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REVIEW ARTICLE

The *Gnidia* genus: A review.

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ABSTRACT

Gnidia is a member genus of the Thymelaeaceae comprising of about 152 species; several members of which are frequently utilized for a wide variety of ailments like asthma, backache, nightmares, dropsy, boils, sores, induce blistering, treat bruises and burns, constipation, coughs, earache, epilepsy, headache, influenza and fevers, insanity, malaria, measles, pulmonary tuberculosis, poor appetite, smallpox, snake bites, sprains and fractures, tonsillitis, to stabilize heart conditions, stomach and chest complaints, toothache, ulcers and yellow fever and as broad-spectrum purgatives. Several *Gnidia* extracts have also shown antileukemic properties. *Gnidia* elaborates a vast array of biologically active compounds that are chemically diverse and structurally complex. More than 90 compounds have been isolated from different species of *Gnidia*. This review aims at giving an outline of the variety of the secondary metabolites produced by *Gnidia*, as well as their biological activities. The genus *Gnidia* is rich in diterpene esters, coumarins, flavonoids, chromones, lignans, and neolignans. Phytochemical studies on some *Gnidia* species indicated the presence of toxic diterpene esters of daphnane type, which are the main types of plant orthoesters and have remarkable biological activities, such as antineoplastic and cytotoxic. These *gnidia* compounds may be helpful as leads in the synthesis of analogs for treating various ailments.

Keywords: *Gnidia*, Thymelaeaceae, Pharmacological profile, Phytochemistry.

1. INTRODUCTION

Thymelaeaceae family was first established in 1789 by De Jussieu, and currently 45 genera and 800 species are recognized within it. It comprises of many genera with species known to possess toxic, irritant or cocarcinogenic principles which affect animals and humans. It is regarded as a principal source of coumarins and their dimers [1, 2]. The toxic effects of members of this family is due to polyfunctional diterpenoid esters of the daphnane, tigliane and 1-alkyldaphnane type [3]. He et *al*. (2002) reviewed the diversity and biological activities of the structurally unique daphnane-type diterpene derivatives common to the Thymelaeaceae and Euphorbiaceae. Daphnane derivatives are mostly ring C-orthoseters and are more common among Thymelaeaceae than Euphorbiaceae. Daphnetoxin (1) (from several *Daphne* L. species) was the first daphnane-type derivative to be recognized. Later a derivative of daphnetoxin (1), Mezerein (2) was first isolated from *Daphne mezereum* L. It was identified as the poisonous principle responsible for livestock poisoning by the South African species *Gnidia burchellii* (Meisn.) Gilg (= *Lasiosiphon burchellii* Meisn.) [4]. Toxicity of *Gnidia* species to livestock varies with season and locality. For example, flowering plants of *Gnidia polycephala* (C. A. Mey.) Gilg are apparently more toxic than non-flowering plants [5]. *Gnidia* and other Thymelaeaceae genera have tremendous pharmacological potential, but the useful daphnane orthoesters occur in trace amounts and there still is no large-scale cultivation sufficient for commercial purposes [4].

Linnaeus described *Gnidia,* in the first publication of *Species Plantarum* in 1753. The genus was possibly named after the classical Greek port city 'Cnidus', today known as Cumali. Common names of *Gnidia* are night- and evening-scented bush and 'young-lady-gad-about-at-night', due to the flowers that are fragrant at night [6]. *Gnidia* L., when treated in the broad sense (i.e. including *Lasiosiphon* Fresen is the largest genus in the sub-cosmopolitan family,

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Thymelaeaceae, with 140-160 species occurring in Africa, Arabia, India, Madagascar, and Sri Lanka [3,7,8].

Gnidia can be found in growth forms differing from perennial herbs to shrublets, under-shrubs, shrubs or trees, arising from a woody base or rhizome, and are often ericoid. The bark can vary from a smooth to rough texture with or without lenticels. The branches are slender with alternately positioned, rarely opposite sessile leaves. Several *Gnidia* species are very showy due to their conspicuous flowers. [9-16].

Several species of *Gnidia* are both of medicinal as well as economic importance. Due to the characteristic fibrous bark of Thymelaeaceae, *Gnidia* species are used to tie bundles of wood, thatch and clothing [16]. The flowers of several species of *Gnidia* are employed for dying leather [17].

Species of *Gnidia* have been used in the traditional treatments of a variety of medicinal complaints in humans and animals. They have been used to treat a range of conditions in humans including conception and childbirth, asthma, backache, nightmares, dropsy, boils, sores, induce blistering, treat bruises and burns, constipation, coughs, earache, epilepsy, headache, influenza and fevers, insanity, malaria, measles, pulmonary tuberculosis, poor appetite, smallpox, snake bites, sprains and fractures, tonsillitis, to stabilize heart conditions, stomach and chest complaints, toothache, ulcers and yellow fever and as broad-spectrum purgatives [18-25]. Several *Gnidia* extracts have also shown antileukemic properties [4,18,19,26,27]. The Southern Sotho people believe the smoke from burning *Gnidia anthylloides* bewitches people and makes them quarrelsome. Nevertheless, they will use smoke from this plant to treat fevers and bad dreams. In livestock, *Gnidia* species have been used in the treatment of anthrax and botulism In Madagascar, leaves of *Gnidia gilbertae* Drake are used as a purge to induce vomiting [28]. Crushed roots of *G. kraussiana* are used to make fish poison, and in Madagascar the fibrous barks of *Gnidia* species are used to make rope and twine, paper and ceremonial clothing [28, 29].

Although many *Gnidia* species are used in traditional medicine, severe irritant effects as well as death in humans and animals have been reported, due to the presence of toxic coumarins and diterpene esters [16, 30, 31].

Conflict of Interest: None Declared

1. *Gnidia aberrans* C.H.Wright
2. *Gnidia albosericea* (M.Moss) B.Peterson
3. *Gnidia ambondrombensis* (Boiteau) Z.S. Rogers
4. *Gnidia anomala* Meisn.
5. *Gnidia anthylloides* (L.f.) Gilg
6. *Gnidia apiculata* (Oliv.) Gilg
7. *Gnidia bambutana* Gilg & Ledermann ex Engl.
8. *Gnidia baumiana* Gilg
9. *Gnidia baurii* C.H.Wright
10. *Gnidia bojeriana* (Decne. ex Cambess.) Baill.
11. *Gnidia burchellii* (Meisn.) Gilg
12. *Gnidia burmanii* Eckl. & Zeyh. ex Meisn.
13. *Gnidia burmanni* Eckl. & Zeyh. ex Meisn.
14. *Gnidia caffra* (Meisn.) Gilg
15. *Gnidia calocephala* (C.A.Mey.) Gilg
16. *Gnidia caniflora* Meisn.
17. *Gnidia canoargentea* (C.H.Wright) Gilg
18. *Gnidia capitata* L.f.
19. *Gnidia cayleyi* C.H.Wright
20. *Gnidia chapmanii* B.Peterson
21. *Gnidia chrysantha* (Solms) Gilg
22. *Gnidia chrysophylla* Meisn.
23. *Gnidia clavata* Schinz
24. *Gnidia compacta* (C.H.Wright) J.H.Ross
25. *Gnidia conspicua* Meisn.
26. *Gnidia coriacea* Meisn.
27. *Gnidia cuneata* Meisn.
28. *Gnidia danguyana* Leandri
29. *Gnidia decaryana* Leandri
30. *Gnidia decurrens* Meisn.
31. *Gnidia dekindtiana* Gilg
32. *Gnidia denudata* Lindl.
33. *Gnidia deserticola* Gilg
34. *Gnidia dregeana* Meisn.
35. *Gnidia dumicola* S.Moore
36. *Gnidia emini* Engl. & Gilg
37. *Gnidia ericoides* C.H.Wright
38. *Gnidia fastigiata* Rendle
39. *Gnidia flanagani* C.H.Wright
40. *Gnidia foliosa* (H.Pearson) Engl.
41. *Gnidia francisci* Bolus
42. *Gnidia fraterna* (N.E.Br.) E.Phillips
43. *Gnidia fruticulosa* Gilg
44. *Gnidia fulgens* Welw.
45. *Gnidia galpini* C.H.Wright
46. *Gnidia geminiflora* E.Mey. ex Meisn.
47. *Gnidia gilbertae* Drake
48. *Gnidia glauca* (Fresen.) Gilg
49. *Gnidia gnidioides* (Baker) Domke
50. *Gnidia goetzeana* Gilg
51. *Gnidia gossweileri* (S.Moore) B.Peterson
52. *Gnidia gymnostachya* (C.A. Mey.) Gilg
53. *Gnidia harveyana* Meisn.
54. *Gnidia heterophylla* Gilg
55. *Gnidia hibbertioides* (S. Moore) Rogers
56. *Gnidia hirsuta* (L.) Thulin
57. *Gnidia hockii* De Wild.
58. *Gnidia humbertii* (Leandri) Z.S. Rogers
59. *Gnidia humilis* Meisn.
60. *Gnidia imbricata* L.f.

