxalanocyclo F | *C. dispar* | stem bark | [29] |
| 70 | Mammea A/BA | *C. brasiliense* | leaf | [24] |
| 71 | Mammea A/BB | *C. brasiliense* | leaf | [24] |
| 72 | Mammea B/BA | *C. brasiliense* | leaf | [24] |
| 73 | Mammea B/BB | *C. brasiliense* | stem bark | [11] |
| 74 | Mammea C/OA | *C. brasiliense* | leaf | [24] |
| 75 | Mammea C/OB | *C. brasiliense* | leaf | [24] |
| 76 | Isodispar B | *C. dispar* | fruit | [29] |
| 77 | Disparinol D | *C. dispar* | stem bark | [29] |
| 78 | Disparpropylinol B | *C. dispar* | stem bark | [29] |
| 79 | Disparinol B | *C. dispar* | stem bark | [29] |
| 80 | Disparadiol B | *C. dispar* | stem bark | [29] |
| 81 | Inocalophyllin A | *C. inophyllum* | seed | [23] |
| Compound | Name | Plant | Part       | Ref.   |
|----------|------|-------|------------|--------|
| 82       | Inocalophyllin A methyl ester | C. inophyllum | seed       | [23]   |
| 83       | Inocalophyllin B               | C. inophyllum | seed       | [23]   |
| 84       | Inocalophyllin B methyl ester  | C. inophyllum | seed       | [23]   |
| 85       | 7-Hydroxy-8-methoxyxanthone    | C. caledonicum | trunk bark | [4]    |
| 86       | 7,8-Dimethoxyxanthone          | C. caledonicum | trunk bark | [4]    |
| 87       | 6-Hydroxy-5-methoxyxanthone    | C. caledonicum | trunk bark | [4]    |
| 88       | 7-Hydroxy-5,6-dimethoxyxanthone| C. caledonicum | trunk bark | [4]    |
| 89       | 1,3,5-Trihydroxy-2-isoprenylxanthone | C. austroindicum | stem wood | [31] |
| 90       | 1-Hydroxy-7-methoxyxanthone    | C. austroindicum | stem wood | [31] |
| 91       | 6-Hydroxy-1,3,5-trimethoxyxanthone | C. austroindicum | stem wood | [31] |
| 92       | 3,6-Dihydroxy-1,5-dimethoxyxanthone | C. austroindicum | stem wood | [31] |
| 93       | 1,3,6-Trihydroxy-5,7-dimethoxyxanthone | C. austroindicum | stem wood | [31] |
| 94       | 2-Methoxyxanthone              | C. austroindicum | bark       | [31]   |
| 95       | 4-Hydroxyxanthone              | C. austroindicum | bark       | [31]   |
| 96       | 1,7-Dihydroxyxanthone          | C. austroindicum | bark       | [31]   |
|          |                                | C. ramiflorum    | heartwood  | [32]   |
|          |                                | C. inophyllum    | heartwood  | [33]   |
|          |                                | C. tomentosum    | heartwood  | [34]   |
|          |                                | C. teysmannii var. inophylloide | wood | [35] |
| 97       | 1,5-Dihydroxyxanthone          | C. inophyllum    | root bark  | [10] [36] |
| 98       | 1,5,6-Trihydroxyxanthone       | C. tomentosum    | heartwood  | [34]   |
| 99       | 1,6-Dihydroxy-5-methoxyxanthone| C. inophyllum    | heartwood  | [33]   |
|          |                                | C. tomentosum    | heartwood  | [34]   |
| 100      | 1,7-Dihydroxy-3,6-dimethoxyxanthone | C. inophyllum    | timber     | [37]   |
| 101      | 1-Hydroxy-6,7-dimethoxyxanthone | C. ramiflorum    | heartwood  | [32]   |
| 102      | 1,2,8-Trimethoxyxanthone       | C. teysmannii var. inophylloide | wood | [35] |
| 103      | 1,3,5,7-Tetramethoxyxanthone   | C. teysmannii var. inophylloide | wood     | [35] |
| 104      | 2-Hydroxyxanthone              | C. austroindicum | bark       | [31]   |
|          |                                | C. teysmannii var. inophylloide | wood     | [38] |
| 105      | 3-Hydroxy-2,4-dimethoxyxanthone | C. teysmannii var. inophylloide | wood     | [38] |
| 106      | 7-Hydroxy-1,2,8-trimethoxyxanthone | C. teysmannii var. inophylloide | wood     | [38] |
| 107      | 6-Hydroxy-1,2,5-trimethoxyxanthone | C. teysmannii var. inophylloide | wood     | [38] |
| 108      | 3,8-Dihydroxy-1,2,4-trimethoxyxanthone | C. teysmannii var. inophylloide | wood     | [38] |
| 109      | 1,7-Dihydroxy-3-methoxyxanthone | C. teysmannii var. inophylloide | wood     | [38] |
| 110      | 6-Methoxy-2-(methoxycarbonyl)xanthone | C. teysmannii var. inophylloide | wood     | [38] |
| 111      | Caloxanthone E                 | C. inophyllum    | root bark  | [39]   |
| 112      | 1,3,8-Trihydroxy-7-methoxyxanthone | C. inophyllum    | root bark  | [39]   |
| 113      | 1,3-Dihydroxy-7,8-methoxyxanthone | C. inophyllum    | root bark  | [39]   |
| 114      | 6-Hydroxy-1,5-dimethoxyxanthone | C. inophyllum    | root bark  | [39]   |
| Compound | Name                                                                 | Plant                        | Part                          | Ref.          |
|----------|----------------------------------------------------------------------|------------------------------|-------------------------------|--------------|
| 115      | 1,3,5-Trihydroxy-2-methoxyxanthone                                   | *C. inophyllum*              | root bark                      | [39]         |
| 116      | 1,3-Dihydroxy-2,5-dimethoxyxanthone                                 | *C. apetalum*               | stem wood                      | [40]         |
| 117      | 3,8-Dihydroxy-1,2-dimethoxyxanthone                                 | *C. apetalum*               | stem wood                      | [40]         |
| 118      | 1,3,5-Trihydroxyxanthone                                            | *C. apetalum*               | stem wood                      | [40]         |
| 119      | Teysmannic acid                                                     | *C. teysmannii var. inophyloide* | wood                      | [35]         |
| 120      | Scriblitifolic acid                                                 | *C. teysmannii var. inophyloide* | wood                      | [35]         |
| 121      | Caloxanthone H                                                      | *C. cordato-oblongum*       | bark, timber                   | [41]         |
| 122      | 6-(3,3'-Dimethylallyl)-1,5-dihydroxyxanthone; calophyllin B; guanandin | *C. austroindicum*          | stem wood                      | [31]         |
| 123      | 1,5-Dihydroxy-6-(4-hydroxy-3-methylbutyl)xanthone                    | *C. inophyllum*             | timber                          | [37]         |
| 124      | 1,5-Dihydroxy-6-(4-hydroxy-3-methylbut-2-enyl)xanthone               | *C. scriblitifolium*        | heartwood                      | [43]         |
| 125      | 8-(3,3'-Dimethylallyl)-1,5-dihydroxyxanthone                         | *C. brasiliense*            | heartwood                      | [42]         |
| 126      | 2-(3,3-Dimethylallyl)-1,3,5-trihydroxyxanthone                      | *C. inophyllum*             | heartwood                      | [33][44]    |
| 127      | 1,3,5,6-Tetrahydroxy-2-(3-hydroxy-3-methylbutyl)xanthone             | *C. inophyllum*             | heartwood                      | [44]         |
| 128      | 2-(3,3-Dimethylallyl)-1,3,5,6-tetrahydroxyxanthone                  | *C. neo-ebudicum*           | heartwood                      | [45]         |
| 129      | 6-Deoxy-γ-mangostin                                                 | *C. inophyllum*             | root bark                      | [44][46]    |
| 130      | Calocalabaxanthone                                                  | *C. calaba*                 | bark                           | [50]         |
| 131      | Caledonixanthone D                                                  | *C. caledonicum*            | trunk bark                     | [4]          |
| 132      | 1-Hydroxy-3,5,6-Trihydroxy-2-(3-methylbut-2-enyl)xanthone            | *C. ramiflorum*             | heartwood                      | [32]         |
| 133      | Apetalinone A                                                        | *C. apetalum*               | root                           | [40]         |
| 134      | Osajaxanthone                                                       | *C. enervosum*              | stem bark                      | [51]         |
| 135      | Jacareubin                                                          | *C. austroindicum*          | stem wood                      | [31]         |
|          |                                                                    | *C. austroindicum*          | heartwood                      | [32]         |
|          |                                                                    | *C. tomentosum*             | heartwood                      | [34]         |
|          |                                                                    | *C. cordato-oblongum*       | bark, timber                   | [41]         |
|          |                                                                    | *C. brasiliense*            | heartwood                      | [42]         |
|          |                                                                    | *C. neo-ebudicum*           | heartwood                      | [45]         |
|          |                                                                    | *C. inophyllum*             | heartwood                      | [33][44][46] |