61. *Gnidia inconspicua* Meisn.
62. *Gnidia insignis* Compton
63. *Gnidia involucrata* Steud. ex A.Rich.
64. *Gnidia juniperifolia* Lam.
65. *Gnidia kasaiensis* S.Moore
66. *Gnidia kraussiana* Meisn.
67. *Gnidia kundelungensis* S.Moore
68. *Gnidia lamprantha* Gilg
69. *Gnidia latifolia* (Oliv.) Gilg
70. *Gnidia laxa* (L.f.) Gilg
71. *Gnidia leipoldtii* C.H.Wright
72. *Gnidia linearifolia* (Wikstr.) B.Peterson
73. *Gnidia linearis* (Leandri) Z.S. Rogers
74. *Gnidia linoides* Wikstr.
75. *Gnidia lucens* Lam.
76. *Gnidia macropetala* Meisn.
77. *Gnidia macrorrhiza* Gilg
78. *Gnidia madagascariensis* (Lam.) Baill.
79. *Gnidia meyeri* Meisn.
80. *Gnidia microcephala* Meisn.
81. *Gnidia microphylla* Meisn.
82. *Gnidia mollis* C.H.Wright
83. *Gnidia montana* H.Pearson
84. *Gnidia multiflora* Bartl. ex Meisn.
85. *Gnidia myrtifolia* C.H.Wright
86. *Gnidia nana* (L.f.) Wikstr.
87. *Gnidia newtonii* Gilg
88. *Gnidia nitida* Bolus ex C.H.Wright
89. *Gnidia nodiflora* Meisn.
90. *Gnidia obtusissima* Meisn.
91. *Gnidia occidentalis* (Leandri) Z.S. Rogers
92. *Gnidia oliveriana* Engl. & Gilg
93. *Gnidia oppositifolia* L.
94. *Gnidia orbiculata* C.H.Wright
95. *Gnidia pallida* Meisn.
96. *Gnidia parviflora* Meisn.
97. *Gnidia parvula* Dod
98. *Gnidia pedunculata* Beyers
99. *Gnidia penicillata* Licht. ex Meisn.
100. *Gnidia perrieri* (Leandri) Z.S. Rogers
101. *Gnidia phaeotricha* Gilg
102. *Gnidia pinifolia* L.
103. *Gnidia pleurocephala* Gilg
104. *Gnidia poggei* Gilg
105. *Gnidia polyantha* Gilg
106. *Gnidia polycephala* Gilg ex Engl.
107. *Gnidia polystachya* P.J.Bergius
108. *Gnidia propinqua* (Hilliard) B.Peterson
109. *Gnidia pulchella* Meisn.
110. *Gnidia quadrifaria* C.H.Wright
111. *Gnidia quarrei* A.Robyns
112. *Gnidia racemosa* Thunb.
113. *Gnidia razakamalalana* Z.S .Rogers
114. *Gnidia rendlei* Hiern
115. *Gnidia renniana* Hilliard & B.L.Burtt
116. *Gnidia rivae* Gilg
117. *Gnidia robusta* B.Peterson
118. *Gnidia robynsiana* Lisowski
119. *Gnidia rubescens* B.Peterson
120. *Gnidia rubrocincta* Gilg
121. Gnidia scabra Thunb.
122. Gnidia scabrida Meisn.
123. Gnidia sericea L.
124. Gnidia sericocephala (Meisn.) Gilg ex Engl.
125. Gnidia setosa Wikstr.
126. Gnidia similis C.H.Wright
127. Gnidia singularis Hilliard
128. Gnidia squarossa
129. Gnidia socotrana (Balf.f.) Gilg
130. Gnidia somalensis (Franch.) Gilg
131. Gnidia sonderiana Meisn.
132. Gnidia sparsiflora Bartl. ex Meisn.
133. Gnidia spicata (L. f.) Gilg
134. Gnidia splendens Meisn.
135. Gnidia squarrosa (L.) Druce
136. Gnidia stellatifolia Gand.
137. Gnidia stenophylla Gilg
138. Gnidia stenophylloides Gilg
139. Gnidia strigillosa Meisn.
140. Gnidia styphelioides Meisn.
141. Gnidia suavissima Dinter
142. Gnidia subulata Lam.
143. Gnidia tenella Meisn.
144. Gnidia thesioides Meisn.
145. Gnidia tomentosa L.
146. Gnidia triplinervis Meisn.
147. Gnidia usafuae Gilg
148. Gnidia variabilis (C.H.Wright) Engl.
149. Gnidia variegata Gand.
150. Gnidia welwitschii Hiern
151. Gnidia wickstroemiana Meisn.
152. Gnidia woodii C.H.Wright

Table 1: List of Species in *Gnidia* genus

2. PHYTOCHEMICAL ASPECTS:

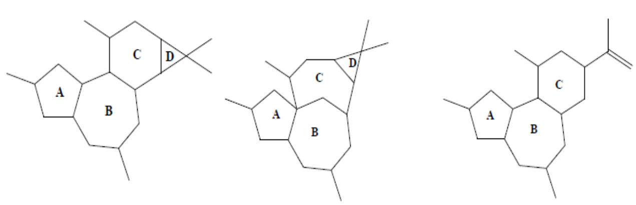
This chapter aims at giving an outline of the variety of the secondary metabolites produced by *Gnidia*, as well as their biological activities. The Thymelaeaceae plants contain coumarins, flavonoids, chromones, lignans, and neolignans [32-34]. Phytochemical studies on the Thymelaeaceae plants due to their widespread uses in medicine have been reported and there are reports on the toxicity of these plants [18]. In the last 70 years, several species of Thymelaeaceae have been the subject of numerous phytochemical studies. Initially, interest may have been due to the marked toxicity of these plants, but the widespread use of some species medicinally has certainly played a part in sustaining this interest [3]. Several genera such as *Daphne*, *Thymelaea*, *Pimelea*, *Wikstroemia* and *Gnidia* have been researched upon extensively. The *Daphne* genus is of prime importance owing to its richness in a variety of different classes of natural products, especially, coumarins [35-37], lignans [35, 38, 39], flavones [38,40,41], daphnane-type diterpene esters[42-45], steroids and guianolides [9]. *Gnidia* genus has similar chemical constitution as that *Daphne*. Chemical studies done on some *Gnidia* species indicated the presence of toxic diterpene esters of daphnane type, which are the main types of plant orthoesters known [46] and have remarkable biological activities, such as antineoplastic and cytotoxic [23,31,32,47-50]. Furthermore, phytochemical investigations revealed the occurrence of coumarins [48], lignans [51], flavonoids and benzophenone glycosides [25], umbelliferylflavonoids and spiro-bis-γ-lactone [30].

Diterpenes

Several species of Thymelaeaceae as well as Euphorbiaceae are well known for their interesting physiological and toxic effects. More than 40 years ago, Hecker isolated and finally elucidated the structure of the tumour-promoting phorbol-12,13-diesters from the seeds oil of *Croton tiglium* (Euphorbiaceae), which initiated intensive research into the pro-inflammatory and tumour-promoting diterpenes of the two plant families[52]. The chemical nature of toxic diterpenes of Thymelaeaceae has been known only for about thirty years. Although from a large structural variety, they derive all the toxicity from the basic skeletons tigliane, ingenane and daphnane type.

The tigliane, daphnane, and ingenane diterpenes esters are noted for their skin irritant and cocarcinogenic effects [53]. These compounds occur widely in toxic species of the Euphorbiaceae and Thymelaeaceae. However, many of the group, particularly orthoesters of the daphnane series, exhibit potent antileukemic activity. Hence, there has been marked interest in the structural features of this series that are conducive to antitumor activity in contrast to those that are responsible for irritant properties. Representative of the daphnane tumor inhibitors include Gnididin (8) from Gnidia *lamprantha* Gilg., Gnidimacrin (23) from *G. subcordata* (Meissn.) Engl. and Mezerein (2) from *Daphne mezereum* L [48, 50, 54-56].

Explanation on the class of Daphnanes has been emphasized owing to the above stated fact and also because they were found to be much prevalent in species of *Gnidia* and frequently occur as orthoesters. Although there exists large structural variations among these classes, but the toxicity is derived from their basic skeleton [53].



Tigliane-type Ingenane-type Daphnane-type

Tiglianes:

Tiglianes consist of a group of tetracyclic compounds which are present in plants in the form of polyhydroxyl diterpenes. They have a tricyclo[9.3.0.0]tetradecane ring system as tof hatdaphnanes; in addition a gem-dimethyl cyclopropane is fused to the 6-membered ring. They are found as mixture of many esters from Euphorbiaceae and Thymelaeaceae [53]. The most well-known member is Phorbol (21), occurs naturally in the form of its 12,13-diesters and 12,13,20-triesters. These trimesters are known as 'cryptic irritants' because they do not exhibit pro-inflammatory activity on mammalian skin unless the C-20 acyl group is removed by hydrolysis; they are potent tumour-promoting agents, inducing susceptibility at levels of carcinogen below the normal threshold [57,58].

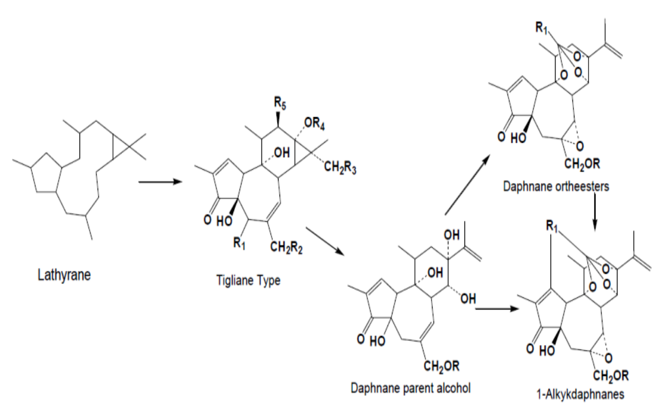
Ingenanes:

Ingenanes represent a structurally unique class of highly oxygenated teracyclic diterpene esters and are made up of Bicyclo[4.4.1]undecane ring system. They possess potent tumour-promoting properties. Ingenol (22) serves as the parent diterpene nucleus from which many of these biologically active esters are derived [59].

Daphnane Diterpenes (Daphnetoxin class diterpenes):

Quite clearly, this class of compounds is characteristic of Thymelaeaceae family. They are found in all the parts of the plant like, root, stem, leaf, fruit, and kernel. Plants from the Thymelaeaceae and the Euphorbiaceae families provide rich sources of daphnane derivatives, which generally occur as ring C-orthoesters. Most of the daphnanes possessing an orthoester function exhibit various physiological activities. They are very irritating to the mucous membranes and are powerful vesicant. This explains the use of bark of some of the species of *Gnidia* as pesticide and fish poison. They have remarkable biological activities, such as cytotoxic [23,32,48,50,60,61], neurotrophic [32, 62], antifertility [63-66], pesticidal [67], antihyperglycemic [68], anti-bladder-hyper-reflexia [69], and anti-HIV activities [70] properties.

Daphnanes are tricyclic diterpenes formed by opening of cyclopropane ring of a 12-deoxyphorbol derivative, followed by reduction of the resulting 13,14-ketol ester to 13β-isopropenyl moiety. These compounds predominantly occur naturally as orthoesters and are of considerable interest since they possess several biological actions in animals [53, 60].



Based on the presence of oxygen containing functions at the B and C rings, as well as on the substitution pattern of A ring; these daphnane derivatives are classified into four major structural classes: classes 1, 2, 3 and 4 of daphnane derivatives have been outlayed as daphnetoxins, 12-hydroxydaphnetoxins, alkyldaphnanes and resiniferonoids, respectively. Classes 1-3 possess a 5β-OH and 6α,7α-epoxy groups in the seven-membered B ring. Biological activities of structurally similar compounds vary even with small changes such as the length of a carbon chain or the position of an ester group. [4, 71].

- ***Daphnetoxins***

The compounds of class 1 are based on the absence of C-12 hydroxylation represented by daphnetoxin (1), an orthobenzoate [72]. It is isolated from plants of the Thymelaeaceae, though its analog with an aliphatic orthoester chain, huratoxin (3) [73, 74], which possesses piscicidal activity, was also found in plants of the Euphorbiaceae.

- ***12β-hydroxydaphnetoxin***

The daphnane-type orthoesters of class 2 contain a 12β-OH group, which is either free as in 12-β-hydroxydaphnetoxin (4) [75] or esterified as in 12β-acetoxyhuratoxin (5) [62, 76], kirkinine (6) [32] and kirkinine D (7) [62].

Mezerein (2) was isolated from *Lasiosiphon burchellii*, which was known to cause poisoning of sheep and other animals in South Africa[75]. It is also known to shown potent anti-leukemic property against P-388 and L-1210 leukemia in mice [53]. Structurally similar compound series such as gnididin (8), gniditrin (9), gnidicin (10) has been isolated from *Gnidia lamprantha*, which were found to possess antileukemic and weak carcinogenic effect compared with many phorbol esters[48, 77]. Interestingly, 12-hydroxydaphnetoxin (4), which bears no ester function at C-12 shows neither anti-leukemic nor carcinogenic activity [53, 78]. However its benzoate ester demonstrated activity of the same order of other esters [48]. This affirms the hypothesis that esters at C-12 may act as carrier moiety in processes concerned with cell penetration or selective complex formation [48, 67].

Similar two antileukemic diterpenes having an aliphatic orthoester and a benzoate ester at C-12, gnidilatin (11) and gnidilatidin (12) and their corresponding palmitate analogues were isolated from the same plant. Gnidilatin (11) showed moderate activity while gnidiglaucin (15) and gnidilatidin (12) did not show any activity[23, 48].

- ***1α-alkyldaphnanes***

Class 3 is those of the so-called 1α-alkyldaphnanes which contain an orthoester group incorporating to a macrocyclic bridge from C-1' to C-1 of the daphnane skeleton. Subsequently, C-1 double bond in A ring is absent and sometimes the keto group is replaced by a benzoate ester at C-3 of ring A [50, 79-84]. These represent a newer group of diterpene esters most of which are isolated from the Thymelaeaceae, and have not yet been found in Euphorbiaceae. Gnidimacrin (23) was the first compound to be encountered in this group and was isolated from *Gnidia subcordata*. Gnidimacrin (23) and its 20-palmitate (24) make part of a subclass possessing 3β-benzoyloxy group instead of the 3-C carbonyl function. Both compounds were demonstrated to have potent *in vivo* antileukaemic activity. These were the first reported diterpenoids known to contain a novel macrocyclic ring with one terminus at the orthoester carbon [50, 50, 80]. Similar compounds have been isolated from *Pimelea, Daphnopsis* and other *Gnidia* species. Daphnopsis factor R_1 (Gnilatmacrin) (25) was isolated from *Daphnopsis racemosa* and *Gnidia kraussiana* [31].

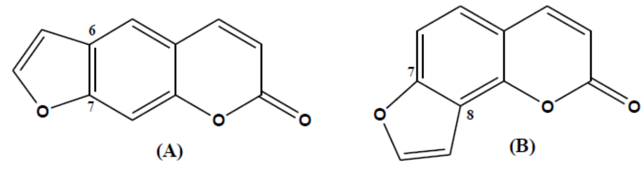
- ***Resiniferonol:***

Class 4 is that of the resiniferonols, differ from the previous type of orthoester in a way; they possess 6,7-double bonds typical of the phorbol-type esters and the secondary hydroxyl function at C-5 is absent. Resiniferonols have a very narrow distribution in plants, specifically occurring in *Euphorbia* genus [69, 85].

Resiniferatoxin (27) was isolated from *Euphorbia resinifera* and *E. unispina*, based on its extraordinary irritant activity. It is ultrapotent analog of capsaicin, and has attracted special therapeutic interest as an analgesic agent [86].

Coumarins

Generally, coumarins and its derivatives furanocoumarin are found to be present in a plethora of naturally occurring plants. Furanocoumarins are toxic compounds formed by fusion of furan ring to coumarin at C-6 and C-7 position (Linear) (B) for example, psoralen or at C-7 and C-8 position (Angular) (B) for example, angelicin as shown in figure. Even though both linear and angular furanocoumarins are derived from a common 7-hydroxycoumarin precursor (umbelliferone), they differ in their toxicological properties. [86-88].



Coumarins and Furanocoumarins are present either in the free-state or its corresponding glycosides form in nature. These are reported to be present in about 150 different species spreading over to nearly 30 different families, of which a few important ones are *Leguminosae, Umbelliferae, Solaneceae, Oleaceae, Rubiaeceae,* and *Caprifoliaceae* [87, 86].

Coumarins play a very important role in the chemotaxonomically Thymelaeaceae. More than 40 coumarins with various skeletal patterns have been reported to be isolated from several genera of Thymelaeaceae [18, 89, 90]. They are found in the form of simple coumarins, or as dimers and trimers, or in conjugated form as coumarin glycosides, flavone-coumarin, coumarinolignans etc.

***Bicoumarins*:**

The bicoumarins are a comparatively new class of coumarins and only 29 have been encountered in nature so far. The first of these series of compounds to be isolated was dicoumarol (28) in 1941 [91]. The bicoumarins isolated from plant sources fall into the following categories:

(i) The two coumarin units are linked at C3-C3' through a methylene group, i.e. dicoumarol (28) [91], gerberinol (29) [92];

(ii) The two coumarin units are linked by an ether bridge, i.e. daphnoretin (33) [93-112], acetyldaphnoretin (34) [113], edgeworthin (35) [100], candicanin (36) [114], lasiocephalin (37) [115];

(iii) In this type, two coumarin systems are attached through a carbon-carbon bond, i.e. bicoumol (38) [116], bhubaneswin (39) [117], matsukaze lactone (40) [117, 118], kotanin (41) [119-121], desmethylkotanin (42) [119], orlandin (43) [121], euphorbetin (44) [122-124], isoeuphorbetin (45) [123, 125], ipomopsin (46) [126];

(iv) Here the two coumarin units are linked through a C-10 alkyl residue (monoterpene unit), i.e. phebalin (48) [127], toddasin/mexolide (49) [128, 129], thamnosin (50) [126, 130-132], and

(v) where the two coumarin nuclei are linked through 7-methyljuglone unit as in ismailin (51) [133, 134]. In addition, there are two other bicoumarins where the two coumarin units are linked by an ether bridge at C7-C7' as well as a C-C bond at C8-C8' as in gnidicoumarin (52) [47] and in lasioerin (53) [135] the corresponding linkages are through C7-0" and C6-C6' respectively. In the only naturally occurring bicoumarin - rhamnoside, eriocephaloside (54), the coumarin nuclei are linked through an ether bridge C4-C7' and the C-C bond is at C3-C8'.

Bhandari *et al* reported isolation of a new coumarin glycoside, Erioside (55) from *Lasiosiphon eriocephalus.* From the aerial parts of the same taxon Lasiocephalin (37) was isolated, which was the first report of bicoumarin glycoside found in nature. Eriocephaloside (54), isolated from the same taxon, represents a new group of furanobiscoumarins in which the aryl ring of one unit is linked through both oxygen and carbon to the lactone ring of the second unit[1,136]. K. Franke *et al*. (2000), reported a biscoumarin 7,7'-dihydroxy-3,8'-biscoumarin (47), similar to the one with linked between C-3 and C-8'which was previously isolated from *Ipomopsis aggregata* (Polemoniaceae) [30].