**Table** (cont.)
| Compound | Name                                      | Plant             | Part            | Ref.       |
|----------|-------------------------------------------|-------------------|-----------------|------------|
| 136      | 6-Dehydroxyjacareucin                     | C. austroindicum  | stem wood       | [31]       |
|          |                                            | C. tomentosum     | heartwood       | [34]       |
|          |                                            | C. brasiilense    | wood            | [42]       |
|          |                                            | C. neo-ebudicum   | heartwood       | [45]       |
|          |                                            | C. inophyllum     | heartwood/timber| [33],[44],[46],[37] |
| 137      | Caloxanthone A                            | C. inophyllum     | root bark       | [10],[36]  |
| 138      | Caloxanthone C                            | C. caledonicum    | root bark       | [49],[52]  |
|          | (Inoxanthone)                             | C. inophyllum     | root bark       | [10]       |
|          | (Blancoxanthone)                         | C. blanco         | root            | [53]       |
| 139      | 3-Hydroxyblancoxanthone                   | C. inophyllum     | root bark       | [10],[36]  |
|          | (Maeturaxanthone)                        | C. caledonicum    | root bark       | [49]       |
|          |                                            | C. blanco         | root            | [53]       |
| 140      | Acetylblandoaxanthone                     | C. blanco         | root            | [53]       |
| 141      | Trapezifoliixanthone                      | C. calaba var. calaba | root bark | [47]       |
|          |                                            | C. thwaitesii     | root bark       | [48]       |
| 142      | Calabaxanthone                            | C. tomentosum     | bark             | [34]       |
|          |                                            | C. bracteatum     | root bark       | [47]       |
| 143      | Demethylcalabaxanthone                    | C. thwaitesii     | root bark       | [48]       |
|          |                                            | C. caledonicum    | root bark       | [49]       |
|          |                                            | C. walkeri        | stem bark       | [54]       |
| 144      | Dombakinaxanthone                         | C. caledonicum    | root bark       | [49]       |
|          |                                            | C. moonii         | root bark       | [55]       |
| 145      | Caledonixanthone B                        | C. caledonicum    | trunk bark      | [4]        |
| 146      | Dehydrocycloguanandin                     | C. brasiliense    | wood            | [42]       |
| 147      | Calothwaitesixanthone                     | C. thwaitesii     | root bark       | [47],[48]  |
|          |                                            | C. caledonicum    | root bark       | [49]       |
| 148      | Pyranojacaeubin                           | C. blanco         | root            | [53]       |
| 149      | Caloxanthone                              | C. blanco         | root            | [53]       |
| 150      | Thwaiteixanthone                          | C. austroindicum  | bark             | [31]       |
|          |                                            | C. thwaitesii     | root bark       | [47],[48]  |
|          |                                            | C. walkeri        | stem bark       | [54]       |
| 151      | Thwaiteixantholon                         | C. walkeri        | stem bark       | [54]       |
| 152      | 11,12-Dihydrothwaiteixanthone             | C. thwaitesii     | root bark       | [48]       |
| 153      | Cordato-oblonguxanthone                   | C. cordato-oblongum | bark, timber  | [41]       |
| 154      | Caloxanthone G                            | C. austroindicum  | stem wood       | [31]       |
| 155      | Caledonixanthone A                        | C. caledonicum    | trunk bark      | [4]        |
| 156      | Caledonixanthone B                        | C. inophyllum     | root bark       | [10],[36]  |
| 157      | Caloxanthone F                            | C. austroindicum  | stem wood       | [31]       |
| 158      | Caledonixanthone C                        | C. caledonicum    | trunk bark      | [4]        |
| 159      | 2'-Isopropenyl-3'-hydroxydihydrofuranodemethylcalabaxanone | C. walkeri | stem bark | [54] |
| 160      | Caloxanthone D                            | C. inophyllum     | root bark       | [39]       |
| 161      | Apetalinone B                             | C. apetalum       | root            | [40]       |
| 162      | Calozeyloxanthone                         | C. apetalum       | root            | [40]       |
|          |                                            | C. moonii         | root bark       | [55]       |
|          |                                            | C. zeylanicum     | bark            | [56]       |
|          |                                            | C. caledonicum    | root bark       | [40]       |
| Compound | Name | Plant | Part | Ref. |
|----------|------|-------|------|-----|
| 163      | Zeyloxanthone | C. apetalum | root | [40] |
| 164      | Tomentonone | C. apetalum | stem bark | [40] |
| 165      | Apetalinone C | C. apetalum | root | [40] |
| 166      | Apetalinone D | C. apetalum | stem bark | [40] |
| 167      | (−)-Epicatechin | C. austroindicum | bark | [31] |
|          |          | C. inophyllum | root bark | [36] |
|          |          | C. enervosum | stem bark | [51] |