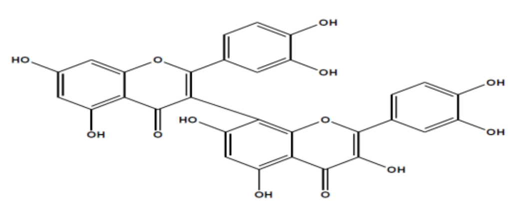
Flavonoids:

Another chemotaxonomically remarkable characteristics of Thymelaeaceae is the presence of diverse flavonoids metabolites such as flavones, flavonols, flavanones, C-glycosylflavones, C-methyl lipophilic flavonoids, less oxygenated flavones, different types of biflavonoides (spiranobiflavonoids, furanobiflavonoids), flavone-coumarin hybrids etc. More than 60 different flavonoids moieties have been reported from this family [18, 89, 90].

***Biflavanone*:**

Biflavonoids are apparently primitive chemical markers in higher plants, since they occur primarily in bryophytes, tracheophytes and gymnosperms. They are, by contrast, far less common in dicotyledonous angiosperms [137]. As compared to the monomeric flavonoids, biflavonoids are limited in structural variation. They are confined largely to oxidative coupling products of chalconaringenin. Biflavonoids are dimers of flavonoids that do not result in cleavage to anthocyanidins on treatment with strong acid. They are products of oxidative coupling mainly of flavones, flavanones and/or aurones and thus, they possess a carbonyl group at C-4 [30, 138]. As a result of this C-4 carbonyl group, the biflavonoids do not produce anthocyanidins upon hydrolysis in strongly acidic environments [139, 140].

The structure of the biflavone, manniflavanone (56) is shown below. This compound has a C-C interflavanyl linkage between the C-3 and C-8 carbons on each flavone moiety. Several biflavonoids with C-O-C interflavanyl bonds have recently been identified [139-145].



Manniflavanone (56)

Flavone–Coumarin Hybrids

This is comparatively a new class of compounds and only two flavones of this type are known so far. K. Franke et al. (2000), reported 6-(8''-Umbelliferyll)-apigenin (57) and 8-(6''-Umbelliferyll)-apigenin (58), from *Gnidia socotrana* (Thymelaeaceae) [30, 146], which represent a new structural type of natural products. However, biscoumarins and flavonoid dimers are frequently described in Thymelaeaceae [147].

Glycosides:

C-Glycosyl Flavonoids:

C-Glycosides are a special type of glycoside since the aglycone is directly attached to carbon 1 of a pyranose ring of a sugar while O-glycosides possess a hemiacetal linkage. Presently over one hundred C-glycosyl flavonoids are known to exist in the plant kingdom. Most C-glycosylflavones are known to occur naturally in pairs as 6- and 8-C-glycosyl isomers. The model compound and one of the first to be isolated was vitexin (64) (8-C-3-D-glucopyranosylapigenm), the structure of which was established by NMR spectroscopy by Horowitz and Gentjlini. The 6-C-glycosyl isomer of vitexin (64), named isovitexin (saponaretin) (65), may be formed by an intramolecular rearrangement [148,149].

Xanthone C-glucoside:

It was the first compound with a C-glucosyl residue linked to a polyoxygenated xanthone nucleus was obtained by Wiechowski in 1908 from *Mangifera indica* [34] but the final structure of mangiferin (67) as 2-C--D-glucopyranosyl-1,3,6,7-tetrahydroxyxanthone was not established until 60 years later [35-41]. Mangiferin (67), being the best-known C-glucosyl xanthone, represents the most important features of all other hitherto known related substances: the glucosyl residue is either attached to carbon 2 or 4 of the xanthone nucleus which is oxygenated in 1, 3, 6 and 5 or 7 positions, respectively.[150]

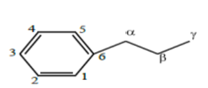
Benzophenone glycosides

Benzophenone glycosides have been isolated from several species of plants kingdom. Ferrari et al (2000) reported two benzophenone-C-glycosides, 2,3,4',5,6-pentahydroxybenzophenone-4-C-glucoside (68) and 2,4',6-trihydroxy-4-ethoxy benzophenone-2-O- glucoside (69)

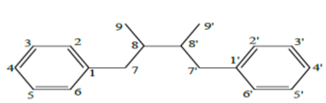
Phenylpropanoic acid glycosides

Franke *et al* (2002) reported 2-O-β-D-glucosyloxy-4-methoxybenzenepropanoic acid (70) and Methyl-2-O-β-D-glucosyloxy-4-methoxybenzenepropanoate (71) from *Gnidia socotrana.*

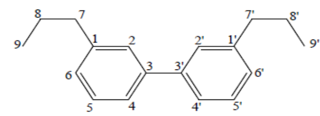
Lignans



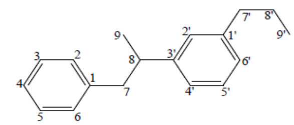
parent structure lignane



8,8'-Lignans



3,3'-Neolignans



8,3'-Neolignans

Lignans and neolignans dimers consisting of two phenyl propane monomers linked through C–C or C–O bonds and probably play an important role in defense system of in vascular plants and provide resistance against opportunistic pathogens. They also display several pharmacological activities such as antibacterial, antifungal, antitumour, antimitotic, [151-154].

A variety of lignans and neolignans have been reported from Thymelaeaceae such as furan lignans (lariciresinol (74), taxiresin (75)), furofuran lignans (pinoresinol (76)), dibenzylbutyrolactone lignans (wikstromol (78), kusunokinin (79), matairesinol (80)), diepoxy lignan (macronone (81)), coumarinolignan (daphneticin (82), daphneticin-4''-O-α-D-glucopyranoside (83)), etc. [37, 101 155-160]. Adicardin (84) and Syringin (85) were reported from *Gnidia scotrana* by Franke *et al* (2002) [30].

Spiro-bis-γ-lactone

Murray and Bradshaw (1966) suggested these substances possibly have a role of as carbohydrate storage compounds or as products of a detoxification mechanism that removes phenolic compounds. On the other hand these compounds could represent ascorbigens which are formed by the coupling of ascorbic acid and p-coumaric acid or 3-hydroxy-3-p-hydroxyphenylpropionic acid [161, 162].

K. Franke et al. (2000), for the first time reported compounds with the rare spiro-bis-g-lactone structure 4',6'-Diacetyl-viburnolide A (87), 4',6'-Diacetyl-12-coumaroyl-viburnolide A (88) and Tetraacetylviburnolide A (89), in the family of Thymeleaeceae [30]. Similar compounds, such as conocarpin, leucodrin and related substances, are typical constituents of Proteaceae [163, 164]. Murray and Bradshaw (1966) discussed a possible role of these substances as carbohydrate storage compounds or as products of a detoxification mechanism that removes phenolic compounds.

Sesquiterpenes (Guanine-type)

The sesquiterpenes are a class of compounds that have 15 carbon atoms that are formally assembled from 3 isoprene (2-methylbutane) units.

Gnididione (90) is a Furanosesquiterpene of the guaiane class, isolated from the stem wood and stem bark of the Kenyan shrub Gnidia latifolia by Kupchan and his co-workers. This was the first (and so far, only) member of the guaiane family that contains a furan ring.

Compound	Physical data	Molecular wt. (g/mol)	Molecular formula	Source and Plant part	References
Daphnane Diterpenes					
Daphnetoxin (1)	194-196^{0}C	482.52	$C_{27}H_{30}O_8$	*G.polystachya*	[165]
Mezerein (2)	258-262^{0}C	654.71	$C_{38}H_{38}O_{10}$	*L. bruchelli* *G. kraussiana*	[53, 71, 75, 166, 167]
12-Hydroxydaphnetoxin (6)	-	498	$C_{27}H_{30}O_9$	*L. burchellii*	[75, 168- 170]
Gnididin (8)	241.8^{0}C	648.73	$C_{37}H_{44}O_{10}$	*G. lamprantha*	[48, 71, 170]
Gniditrin (9) Syn: Daphne factor P_1	246.21^{0}C	646.27	$C_{37}H_{42}O_{10}$	*G. kraussiana* *G. lamprantha*	[31,48, 71, 170, 171]
Gnidicin (10) = Thymeleatoxin, *12-O-Cinnamoyl-5-hydroxy-6,7-epoxy-resiniferonol-9,13,14-orthobenzoate*	-	628.66	$C_{36}H_{36}O_{10}$	*G. kraussiana* *L.. burchellii*	[31, 75,170, 171]
Gnidilatin (11)	234.34^{0}C	652	$C_{37}H_{48}O_{10}$	*G. latifolia* *G. kraussiana*	[23,31, 71, 170]
Gnidilatidin (12) = odoracin, Yuanhuacine	204-206^{0}C	648.29	$C_{37}H_{44}O_{10}$	*G. latifolia* *G. kraussiana*	[23] [31]
Gnidilatin-20-palmitate (13)	241.02^{0}C	890	$C_{53}H_{78}O_{11}$	*G. latifolia*	[23, 71, 170]
Gnidilatidin-20-palmitate (14)	242.5^{0}C	886	$C5_3H_{74}O_{11}$	*G. latifolia*	[23, 31]
Gnidiglaucin (15)	219.8^{0}C	590.70	$C_{32}H_{46}O_{10}$	*G. glaucus*	[23, 170]
Gnidimacrin (23)	172-174^{0}C	774.89	$C_{44}H_{54}O_{12}$	*G. subcordata*	[23, 50, 71, 170]
Gnidimacrin-20-palmitate (24)		1012	$C_{60}H_{84}O_{13}$	*G. subcordata*	[50, 71]
Compound	**Physical data**	**Molecular wt. (g/mol)**	**Molecular formula**	**Source and Plant part**	**References**
Gnilatmacrin (25) = Pimelea factor P_2, Daphnopsis factor R_1	228.8^{0}C	638.78	$C_{37}H_{50}O_9$	*G. kraussiana*	[31]
Excoecariatoxin (16)	215.5^{0}C	528.63	$C_{30}H_{40}O_8$	*G. kraussiana* *G. lamprantha*	[31] [48, 172]
Pimelea factor P_1 (17) Wikstrotoxin D	212.8^{0}C		$C_{30}H_{44}O_8$	*G. lamprantha* *L.kraussiana*	[172]
Montanin (18)	214.2^{0}C	560	$C_{32}H_{48}O_8$	*G. kraussiana*	[31]
Kraussianin (80) = Linimacrin C	242.8^{0}C	654.78	$C_{37}H_{50}O_{10}$	*G. kraussiana*	[31, 173]
5β-dihydroxyresiniferonol-6α,7α-oxide (81) = Excoecaria factor O_1	-	525	$C_{30}H_{38}O_8$	*L. burchellii* *G. lamramtha*	[174]