| 168      | (−)-Epiafzelechin | C. apetalum | stem wood | [40] |
| 169      | Myricetin | C. inophyllum | andraecium of flowers | [57] |
| 170      | Myricetin-7-glucoside | C. inophyllum | andraecium of flowers | [57] |
| 171      | Quercetin | C. inophyllum | andraecium of flowers | [57] |
| 172      | 5,7,3′,4′-Tetrahydroxyisoflavone | C. polyanthum | seed | [25] |
| 173      | GB-1 | C. panciflorum | stem bark | [58] |
| 174      | GB-2 | C. panciflorum | stem bark | [58] |
| 175      | GB-1a | C. panciflorum | stem bark | [58] |
| 176      | GB-2a | C. panciflorum | stem bark | [58] |
| 177      | Pancibiflavonone | C. panciflorum | stem bark | [58] |
| 178      | Garcinianin | C. panciflorum | stem bark | [58] |
| 179      | GD-IV | C. panciflorum | stem bark | [58] |
| 180      | Amentoflavone | C. brasiliense | leaf | [24] |
|          |          | C. calaba | leaf | [59] |
| 181      | Isocalolonic acid | C. recedens | bark | [26] |
| 182      | 2,3-Dihydro-5-hydroxy-2,3,8,8-tetramethyl-2H-[1]benzopyran-6-(1-phenylethyl)-4H,8H-benzo[1,2-b:3,4-b′]dipyran-4-one | C. tomentosum | leaf | [60] |
| 183      | (2S,3R)-2,3-Dihydro-5-hydroxy-2,3,8,8-tetramethyl-6-(1-phenylethyl)-4H,8H-benzo[1,2-b:3,4-b′]dipyran-4-one | C. inophyllum | leaf | [61] |
| 184      | Inophynone ((2R,3R)-2,3-Dihydro-5-hydroxy-2,3,8,8-tetramethyl-6-(1-phenylethyl)-4H,8H-benzo[1,2-b:3,4-b′]dipyran-4-one) | C. inophyllum | leaf | [61][62] |
| 185      | Isoinophynone | C. inophyllum | leaf | [62] |
| 186      | Papuanic acid | C. papuanum | bark resin | [63] |
| 187      | Isopapuanic acid | C. papuanum | bark resin | [63] |
| 188      | Recedensis acid | C. recedens | bark | [26] |
| 189      | Caloverticillic acid C | C. verticillatum | stem bark | [64] |
| 190      | Caloverticillic acid A, Caloverticillic acid B | C. verticillatum | stem bark | [64] |
| 191      | Brasiliensophyllic acid B | C. brasiliense | bark | [65] |
| 192      | Brasiliensophyllic acid B | C. brasiliense | bark | [65] |
| 193      | Brasiliensophyllic acid A | C. brasiliense | bark | [65] |
| 194      | Brasiliensophyllic acid A | C. brasiliense | bark | [65] |
| 195      | Brasiliensophyllic acid A | C. brasiliense | bark | [65] |
| 196      | Brasiliensophyllic acid C | C. brasiliense | bark | [65] |
| 197      | Isobrasiliensophyllic acid C | C. brasiliense | bark | [65] |
| 198      | Caloeylanic acid | C. walkeri | leaf | [20] |
|          |          | C. lankaensis | leaf | [60] |
| 199      | Calofloridé | C. verticillatum | seed | [67] |
| Compound | Name                  | Plant                      | Part            | Ref. |
|----------|-----------------------|----------------------------|-----------------|------|
| 200      | Thwaitesic acid        | *C. lankaensis,* *C. thwaitensis* | leaf            | [66] |
| 201      | Isothwaitesic acid     | *C. lankaensis,* *C. thwaitensis* | leaf            | [66] |
| 202      | Apetalic acid          | *C. blancoi*               | seed            | [27] |
| 203      | Isoapetalic acid       | *C. blancoi*               | stem bark       | [54] |
| 204      | Apetalic acid methyl ester | *C. blancoi*               | seed            | [27] |
| 205      | Apetalic acid 5-O-acetate | *C. blancoi*               | seed            | [27] |
| 206      | Isoapetalic methyl ester | *C. blancoi*               | seed            | [27] |
| 207      | Isoapetalic acid 5-O-acetate | *C. blancoi*               | seed            | [27] |
| 208      | Chapelieric acid       | *C. calaba*                | leaf            | [59] |
| 209      | Isochapelieric acid    | *C. calaba*                | leaf            | [59] |
| 210      | Cordato-oblongic acid  | *C. cordato-oblongum*      | twig            | [17] |
| 211      | Isocordato-oblongic acid | *C. cordato-oblongum*      | stem bark       | [68] |
| 212      | Friedelin              | *C. cordato-oblongum*      | leaf            | [16] |
| 213      | Canophyllol            | *C. cordato-oblongum*      | twig            | [17] |
| 214      | Canophyllal            | *C. cordato-oblongum*      | leaf            | [66] |
| 215      | 3-Oxo-27-hydroxyacetate friedelan-28-oic acid | *C. inophyllum*           | leaf            | [69] |
| 216      | Canophyllic acid       | *C. inophyllum*            | leaf            | [69] |
| 217      | Friedelan-3β-ol        | *C. inophyllum*            | timber          | [37] |
|          |                       | *C. inophyllum*            | branch timber,  |      |
|          |                       | *C. tomentosum*            | sapwood         |      |
|          |                       | *C. lankaensis*            | bark            | [70] |
|          |                       | *C. thwaitensis*           | root bark       | [48] |
|          |                       | *C. calaba*                | leaf            | [66] |
|          |                       | *C. verticillatum*         | stem bark       | [64] |
|          |                       | *C. lankaensis*            | leaf            | [66] |
|          |                       | *C. apetalum*              | bark            | [70] |
|          |                       | *C. gracilipes*            | leaf            | [71] |
|          |                       | *C. thwaitensis*           | root bark       | [48] |
|          |                       | *C. calaba*                | leaf            | [66] |
|          |                       | *C. verticillatum*         | stem bark       | [64] |
|          |                       | *C. lankaensis*            | leaf            | [66] |
|          |                       | *C. thwaitensis*           | leaf            | [66] |
|          |                       | *C. inophyllum*            | leaf            | [69] |
|          |                       | *C. calaba*                | leaf            | [59] |
|          |                       | *C. inophyllum*            | leaf            | [69] |
|          |                       | *C. inophyllum*            | leaf            | [72] |
|          |                       | *C. inophyllum*            | leaf            | [69] |
|          |                       | *C. calaba*                | leaf            | [59] |
| Compound Name                                      | Plant                  | Part                          | Ref.   |
|----------------------------------------------------|------------------------|-------------------------------|--------|
| 218 Friedelane-3β,28-diol                          | *C. calaba*            | leaf                          | [59]   |
| 219 27-Hydroxyacetate canophyllinic acid           | *C. inophyllum*        | leaf                          | [72]   |
| 220 Ursolic acid                                   | *C. polyanthum*        | seed                          | [25]   |
| 221 Taraxerol                                      | *C. moonii*            | bark, branch, timber, sapwood | [34]   |
| 222 Taraxerone                                     | *C. tomentosum*        | root bark                     | [55]   |
| 223 α-Amyrin                                        | *C. verticillatum*     | stem bark                     | [64]   |
| 224 β-Amyrin                                        | *C. inophyllum*        | timber                        | [37]   |
| 225 Betulinic acid                                 | *C. tomentosum*        | bark                          | [54]   |
| 226 Lupeol                                          | *C. graciipes*         | leaf                          | [71]   |
| 227 Lupenone                                        | *C. graciipes*         | leaf                          | [71]   |
| 228 3β-Hydroxy-30-norlupan-20-one                  | *C. graciipes*         | leaf                          | [71]   |
| 229 Lupane-3β,20-diol                              | *C. graciipes*         | leaf                          | [71]   |
| 230 (20R)-3β-Hydroxylupan-29-oic acid              | *C. graciipes*         | leaf                          | [71]   |
| 231 3,4-Secofriedelane-3,28-dioic acid             | *C. inophyllum*        | leaf                          | [72]   |
| 232 Apetalactone                                   | *C. moonii*            | leaf                          | [20]   |
| 233 Squalene                                        | *C. lankaensis*        | leaf                          | [67]   |
| 234 Graciipes                                       | *C. graciipes*         | leaf                          | [71]   |
| 235 Sitosterol                                      | *C. ordato-oblongum*   | twig, bud                     | [17]   |
|                                                   | *C. moonii*            | leaf                          | [20]   |
|                                                   | *C. polyanthum*        | seed                          | [25]   |
|                                                   | *C. ramiflorum*        | heartwood                     | [32]   |
|                                                   | *C. inophyllum*        | timber                        | [37]   |
|                                                   | *C. thwaitesii*        | heartwood                     | [44]   |
|                                                   | *C. macrocarpum*       | stem bark                     | [54]   |
|                                                   | *C. apetalum*          | bark                          | [70]   |
|                                                   | *C. tomentosum*        | branch timber, sapwood        | [34]   |
| 236 β-Daucosterol                                   | *C. polyanthum*        | leaf                          | [71]   |
| 237 Cholesterol                                    | *C. inophyllum*        | leaf                          | [62]   |
| 238 Stigmasterol                                   | *C. macrocarpum*       | stem bark                     | [54]   |
| 239 Enervosanone: 8,8-dimethyl-5-geranyl-1,7-bis(3-methylbut-2-enyl)bicyclo[3.3.1]nonane-2,4,9-trione | *C. enervosum*        | stem bark                     | [51][73] |
| 240 Cambogin                                        | *C. enervosum*         | stem bark                     | [51]   |
| 241 Sundaicumone A                                 | *C. sundaicum*         | leaf                          | [74]   |
| 242 Sundaicumone B                                 | *C. sundaicum*         | leaf                          | [74]   |
| 243 Soulattrone A                                  | *C. soulattri*         | bark                          | [75]   |
As more coumarins were discovered in recent years, five new types of tricyclic pyranocoumarins were determined (Fig. 3): a) simple coumarins with a pyran ring fused at C(6)–C(7), which bear geminal dimethyl groups, (type D), e.g., compounds 38 and 39; b) simple coumarins with a pyran-4-one moiety fused at C(6)–C(7) (type E), e.g., compounds 40–42; c) tricyclic pyranocoumarins with a noncyclized equivalent of the C ring of the type A (type F) as represented by compounds 43–45; d) tricyclic pyranocoumarins with a noncyclized equivalent of the C ring of the type C (type G), e.g., compound 46; e) tricyclic pyranocoumarins in which the C(11)–C(12) bond of the type G is hydrogenated (type H), compound 47.