Compound	Physical data	Molecular wt. (g/mol)	Molecular formula	Source and Plant part	References
Genkwadaphnin (99) = 12-Benzoxydaphnetoxin	-	602.63	$C_{34}H_{34}O_{10}$	*L. burchellii*	[75, 168-170]
Coumarins					
Umbelliferone (24)	230^{0}C	162.14	$C_9H_6O_3$	*G. polycephala*	[22, 175]
Lasiocephalin (28)	217-218^{0}C	336.06	$C_{19}H_{12}O_6$	*L. eriocephalus*	[1,115,176-179]
Gnidicoumarin (43)	355-365^{0}C	304.11	$C_{18}H_8O_5$	*G. lamprantha*	[23, 47, 180]
Lasioerin (44)	350^{0}C	304.11	$C_{18}H_8O_5$	*L. eriocephalus*	[54, 135, 177]
Eriocephaloside (45)	350^{0}C	466.09	$C_{24}H_{18}O_{10}$	*L. eriocephalus*	[136, 159, 177]
Erioside (46) = *6,8-dihydroxy-7-O-β-D-glucosyloxy-coumarin*	350^{0}C	518	$C_{15}H_{16}O_{10}$	*L. eriocephalus*	[166, 177]
7,7'-dihydroxy-3,8'-biscoumarin (47)	-	322.04	$C_{18}H_{10}O_6$	*G. socotrana* (Leaves and twigs)	[30]
Daphnetin (83) =*3,4-dihydroxycoumarin*	253-256^{0}C	178.14	$C_9H_6O_4$	*L. polycephalus*	[181]
Daphnetin-8-β-D-glucoside (84)	263.4^{0}C	340.07	$C_{15}H_{16}O_9$	*G. polycephala*	[181]
Flavonoids					
Manniflavanone (48)	220-225^{0}C	590	$C_{30}H_{22}O_{13}$	*G. involucrata* (Aerial parts)	[25]
6-(8''-Umbelliferyll)-apigenin (49)	360^{0}C	453.05	$C_{24}H_{14}O_8$	*G. socotrana* (Leaves and twigs)	[30]
8-(6''-Umbelliferyll)-apigenin (50)	270-275^{0}C	453.05	$C_{15}H_{16}O_{10}$	*G. socotrana* (Leaves and twigs)	[30]
Genkwanin (85) = *4',5-Dihydroxy-7-methoxyflavone*	277-279^{0}C	284.27	$C_{16}H_{12}O_5$	*L. eriocephalus*	[136, 177,182]
Genkwanin-4'-0-β-D-glucopyranosyl-(l-3) D-xylopyranoside (86)	-	608.17	$C_{28}H_{32}O_{15}$	*L. eriocephalus*	[182]
Kaempferol-3-O-glucoside (87) =: Astragalin	312.58^{0}C	448.38	$C_{21}H_{20}O_{11}$	*G. involucrata* (Aerial parts)	[25]
Kaempferol-3-(p-coumaroyl)-O-β-D-glucopyranoside(88) =Tiliroside	214-2160C	594.52	$C_{30}H_{26}O_{13}$	*G. kraussiana*	[18]
Gnidia biflavonoid 4a (89) *(2S,2'R,3R,3'R)-2,2',3,3'-Tetrahydro-3',5,5',7,7'-pentahydroxy-2-(4-hydroxyphenyl)-2'-(3,4,5-trihydroxyphenyl)-[3,8'-bi-4H-1-benzopyran]-4,4'-dione*		590.10	$C_{30}H_{22}O_{13}$	*G. involucrata* (Aerial parts)	[141]
C- Glycosyl flavonoids					
Vitexin (51) *8-C-β-D-glucopyranosylapigenin*	262-264^{0}C	432	$C_{21}H_{20}O_{10}$	*G. involucrate*	[25, 183]

Compound	Physical data	Molecular wt. (g/mol)	Molecular formula	Source and Plant part	References
Isovitexin (52) = Saponaretin, *6-C-β-D-glucopyranosylapigenin*	244–246^{0}C.	432	$C_{21}H_{20}O_{10}$	*G. involucrata* (Aerial parts)	[25, 183]
Isoorientin (93)= *Luteolin 6-C-β-D-glucoside*	244–246^{0}C.	448	$C_{21}H_{20}O_{11}$	*G. involucrata* (Aerial parts)	[25, 183]
Yuankanin (94)= Genkwanin-5-O-β-D-primeveroside, *4 ',5-dihydroxy-6-[(6-O-β-D-xylopyranosyl-β--glucopyranosyl) oxy]-7-methoxyflavone*	301.9^{0}C	578.51	$C_{27}H_{30}O_{14}$	*G. involucrata* (Aerial parts)	[25, 184]
Xanthone C-Glycosides					
Mangiferin (53) = *1,3,6,7-Tetrahydroxy-2-[3,4,5-trihydroxy-6-(hydroxymethyl) oxan-2-yl]xanthen-9-one*	271-274^{0}C	422.34	$C_{19}H_{18}O_{11}$	*G. involucrata* (Aerial parts)	[25, 177, 183]
Benzophenone Glycosides					
Mahkoside A (90) = *4,4'-dihydroxy-6-methoxybenzophenone-2-O-β-D-glucopyranoside*	-	422	$C_{20}H_{22}O_{10}$	*G. involucrata* (Aerial parts)	[25, 185, 186]
2,3,4',5,6-pentahydroxybenzophenone-4-C-glucoside (54)	168-171^{0}C	424	$C_{19}H_{20}O_{11}$	*G. involucrata* (Aerial parts)	[25]
2,4',6-trihydroxy-4-methoxybenzophenone-2-O-glucoside (55)	135^{0}C	422	$C_{20}H_{22}O_{10}$	*G. involucrata* (Aerial parts)	[25]
Phenyl propanoid glucosides					
2-O-α-Dglucosyloxy-4-methoxy benzenepropanoic Acid (56)	168–169^{0}C	358	$C_{16}H_{22}O_9$	*G. polycephala*	[22, 318]
Methyl 2-O-β-D-glucosyloxy-4-methoxybenzenepropanoate (57)	168–169^{0}C	372	$C_{17}H_{24}O_9$	*G. polycephala*	[22, 318]
Compound	**Physical data**	**Molecular wt. (g/mol)**	**Molecular formula**	**Source and Plant part**	**References**
Lignans					
Adicardin (71) = *7-O-beta-D-Apiofuranosyl-(1-6)-beta-D-glucopyranosyl-umbelliferone*	201-202^{0}C	456.4	$C_{20}H_{24}O_{12}$	*G. polycephala*	[22, 318]
Syringin (72) = *4-[(1E)-3-Hydroxyprop-1-en-1-yl]-2,6-dimethoxyphenyl β-D-glucopyranoside*	109-111^{0}C	372.37	$C_{17}H_{24}O_9$	*G. polycephala*	[22,136, 177,318]

Compound	Physical data	Molecular wt. (g/mol)	Molecular formula	Source and Plant part	References
Gnidifolin (91) = *[trans-2(2,4-dihydroxy-3methoxybenzyl)-3-(4'-hydroxy-3'-methoxybenzyl) butyrolactone]*	-	374	$C_{20}H_{22}O_7$	*G. latifolia*	[51]
Syringaresinol (92) = *(2,6-bis (4-hydroxy-3,5-dimethoxyphenyl)-3,7-dioxabicyclo [3.3.0] octane)*	183-184^{0}C	418.43	$C_{22}H_{26}O_8$	*L. eriocephalus*	[136, 177, 187]
Spiro-bis-γ-lactone					
4’,6’-Diacetyl-viburnolide A (73)	-	568.13	$C_{25}H_{27}O_{15}$	*G. socotrana* (Leaves and twigs)	[30]
4’,6’-Diacetyl-12-coumaroyl-viburnolide A (74)	-	713.17	$C_{34}H_{33}O_{17}$	*G. socotrana* (Leaves and twigs)	[30]
Tetraacetylviburnolide A (75)	219-221^{0}C -	652.16	$C_{29}H_{32}O_{17}$	*G. socotrana* (Leaves and twigs)	[30]
Sesquiterpenes (Guanine-type) *Guanine Furanosesquiterpenoid*					
Gnididione (76)	-	244.29	$C_{15}H_{16}O_3$	*G. latifolia*	[188- 190]
Isognididione (95)	-	244.29	$C_{15}H_{16}O_3$	*G. latifolia*	[188- 190]
Compound	**Physical data**	**Molecular wt. (g/mol)**	**Molecular formula**	**Source and Plant part**	**References**
Sterols					
β- Sitosterol (96)	136-140^{0}C	414.71	$C_{29}H_{50}O$	*G. kraussiana*	[18, 136, 177]
β- Sitosterol-β-Dglucoside (97)	361^{0}C	576.8	$C_{35}H_{60}O_6$	*G. kraussiana* *L. eriocephalus*	[18, 182]
γ-Pyrone					
Maltol (98) *3-Hydroxy-2-methyl-4H-pyran-4-one*	161-162^{0}C	126.11	$C_6H_6O_3$	*G. kraussiana*	[18]
Lipids and Fatty acids					
n-Eicosanol, 1-Glyceryloctacosanoate, n-Octacosanol, Palmitic acid				*G. kraussiana* *L. meissnerianus*	[18, 191]
Amino acid					
Alanine, γ-Aminobutyric acid, Arginine, Aspartic acid, Cystine, Glutamic acid, Glycine, Aminoacetic acid, Histidine, Isoleucine, Leucine, Lysine, Methionine, Phenylalanine, Proline, Serine, Threonine, Tyrosine, Valine				*L. eriocephalus*	[192]
				L. eriocephalus	[192]
Sugars					
Glucose, Maltose, Raffinose, Rhamnose				*L. eriocephalus*	[192]
Simple organic acids					
Citric acid, Fumaric acid, Malic acid, Malonic acid				*L. eriocephalus*	[192]