Compounds 48–65 belong to furocoumarins, in which the furan ring is fused at C(5)–C(6) (i.e., 48–55), C(6)–C(7) (i.e., 56 and 57), or C(7)–C(8) bonds (i.e., 58–65). Compounds 66, 67, and 68 possess a fused furan ring at C(5)–C(6) bond and a pyran ring at C(7)–C(8) bond. More specially, a 2-dimethylcyclopropane ring is fused to the furan ring. Mammea A/AB dioxalanocyclo F (69) isolated from C. disar has a fused furan ring with a fused dioxolane structure at the C(7)–C(8) bond.
Compounds 70–80 are simple coumarins with differences at C(4), C(6), and C(8). Compounds 81–84 represent a new class of pyranocoumarin derivatives, which contain an isoprene unit and a monoterpenes group at C(8a) of the unique pyranocoumarin ring system [23].

2.2. Xanthones. The genus *Calophyllum* is considered as a rich source of xanthone derivatives which are simply oxygenated and substituted with isoprenyl group(s) [79]. The xanthones with differences from C(1) to C(8), i.e., 85–13 are listed in the Table. Besides OH, MeO, isoprenyl, and COOMe groups, the substituents also include some special groups such as 3-carboxybutyl (*i.e.*, 119 and 120), 2,3-dihydroxy-3-methylbutyl (*i.e.*, 121), 4-hydroxy-3-methylbutyl (*i.e.*, 123), 4-hydroxy-3-methylbut-2-enyl (*i.e.*, 124), and 1,1-dimethylprop-2-enyloxy (*i.e.*, 133). The compound 122 is 1,5-dihydroxy-
| R<sup>1</sup> | R<sup>2</sup> | R<sup>3</sup> | R<sup>4</sup> | R<sup>5</sup> | R<sup>6</sup> | R<sup>7</sup> | R<sup>8</sup> |
|-------|-------|-------|-------|-------|-------|-------|-------|
| 85    | H     | H     | H     | H     | H     | OH    | MeO   |
| 86    | H     | H     | H     | H     | H     | MeO   | MeO   |
| 87    | H     | H     | H     | H     | H     | MeO   | OH    | H     |
| 88    | H     | H     | H     | MeO   | MeO   | MeO   | OH    | H     |
| 89    | H     | H     | H     | MeO   | MeO   | MeO   | OH    | H     |
| 90    | H     | H     | H     | H     | H     | MeO   | H     |
| 91    | MeO   | H     | MeO   | H     | MeO   | OH    | H     |
| 92    | MeO   | H     | OH    | H     | MeO   | OH    | H     |
| 93    | OH    | H     | OH    | H     | MeO   | OH    | MeO   |
| 94    | H     | MeO   | H     | H     | H     | H     |
| 95    | H     | H     | OH    | H     | H     | H     |
| 96    | OH    | H     | H     | H     | H     | OH    | H     |
| 97    | H     | H     | OH    | H     | H     | H     | OH    |
| 98    | OH    | H     | H     | OH    | OH    | H     | H     |
| 99    | OH    | H     | H     | MeO   | OH    | H     |
| 100   | OH    | H     | MeO   | H     | MeO   | OH    |
| 101   | OH    | H     | H     | MeO   | MeO   | H     |
| 102   | MeO   | MeO   | H     | H     | H     | H     | MeO   |
| 103   | MeO   | H     | MeO   | H     | MeO   | OH    | MeO   |
| 104   | H     | OH    | H     | H     | H     | H     |
| 105   | H     | MeO   | OH    | MeO   | H     | H     |
| 106   | MeO   | MeO   | H     | H     | H     | OH    | MeO   |
| 107   | MeO   | MeO   | H     | H     | MeO   | OH    | H     |
| 108   | MeO   | MeO   | OH    | MeO   | H     | H     | OH    |
| 109   | OH    | H     | MeO   | H     | H     | OH    | H     |
| 110   | H     | COOMe | H     | H     | H     | MeO   | H     |
| 111   | OH    | H     | OH    | H     | OH    | OH    | MeO   |
| 112   | OH    | H     | OH    | H     | H     | MeO   | OH    |
| 113   | OH    | H     | OH    | H     | H     | MeO   | MeO   |
| 114   | MeO   | H     | H     | MeO   | OH    | H     |
| 115   | OH    | MeO   | OH    | H     | OH    | H     |
| 116   | OH    | MeO   | OH    | MeO   | H     | H     |
| 117   | MeO   | MeO   | OH    | MeO   | H     | H     |
| 118   | OH    | H     | OH    | H     | OH    |
| 119   | H     | H     | H     | MeO   | A     | H     |
| 120   | OH    | H     | H     | MeO   | A     | H     |
| 121   | OH    | H     | H     | OH    | B     | H     |
| 122   | OH    | H     | H     | OH    | isoprenyl | H     |
| 123   | OH    | H     | H     | OH    | C     | H     |
| 124   | OH    | H     | H     | OH    | D     | H     |
| 125   | OH    | H     | H     | OH    | H     | isoprenyl |
| 126   | OH    | isoprenyl | OH    | H     | OH    | H     |
| 127   | OH    | E     | OH    | H     | OH    | H     |
| 128   | OH    | isoprenyl | OH    | H     | OH    | H     |
| 129   | OH    | isoprenyl | OH    | H     | H     | OH    | isoprenyl |
| 130   | OH    | isoprenyl | OH    | H     | MeO   | isoprenyl |
| 131   | OH    | MeO   | OH    | isoprenyl | OH    | H     |
| 132   | OH    | isoprenyl | MeO   | H     | MeO   | MeO   |
| 133   | OH    | isoprenyl | OH    | H     | MeO   | F     | isoprenyl |
6-(3,3-dimethylbut-2-enyl)-1,5-dihydroxyxanthone, named as calophyllin B by Jackson et al. [46], while Iinuma et al. and Gottlieb et al. named it as guanandin [31][42]. Apetalinone A (133) was a novel xanthone with 1,1-dimethylprop-2-enyloxy ether moiety, which indicated a new biosynthetic pathway including Claisen rearrangement and Diels–Alder reaction. The occurrence of a xanthone with a 1,1-dimethylallyl group was reported for the first time in 1997 [40]. Compounds 134–147 were pyranoxanthones that possess a pyran ring at C(5)–C(6), C(6)–C(7), or C(7)–C(8). Two of them were named differently by different authors, compound 138 was named as caloxanthone C, inoxanthone, or blancoxanthone [10][49][53]; compound 139 was named as macluraxanthone and 3-hydroxyblancoxanthone [10][36][49][53]. Jacareubin (135) and 6-dehydroxyjacareubin (136) are very common constituents in genus *Calophyllum*. They have been found in *C. cordato-oblongum*, *C. tomentosum*, *C. neoebudicum*, *C. brasiliense*, *C. inophyllum*, *C. ramiflorum*, and *C. austroindicum* [31–34][37][41][42][44–46]. *C. moonii* afforded a trioxygenated diprenylated chromen-xanthone, dombakinaxanthone (144) [55]. The pyranoxanthones 148–151 possess two pyran rings at C(2)–C(3) and C(6)–C(7) or C(7)–C(8). A 2,2-dimethyl-3,4-dihydropyrane ring was united in xanthones 156–160, while a furan ring was united in xanthones 156–160. Compounds 161–166 were isolated from *C. apetalum*. Iinuma et al. listed the biosynthesis of compounds 161–163 and 165 (Schemes 1 and 2) [40][56].

![Chemical structures](image)

**2.3. Chromanones. 2.3.1. Flavonoids.** Compounds 157–171 are simple flavonoids obtained from genus *Calophyllum* [31][36][40][51][57]. The isoflavone 172 was isolated from *C. polyanthum* [25].

**2.3.2. Biflavonoids.** The types of biflavonoids isolated from *Calophyllum* species are: a) flavanone-flavonol, 173 and 174; b) flavanone-flavanone, 175 and 176; c) flavanone-flavonol, 177 and 178; d) flavanone-flavone, 179; and e) flavone-flavone, 180) [24][58][59].
2.3.3. Further Chromanone Derivatives. Compounds 181–185 are five 1-benzopyran-4-one derivatives which possess an additional pyran ring fused at C(7)–C(8) bond. Papuanic and isopapuanic acids (186 and 187, resp.) represented the first pair of stereoisomeric products isolated from a species of Calophyllum [63]. Compounds 189–191 were isolated from *C. verticillatum* [64]. They have a rarely occurring cyclobutane moiety derived from the equally unusual lavandulyl chain. Compounds 190 and 191 are definitely distinct substances, since they can be easily separated on TLC plates. Small, but significant differences were also observed in the 1H-NMR spectra, particularly in the chemical shifts of the signals for the two side chains. It was proposed that the absolute configuration at C(6) may differ in compounds 190 and 191, although changes in the absolute configuration at C(22) and C(23) cannot be totally ruled out.
Unfortunately, this point was not further investigated [64]. Compounds 192–197 were obtained from the bark of C. brasiliense. Four of them also exhibit an unusual cyclobutane ring (i.e., 192–195) [65]. Calozyelianic acid (198) appears to be the biogenetic precursor of chapelieric acid (208) found in the leaf extract of C. calaba [20]. In 1984, two neoflavonoids, thwaitesic acid (200) and isothwaitesic acid (201), were isolated from C. thwaiteii and C. lankaensis. The presence of the same acids in the leaves as well as in the bark of the same plant is of biogenetic significance [66]. Compounds 202–211 are ten pyranochromanone derivatives isolated from various Calophyllum species [27][54][59][68][17].

2.4. Triterpenes and Steroids. Among the triterpenes and steroids isolated from genus Calophyllum, friedelin (212), canophyllol (213), betulinic acid (225), and sitosterol (235) are most frequent. Compound 231 is a seco-triterpenoid. Apetalactone (232) from C. lankaensis and C. moonii possesses a lactone ring. Squalene (233) and gracilipene (234) were isolated from the leaves of C. gracilipes. Gracilipene (234) is a heterocyclic trisnor-triterpene that shows an unprecedented rearranged trisnor-seco-oleanane structure with a dihydropyran ring A. The possible biosynthesis of gracilipene (234) is depicted in Scheme 3 [71].

2.5. Others. In 2005, Taher et al. isolated two phloroglucinol derivatives, enervosanone (239) and cambogin (240), from the stem bark of C. enervosum [51]. Later, Cao et al. also isolated two similar compounds, 241 and 242, from C. sundaicum, of which the structures contain a 3-propylpropanoic acid moiety not previously reported in other polypropylated acylphloroglucinols [74]. The structure of soulattrone A (243), a C24 terpenoid isolated from the bark of C. soulattri, does not obey the terpene rules sensu stricto, but it might be considered as either a modified sesterterpene or a diprenylsesquiterpene derivative [75].

3. Biological Activity. – 3.1. Antiviral Activities. Five isolated pyranoxanthones, i.e., blancoxanthone (138), 3-hydroxyblancoxanthone (139), acetylblancoxanthone (140), pyranojacaeubin (148), and caloxanthone (149), were tested against coronavirus in vitro. Compounds 138 and 148 exhibited viral inhibition with EC50 values of 3 and 15 μg/ml, respectively. This result suggested that compound 138 might be a potential candidate in the treatment of coronavirus infection [53].

Scheme 3. Plausible Biosynthesis of Gracilipene (234)
Besides, the highest attention was focused on anti-HIV activities. The calanolides and inophyllums, isolated from the genus *Calophyllum*, can be considered as NNRTIs, as they are primarily active against HIV-1 RT, but differ from the classical (synthetic) NNRTIs in their HIV sensitivity/resistance profile [80]. The following developments should be mentioned.

In 1992, eight coumarins, 7–10, 12, 26, 34, and 35, isolated from *C. lanigerum* were evaluated for their anti-HIV activity [3]. Calanolides A and B (7 and 10, resp.) were completely protective against HIV-1 replication and cytopathicity (*EC*<sub>50</sub> values of 0.1 and 0.4 μM, resp.). 12-Acetoxycalanolide A (8) was also active, albeit less potent (*EC*<sub>50</sub> 2.7 μM). The apparent *in vitro* therapeutic indices (*TI*) for compounds 7, 8, and 10 were 200, 5, and 37, respectively. Studies with purified bacterial recombinant RT revealed that the calanolides are HIV-1-specific RT inhibitors distinct from any previously known pharmacologic class. Moreover, calanolide A (7) was active not only against AZT-resistant viral strains, as well as against the A 17 strain, which is known to be resistant to non-nucleoside RT inhibitors. Therefore, the pyranocoumarins provide a
new class of anti-HIV compounds [3]. In 1993, Kashman et al. tested compounds 1, 2, 14, 16–19, 36, 37, 66, and 67 for their inhibitory activity against HIV-1 RT. Inophyllums B and P (16 and 17, resp.) inhibited HIV RT with IC$_{50}$ values of 38 and 130 µM, respectively, and both were active against HIV-1 in cell culture (IC$_{50}$ 1.4 and 1.6 µM, resp.). The configuration at C(12) is not critical, because 16 and 17 are both active at submicromolar concentrations, but the presence of a C=O group at this position lowered the activity significantly. The other compounds were much less active or inactive [2]. Soullattrolide (15), the enantiomer of inophyllum P (17), which was isolated from C. teysmannii latex, also found to be a potent inhibitor of HIV-1 RT with an IC$_{50}$ value of 0.34 µM [21]. In 2003, Yu et al. reviewed the recent progress in the development of coumarin derivatives as potent anti-HIV agents [81]. For the coumarins isolated from genus Calophyllum, they determined the structure–activity relationship as well as the mechanism of action. First, bulky substituents are required at C(4); second, both calanolides and inophyllums require Me groups at C(10) and C(11) of the chromanol ring to be trans-diaxial; third, both calanolides and inophyllums require a H-bond acceptor at C(12). In case of calanolides, the configuration at C(12) should be (S), or C=O group can be present. The configuration at C(12) of inophyllins can be either (S) or (R), but a C=O group is not allowed.