Table: 2: Phytochemical aspects of *Gnidia* species

Biological Aspects:

Plants of Thymelaeaceae as well as Euphorbiaceae are well known for their interesting physiological activities. Several *Gnidia* and other African Thymelaeaceae species have been used in the traditional treatments of a variety of medicinal complaints in humans and animals. The toxicity of plants in the Thymelaeaceae is well established for humans as well as for several animal species [3]. The diterpenes esters of tigliane and daphnane type are of violent purgatives, which trigger off, by contact with the skin or mucous membranes, an intense inflammatory reaction [193].

The symptoms of systematic toxicity resulting from ingestion of the plant material include: inflammation of lips, larynx and pharynx, dryness buckle cavity followed by salivation, difficult in swallowing, thirst; rhinitis, edema of eyelids; dizziness, abdominal pain, vomiting, diarrhoea with discharge of blood; albuminuria and blackwater fever, slow respiration, rapid pulse; pale, cold and moist skin; muscular twitching, delirium and drowsiness which can last several days. These symptoms are followed by convulsion and death in 20-25% of cases [194,3].

From Anti-feedant experiments of *Lasiosiphon anthylloides* Meisn., Watt and Breyer-Brandwijk concluded that, the plant in its flowering stage, on ingestion of 4 oz. by sheep or 12 oz. by cattle and horses produced death so rapidly that without any symptoms, apart from acute abdominal pain. Ingestion of smaller amounts produces hemorrhagic gastro-enteritis, pyrexia, inflammatory changes in the intestines, and death. Hutchence fed one pound of *Gnidia ovalifolia* Meisn. leaves daily to cattle and observed development of frothing in the mouth, dullness, absence of rumination, pyrexia, progressive diarrhea, anorexia, progressive weakness, mucous discharge from the eyes, nostrils and vagina, gastroenteritis, hyperemia of the stomach and intestines, congestion of the kidney and death in fifteen days[3, 195].

The toxicity of plants in the Thymelaeaceae is of considerable economic importance beyond its effects on the livestock industry. Several genera including *Gnidia* and *Lasiosiphon* are used as fish poisons in Europe, Africa, Asia, and the islands of the South Pacific. Several genera are also used as hunting poisons in Africa and Asia. [3].

In France, extracts of *Lasiosiphon kraussiana* Hutch. et Dalz, have been patented for use in the treatment of leprosy [375,376] [3]. Clinical trials are being conducted in China on preparations of *Daphne, Gnidia, Wikstroemia* and Pimelea species that have been reported to have anticancer activity [46,133,184,186,187,189,212,355,368,431]. The abortifacient and anticancer activities of these products have been shown to be due primarily to the presence of daphnane esters. Plants of this family have been included in several large-scale screening studies [24, 25, 72, 73,161,228] investigating various biological activities.

Esters of diterpene alcohols having the daphnane and tigliane skeleta are reported to be responsible for the irritancy, cocarcinogenicity, abortifacient activity and antileukemic activity of this plant family. This class of compounds has been extensively reviewed [3,87,124-126].

Sr No.	Species	Traditional Use / effects noted
1.	*Gnidia spp*	Abdominal pain, sore throat, as a purgative, as laxative, wounds healing, burns, snakebites, as molluscicidal agent, as arrow and fish poison[30], Asthma, eye diseases and pthisis, drastic purgative (root), blood purifier (root-bark), cough, headche, toothache, analgesic (Root-wood) [195-198], caused diarrhoea and emphysema [199], Analgesic, Antispasmodic, decongestant, toxic (leaves)[200], Vesicant [201]
2.	*G. anthylloides (L.f.) Gilg*	Cough [195, 202]
3.	*G. buchananii*	Bronchitis and abdominal pain(root) [198]
4.	*G. burchelli* (Meisn.) Gilg.	Caused severe irritation to eyes, nose and skin, dyspnoea. Coughing headache and nausea [5], caused diarrhoea and emphysema [199, 203, 204], Toxic and irritant [204, 205, 317]
5.	*Gnidia capitata* L. f. *(syn. Lasiosiphon capirarus)*	Leaves snuffed and also applied as a poultice for toothache[196, 204], Roots Smoke is inhaled for asthma, [206, 204], Anthrax (root)[207, 208],Treats constipation and menstrual pains, gastrointestinal complaints, earache, appetite, burns snake bite, boils and eases child birth [209], used in pregnancy and childbirth [210, 167], toxic and irritant [211].
6.	*G. carinata* Thunb.	Emetic (Fruit and leaves) [198, 212]
7.	*G. chrysantha* Gilg	Abortifacient, purgative, as body wash in fever (Root and leaves) [196], toxic and irritant [196]
8.	*G. cuneata* Meisn. (syn. *Lasiosiphon meisneri* End.)	Roots used for snakebite and toothache [20,204]
9.	*Gnidia danguyana* J. Leand.	Anti-Malarial and febrifuge (Aerial parts)[213]

10.	*G. genkwa*	[62]
11.	*G. glabra*	Laxative and emetic (root)[214]
12.	*G. goetzeana* Gilg.	Antitussive (root) [198]
13.	*G. gymnostachya* Glig.	Analgesic [215, 204] Analgesic, Antispasmodic, decongestant, toxic (leaves) [215, 204]
14.	*G. involucrata* Steud.	To reduce the size of the vaginal orifice and as fish poison (roots) [25], Laxative and Vermifuge (root) [25, 214,216], as insecticide, insect repellant and anti-malarial [217]
15.	*G. kraussiana* Syn: *L. kraussiana* Hutch. et Dalz.	For chest complaints [26, 202], Stomach ache and enema (Root), Leaves for earache and toothache, Measles, Dropsy, Anorexia, Ulcers (root) [206, 214, 218, 219], Molluscicidal agent (leaves)[205], Arrow and Fish Poison (Leaves and root) [220-222], as an emetic or purgative and also to treat a condition called chidyiso, which is attributed to bewitched food and characterized by gastrointestinal pain [223], Anorexia and Antipsychotic (root) [224], Diarrhoea (stem bark) [225], ear ache, abdominal pain, toothache (leaves) [204], fractures [208], to induce labour, abortifacient, relieves stomach troubles. Fever, menstrual pain, cold and rheumatism [209], used in pregnancy and childbirth; severe gastrointestinal irritation and death of stock [167, 226, 227,317], leprosy (root) [228, 229], Treatment of burns, snake bites, stomach complaints, used to ensure easy birth [230, 26], constipation [193,315]
16.	*G. kraussi*	Snake bite [231]
17.	*G. latifolia*	Purgative (root-bark) [198], Antifeedant effects [190, 321]
18.	*G. macrorrhiza*	Stimulant [232]
19.	*G. microcephala*	Aphordisiac (root) [198]
20.	*G. polycephala* Gilg.	Toxic and irritant [205, 204, 317], Severe irritation to eyes, nose and skin, dyspnoea. Coughing. Headache and nausea [5, 199, 203, 204], constipation (root) [233], for stabilising heart conditions, treatment of tuberculosis and tonsillitis, and ashes are applied onto wounds [22, 234]
21.	*G. socotrana*	Obstipation (Leaf and fruit) [235]
22.	*G. somalensis* Gilg.	Tuberculosis (root) [214]
23.	*G. stenophylla*	Malaria, Acaries, Rabies [236]
24.	*G. stenophylloides* Gilg.	Antiblennorrhagic (root) [237]
25.	*G. vatkeana* Engl. Et Gilg.	Purgative, Vesicant (root) [196, 201]
26.	*Lasiosiphon spp.*	Anticatarrh, Headache, Rubefacient, Wound dressing [197], Eruptive fever, Ophthalmia, Snakebite (root) [196,195], Blood purifier, Sore throat, Tonic (root-bark) [191, 238]
27.	*L. anthylloides*	Febrifuge, bad dreams [196], Cough, Influenza, Snakebite (root) [196,195, 197, 238], Respiratory tract irritant (root) [201]
28.	*L. bipinnatum*	Hepatotoxic and respiratory irritant [5, 199], cattle and sheep Poisoning [239]
29.	*L. burchellii*	Respiratory tract irritant (root) [201]
30.	*L. captitatus*	Fractures and sprains, Toothache [196, 220], Burns, Aid women in conception, Aid in childbirth, Emetic in anthrax, Enema for backache, Febrifuge, Prevent scalding in febrile patients, Stomachic, Wash for babies, Sore throat (root) Headache (leaf)[196]
31.	*L. kraussii* Meisn	Arrow, Animal and Fish Poison (Leaves and roots)[195-197, 240], Snake bite, sore throat, washing wounds and bruises [195-197, 238], Burns (leaves) [197], Purgative (leaves and root) [241, 242], for snake bite [231,243]
32.	*L. linifolius*	Toothache, headache, burns (root), emetic in anthrax (root), purgative and sore throat, for lung inflammations (root)[195,197, 238],
33.	*L. meisnerianus*	Irritant (root) [201], Blood purifier, respiratory diseases, indolent and callous ulcers [191, 196, 195], Blood purifier, Sore throat, Tonic (root-bark) [191], Sores opthalmia, disease of sheep and snake bite [191,196, 195, 220, 238,244,]
34.	*L. perrieri* J. Leand	Anti-Malarial and febrifuge [213]
35.	*L. roridus* S. Moore	Malaria [196]