3.2. Antitumor-Promoting Activity. In 2001, Ito et al. investigated the antitumor-promoting activity of ten natural 4-phenylcoumarins using the short-term in vitro assay of 12-O-tetradecanoylphorbor-13-acetate (TPA)-induced Epstein–Barr virus early antigen (EBV-EA) activation in Raji cells [82]. The compounds are tetracyclic (i.e., 1, 2, 14, and 18), tricyclic (i.e., 19, 39, and 44), and dimethylcyclopropan fused (i.e., 48 and 68) 4-phenylcoumarins, and isocalophylllic acid (37), which were isolated from C. inophyllum. All tested compounds except for inophyllin C (1) and calocoumarin C (68) showed an inhibitory effect on EBV-EA activation, even at 1 × 10$^{-2}$ mol ratio, and only weak cytotoxicity against Raji cells, even at 1 × 10$^{-5}$ mol ratio. Calocoumarin A (44) showed more potent activity than any of the other compounds, suggesting that the prenyl side chain is decisive in increasing the antitumor-promoting effect [83]. Furthermore, calocoumarin A (44) exhibited a marked inhibitory effect on mouse skin tumor promotion in an in vivo two-stage carcinogenesis test. The results of the investigation by Ito et al. indicated that some of these 4-phenylcoumarins might be valuable as potential cancer chemopreventive agents (antitumor promoters) [82]. In 2005, Ito et al. also tested three 4-phenylcoumarins (i.e., 21, 43, and 55), and five 4-propylcoumarins (i.e., 7, 20, 23, 34, and 73), which were isolated from the stem bark of C. brasiliense [11]. All tested compounds showed inhibitory activity against EBV-EA without showing any cytotoxicity. The IC$_{50}$ values of all tested compounds were lower than that of β-carotene. Among 4-propylcoumarins, 7, 23, and 73 showed more significant activities compared with 4-phenylcoumarins, 21, 43, and 55. Mammea B/BB (73), 4-propylcoumarin with a prenyl side chain, exhibited the most potent inhibitory activity. Calanolide A (7) with trans-oriented 10,11-dimethyl groups was more potent than the corresponding cis-derivative, i.e., calanolide C (34). These results are in accordance with the pattern of anti-HIV activity that the functional groups at C(10), C(11), and C(12), and their derivatives are critical for their anti-HIV activity [11].

Besides the coumarins, the antitumor-promoting activity of biflavonoids was also evaluated in the same way. Six biflavonoids, 173–178, isolated from C. paniçiflorum,
along with two others from genus *Garcinia*, showed significant inhibitory effects at high concentrations (1 × 10^3 mol ratio) but weak cytotoxocities in assays of *Raji* cells. Among these compounds, garcinianin (178) showed the most significant inhibitory effect on EBV-EA activation (100% inhibition of activation at 1 × 10^3 mol ratio/TPA) [58].

3.3. Inhibition of the Multidrug Transporter P-glycoprotein. Raad et al. studied the structure–activity relationship of natural and synthetic coumarins originated from the genus *Calophyllum* inhibiting the multidrug transporter P-glycoprotein. Results showed a favorable electrostatic and steric volume, like the (1-hydroxy-1-methyl-ethyl)dihydrofuran moiety, fused at the C(5)–C(6) or C(7)–C(8) bond. In addition, the analysis revealed an important hydrophobic, neutral-charge group, like Ph, at C(4) of the coumarin ring [76].

3.4. Cytotoxic Activity. The coumarins isolated from *C. brasiliense* were cytotoxic against K562, U251, and PC3 human tumor cell lines. The highest activity was exhibited by mammea A/BA (70; IC\textsubscript{50} 0.04 to 0.59 μM). The mixtures of mammea A/BA + A/BB (70 and 71), mammea B/BA + B/BB (72 and 73), and mammea C/OA + C/OB (74 and 75) were also highly active (IC\textsubscript{50} < 4.05 μM). In contrast, mammea B/BA cyclo F (52) pure or in mixture with mammea B/BB cyclo F (53) were less potent with IC\textsubscript{50} values of 5.0–63 μM. The above data suggest that a Pr, pentyl, or Ph group at C(4) (i.e., 70–75) is relevant for high cytotoxic activity. On the other hand, a 6-prenyl chain (i.e., 70–75) increases cytotoxicity, but this effect decreases if this substituent is cyclized to a dihydrofuran or a pyran ring (i.e., 52 and 53) [24]. GUT-70, characterized as a tricyclic coumarin, 5-methoxy-2,2-dimethyl-6-(2-methyl-1-oxobut-2-enyl)-10-propyl-2H,8H-benzo[1,2-b:3,4-b’]dipyran-8-one (23), was tested on six human leukemic cell lines, BV173, K562, NALM6, HL60, SEM, and the colorectal adenocarcinoma cell line HCT116, including a P-glycoprotein over-expressing cell line. It significantly inhibited the growth of leukemic cells by inducing caspase-mediated and p53-independent apoptosis, and can overcome multidrug resistance [84]. The cytotoxic effect against KB cell of a number of known compounds isolated from genus *Calophyllum* was evaluated. Calophyllolide 19 displayed the most significant cytotoxic activity against KB cells with an IC\textsubscript{50} value of 3.5 μg/ml. Other compounds such as caloxanthone A (139), with an IC\textsubscript{50} value of 7.4 μg/ml, was considered, in addition to calastralin (40) and inophyllol E (2), as inactive [10]. The furanocoumarins mammea A/BA cyclo F (49), mammea A/AA cyclo F (63), mammea A/AB cyclo F (64), mammea A/AC cyclo F (65), together with other coumarins, isodispar B (76), disparpropynolol B (78), and disparinol B (79), which were all isolated from *C. dispar*, also exhibited significant activities in this assay, since these compounds inhibited 50% of the cellular growth at concentration ranging from 5 to 9 and 4 to 8 μg/ml, respectively [29][30].

3.5. Antimalarial Activity. Hay et al. tested the activity on a chloroquine-resistant strain of *Plasmodium falciparum* of seven xanthones, 129, 138, 139, 143, 144, 147, and 162, which were obtained from *C. caledonicum*. They showed IC\textsubscript{50} values from 0.8 to 4.4 μg/ml. Regarding the structure–activity relationship, the authors concluded that 1) the position of the OH groups appears to be important; 2) the substitution by a 1,1-dimethylallyl chain, or the presence of an additional pyran ring appear to be factors for good activity, as well as the substitution with two isopentenyl chains, or the combination of one isopentenyl chain and a pyranic ring; and 3) hydroxylation of the prenyl side chain is not required for higher activity [49].
3.6. Antibacterial Activity. The MeOH extracts of leaves, root, and stem barks of *C. soulattri* were partitioned with petroleum ether, CH$_2$Cl$_2$, and AcOEt. All extracts showed a range of activity against all the tested bacteria and protozoan. Fractionation improved the level of activity, particularly the petroleum ether fraction of the root bark [5]. Besides the extracts, the antibacterial activity of several constituents were also evaluated. Six chromanone acids, *i.e.*, 192–197, isolated from *C. brasiliense* showed moderate-to-strong antibacterial activity against the Gram-positive bacteria *Bacillus cereus* and *Staphylococcus epidermidis*. Compounds 194 and 195 were most active against *B. cereus*, while compounds 196 and 197 are less active. Thus, the presence of a cyclobutane ring in compounds 192–195 most probably contributes to the strong antibacterial activity [65]. Mammee A/BA + A/BB (70 + 71), and mammee C/OA + C/ OB (74 + 75) inhibited the growth of *S. aureus*, *S. epidermidis*, and *B. subtilis* [24]. The inhibition of *S. aureus* was also observed with caloeyxanthone. The *MIC* values of caloeyxanthone (162) for *S. aureus* ranged from 4.1 to 8.1 µg/ml. Hence, 162 appears to hold promise as an antimicrobial agent in the treatment of infections with *S. aureus* [85]. In 2004, Yimdjo *et al.* also evaluated the isolated compounds for their antimicrobial and potency against representative Gram-positive (*S. aureus, Vibrio anguillarium*) and Gram-negative (Escherichia coli) bacteria, and yeast, and *Candida tropicalis* organisms, in agar well diffusion assays. At the dose of 20 µg/disc, caloxanthone A (137), calophyllolide (19), and inophyllum C (1) and E (2) were found to exhibit significant inhibitory activity against *S. aureus*, but not against other microorganisms [21].

3.7. Activity in Gastrointestinal Affections. Sartori *et al.* investigated the pharmacological basis for the ethnomedicinal use of stem bark extracts of *C. brasiliense* in gastrointestinal affections. This study examined the effects of a CH$_2$Cl$_2$ fraction, obtained from the hexane extract of bark, on EtOH, indomethacin, and hypothermic restraint stress-induced gastric lesions in mice and rats, respectively. Oral administration of CH$_2$Cl$_2$ fraction at doses ranging from 12.5 to 250 µg/kg significantly inhibited the development of gastric lesions in all three test models. It caused significant decreases of the pyloric-ligation and bethanechol-stimulated gastric secretion, and also the free and total acidities. Besides, CH$_2$Cl$_2$ fraction offered protection against EtOH-induced depletion of stomach-wall mucus and reduction in nonprotein sulfhydryl concentration. The results indicate that CH$_2$Cl$_2$ fraction from *C. brasiliense* possesses antisecretory, antiulcer, and cytoprotective properties [6].

3.8. Inhibition of Sulfotransferases. Four xanthones, 127, 128, 135, and 136, and two coumarins, 70 and 74, which were obtained from *C. brasiliense*, were tested as substrates and inhibitors for two recombinant sulfotransferases (SULTs). Assays were performed using recombinant phenolsulfotransferase (SULT1A1) and hydroxysteroidsulfotransferase (SULT2A1). Two xanthones, 135 and 136, and two coumarins, 70 and 74, tested were substrates for SULT1A1, while the coumarin mammee A/BA (70) was a substrate for SULT2A1. The xanthones 127, 128, 135, and 136 reversibly inhibited SULT1A1 with *IC*$_{50}$ values ranging from 1.6 to 7.4 µM. Both coumarins 70 and 74 inhibited SULT1A1 with *IC*$_{50}$ values of 47 and 185 µM, and SULT2A1 with *IC*$_{50}$ values of 16 and 31 µM. The results indicate that SULT1A1, but not SULT2A1, is highly sensitive to inhibition by xanthones. The potency of this inhibition depends on the position and number of OH
groups. Conversely, SULT2A1 is 3–6 times more sensitive to coumarins than SULT1A1 [86].

4. Conclusions. – The plants of the genus *Calophyllum* are well known as rich sources of bioactive xanthones and coumarins. Biflavonoids and neoflavonoids are also distinctive constituents in this genus. The studies on chemical constituents in recent years have disclosed many different activities of the isolated compounds, such as antiviral activity, antitumor-promoting activity, inhibition of the multidrug transporter P-glycoprotein, cytotoxic activity, antimalarial activity, antibacterial activity, activity in gastrointestinal affections, and inhibition of sulfotransferases, especially anti-HIV activity of calanolides and inophyllins. The possible biosynthetic pathways of several compounds are also reviewed in this article. Nevertheless, there are still many plants of this genus that have not yet received enough attention. This review might provide some motivation for further investigations on genus *Calophyllum*.

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