Table: 3: Biological aspects of *Gnidia* species

Sr No.	Species	Biological Activity
1.	*G. burchellii* Meisn.	Toxicity studies [203]
2.	*G. capitata*	Spasmolytic (leaves) [196], Prostaglandin-synthesis inhibition [245], Antibacterial, anthelmintic, brine shrimp toxicity and toxicity studies[246, 247]
3.	*G. chrysantha* Gilg.	Toxic and irritant [196]
4.	*G. cuneata* Meisn	*In-vitro* antiplasmodial activity absent [248]
5.	*Gnidia gymnostachya* Glig.	Antispasmodic [204, 215]
6.	*G. kraussianus* Hutch. et Daix.	P-388 lypmhocrytic leukaemia [31,], Death [204, 206], Analgesic, antispasmodic, decongestant, toxic (Roots) [200], Anti-Leprotic (root)[228, 229, 249], natural post harvest grains protectant and insecticidal [250, 251], toxicity studies (roots) [252], potent insecticidal activity [172], molluscicidal activity (leaf, stem and root) [205, 253], *In-vitro* antiplasmodial activity absent [248], Acaricidal (root) [254], Antibacterial and antifungal [230]
7.	*G. macropetala*	Prostaglandin-synthesis inhibition [245]
8.	*G. socotrana*	Antimicrobial activity [235]
9.	*G. stenophylla*	Anti-malarial (root) [255, 236], antioxidant (root) [256]
10.	*G. stenophylloides* Gilg.	Antiblennorrhagic (root) [214], toxicity studies and antimalarial [255]
11.	*G. subcordata*	Antileukemic [4, 50]
12.	*Lasiosiphon anthylloides* Meisn.	Toxic [195, 257], Respiratory tract irritant (Root) [201], antifeedant [238]
13.	*Lasiosiphon burchellii* Meisn.	Respiratory tract irritant (Root) [201],
14.	*L. meiasnerianus* Endl.	Irritant (rootbark) [201]

Table: 4: biological activities studies on *Gnidia* species

Sr No.	Plant Part	Traditional Use	Biological Activity
1.	Whole plant	Rubefacient [258, 177], Irritant (bark) [201], Fish poison [259], Insecticide and piscicide [260]vesicant [179], cancers, sore throat, abdominal pain, wounds, burns and snakebites, as molluscicidal, insecticidal, piscicidal, homicidal agents and as arrow poisons [261-264], Rabies [265], tuberculosis [266]	*In vitro* anticoagulant activity due to Biscoumarin [177, 267], antileprosy [166], antioxidant and anthelmintic activity [268], larvicidal [253, 261, 269], showed good insecticidal, herbicidal and fungicidal activities [270], mild antifungal activity [271, 272], Spasmolytic activity [273, 204], Antidiabetic: potent Amylase and Glucosidase Inhibitor [263, 274-276], antimicrobial [277], Biopesticide [278], Larvicidal [319].
2.	Roots	Indigestion [198], Rabies[260]	Antileukemic [260], Acute toxicity studies [279]
3.	Leaves	Teeth loosening effect Snakebite [221, 177, 280-282], as insecticide, fish poison for blisters, contusions and swellings, back ache and joint pains [77, 260, 263],	Bactericidal effect [283], Irriant [201], Anti-inflammatory [77], Larvicidal [284], Insecticidal and fungicidal [260,285], Anti-feedant [260,286], as herbal pesticide [287], Ovicidal [272], pest prevention [288], Antimicrobial [277]
4.	Bark	Arrow and fish poison, for blisters, contusions, swellings and Insecticide [107, 221,260,280,281, 289-291], Diuretic, Sialagogue, Stimulant (bark) [244], Vesicant (bark) [191, 221, 280, 281, 292],	Larvicidal [260], Acute toxicity studies [279], Ovicidal [272], Antimicrobial [277]
5.	Stem	Fish poison [260]	
6.	Root	Rabies [293]	Anti-leukaemia [260]

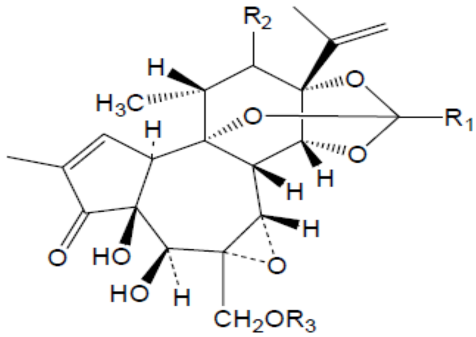
Table: 5: Plant part, traditional use and biological activity of *Gnidia* species

Sr. No.	Isolated Constituents	Activity
1.	Diterpene esters of the daphnane type	Antineoplastic activity[23, 31,48, 50, 50], pesticide and insecticidal [294]
2.	Mezerein (2)	Antileukemic activity [53]
3.	Gnididin (8)	Potent antileukemic activity [170]
4.	Gnidicin (10)	Potent antileukemic activity [77, 170]
5.	Gniditrin (9)	Potent antileukemic activity [170], potential cholesterol lowering activity [295]
6.	Excoecariatoxin (16)	Irritant, Piscicidal, Insecticidal [172]
7.	Gnidilatin (11)	Moderate inflammatory cytokines inhibitory activity [296], Piscicidal [297], Moderate Antileukemic activity [170], Moderate inhibitory effects on interleukin 1 (IL-1alpha, IL-1beta) and tumour necrosis factor (TNF-alpha) biosynthesis [313]
8.	Gnidilatin-20 palmitate (13)	Moderate inflammatory cytokines inhibitory activity [296], Substantial Antileukemic activity [297, 170], Moderate inhibitory effects on interleukin 1 (IL-1alpha, IL-1beta) and tumour necrosis factor (TNF-alpha) biosynthesis [313]
9.	Gnidilatidin (12)	Piscicidal [297], No Antileukemic activity [170, 298, 299], Abortifacient [314]
10.	Gnidilatidin-20-palmitate (14)	Substantial Antileukemic activity [297, 170]
11.	Gnidiglaucin (15)	No Antileukemic activity [170]
12.	Lasiocephalin (28)	Toxicity studies [300]
13.	12-hydroxydaphnetoxin (4)	No antileukemic activity due to absence of ester linkage [170], Potent inhibitory effects on interleukin 1 (IL-1alpha, IL-1beta) and tumour necrosis factor (TNF-alpha) biosynthesis [313]
14.	Genkwanin (59)	Antiplasmodial And Cytotoxic [301], Potent inhibitory effects on interleukin 1 (IL-1alpha, IL-1beta) and tumour necrosis factor (TNF-alpha) biosynthesis [313], Antimicrobial [316]
15.	Genkwadaphnin (60)	Potent inhibitory activity on inflammatory cytokines [296], Antileukemic [302]
16.	Syringaresinol (77)	Lymphatic vessel stabilizer [303]
17.	Syringin (85)	Ineffective on cytokine biosynthesis [296]
18.	Kraussianin (26)	Antileukemic [173]
19.	Mahkoside A (72)	Cytotoxicity [185,312]
20.	Mangiferin (67)	Anti-inflammatory, analgesic, antipyretic, antioxidant, immunomodulator, antitumor, antiviral, and anthelminthic and in obesity treatment, antiallergic, Bronchodilatory, antidiabetic, Antiplasmodial Antiamoebic, Cardioprotective, Radioprotective, Lipolytic, Antibacterial and antifungal [304-307], α-amylase inhibiton [275]
21.	Vitexin (64)	α-Glucosidase Inhibitory Activity [308]
22.	Isovitexin (65)	Antioxidant [309], α-Glucosidase Inhibitory Activity [308]
23.	Isoorientin (66)	Hepatoprotective and hypoglycemic [310], Anti-nociceptive, anti-inflammatory and gastroprotective activities, antioxidant, antimicrobial, myolitic activity [311, 316]
24.	Kirkinine (6)	Potent neurotrophic activity [320]

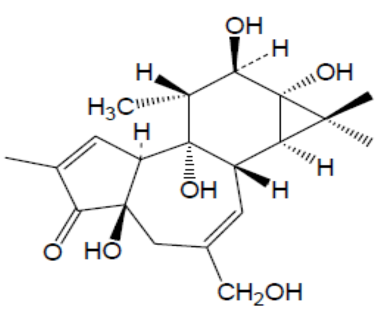
Table: 5: Isolated Constituents and their biological activity of *Gnidia* species

Structures

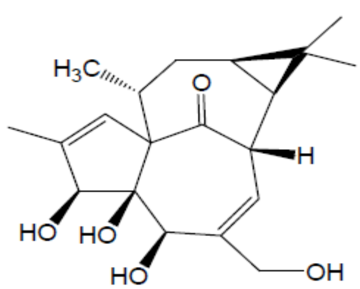
Diterpenes:



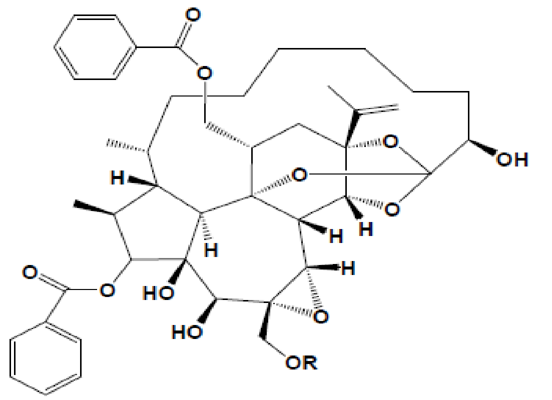
Daphnetoxin	(1)	$R_1 = C_6H_5$	$R_2 = H$	$R_3 = H$
Mezerein	(2)	$R_1 = C_6H_5$	$R_2 = CO(CH{=}CH)_2C_6H_5$	$R_3 = H$
Huratoxine	(3)	$R_1 = (CH{=}CH)_2(CH_2)_8CH_3$	$R_2 = H$	$R_3 = H$
12-β-hydroxydaphnetoxin	(4)	$R_1 = C_6H_5$	$R_2 = OH$	$R_3 = H$
Acetoxyhuratoxin	(5)	$R_1 = (CH{=}CH)_2(CH_2)_8CH_3$	$R_2 = OCOCH_3$	$R_3 = H$
Kirkinine	(6)	$R_1 = (CH{=}CH)(CH_2)_{12}CH_3$	$R_2 = OCOCH_3$	$R_3 = H$
Kirkinine D	(7)	$R_1 = (CH{=}CH)_3(CH_2)_2CH_3$	$R_2 = OCOCH_3$	$R_3 = H$
Gnididin	(8)	$R_1 = C_6H_5$	$R_2 = CO(CH{=}CH)_2(CH_2)_4CH_3$	$R_3 = H$
Gniditrin	(9)	$R_1 = C_6H_5$	$R_2 = CO(CH{=}CH)_3(CH_2)_2CH_3$	$R_3 = H$
Gnidicin	(10)	$R_1 = C_6H_5$	$R_2 = COCH{=}CHC_6H_5$	$R_3 = H$
Gnidilatin	(11)	$R_1 = (CH_2)_8CH_3$	$R_2 = COC_6H_5$	$R_3 = H$
Gnidilatidin	(12)	$R_1 = (CH{=}CH)_2(CH_2)_4CH_3$	$R_2 = COC_6H_5$	$R_3 = H$
Gnidilatin-20-palmitate	(13)	$R_1 = (CH_2)_8CH_3$	$R_2 = COC_6H_5$	$R_3 = CO(CH_2)_{14}CH_3$
Gnidilatidin-20-palmitate	(14)	$R_1 = (CH{=}CH)_2(CH_2)_4CH_3$	$R_2 = COC_6H_5$	$R_3 = CO(CH_2)_{14}CH_3$
Gnidiglaucin	(15)	$R_1 = (CH_2)_8CH_3$	$R_2 = COCH_3$	$R_3 = H$
Excoercariatoxin	(16)	$R_1 = (CH{=}CH)_2(CH_2)_4CH_3$	$R_2 = H$	$R_3 = H$
Pimelea factor P_1	(17)	$R_1 = C_9H_{19}$	$R_2 = H$	$R_3 = H$
Montanin	(18)	$R_1 = C_{11}H_{23}$	$R_2 = H$	$R_3 = H$
5β-dihydroxyresiniferonol-6α,7α-oxide	(19)	$R_1 = (CH{=}CH)_3(CH_2)_2CH_3$	$R_2 = H$	$R_3 = H$
Genkwadaphnin	(20)	$R_1 = C_6H_5$	$R_2 = COCH_3$	$R_3 = H$



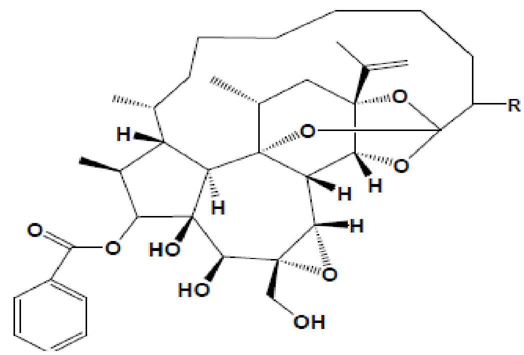
Phorbol (21)



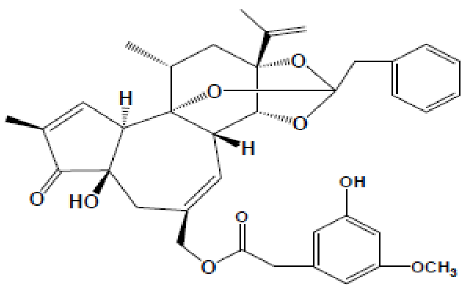
Ingenol (22)



Gnidimacrin (23) R =H
Gnidimacrin-20-palmitate (24) R = $CO(CH_2)_{14}CH_3$

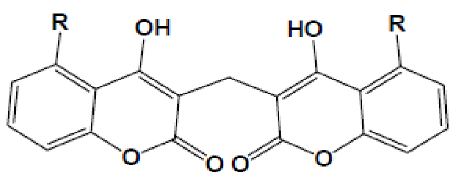


Daphnopsis factor R_1 (Gnilatimacrin) (25) R =H
Kraussianin (26) R = OH

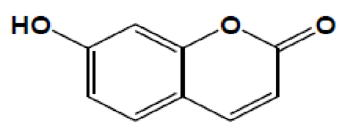


Resiniferotoxin (27)

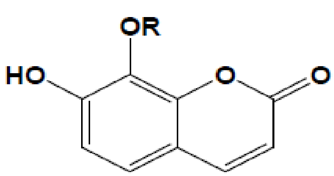
Coumarins:



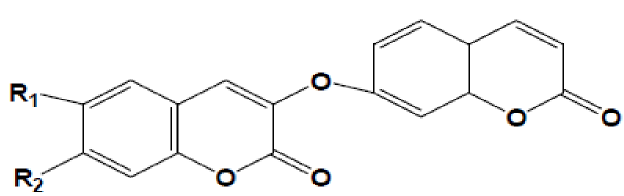
dicoumarol (28), R = H
Gerberinol (29), R = CH_3



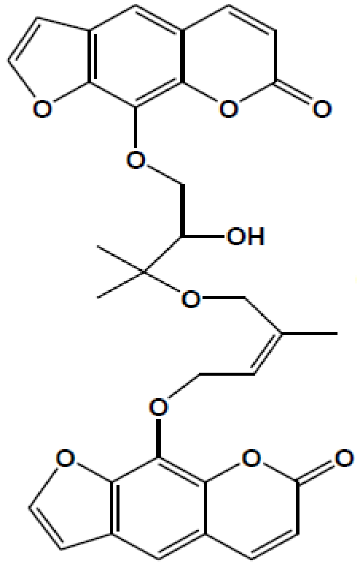
Umbelliferone (30)



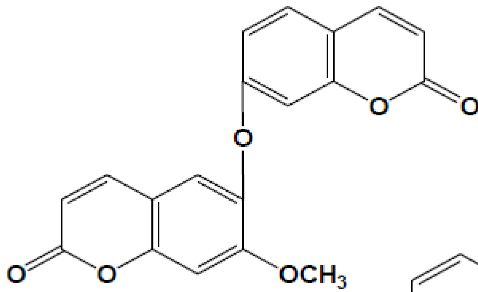
Daphnetin (31) R_1 = H
Daphnetin-8-β-D-glucoside (32) R_1 = Glu



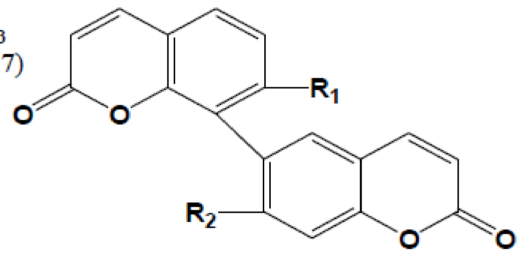
Daphnoretin (33) $R_1 = OCH_3$ $R_2 = OH$
7- acetyldaphnoretin (34) $R_1 = OCH_3$ $R_2 = OCOCH_3$
Edgeworthin (35) $R_1 = OH$ $R_2 = OH$



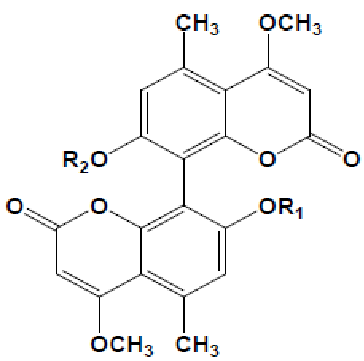
Candicanin (36)



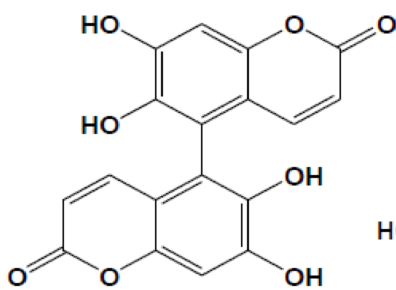
Lasiocephalin (37)



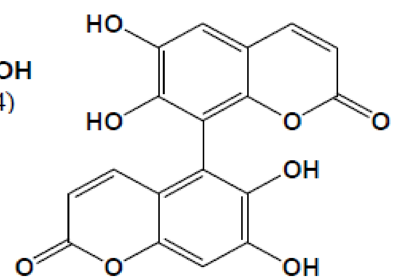
Bicoumol	(38)	R_1 = OH	R_2 = OH
Bhubaneswin	(39)	R_1 = OH	R_2 = OH
Matsukaze lactone	(40)	R_1 = OCH_3	R_2 = OCH_3



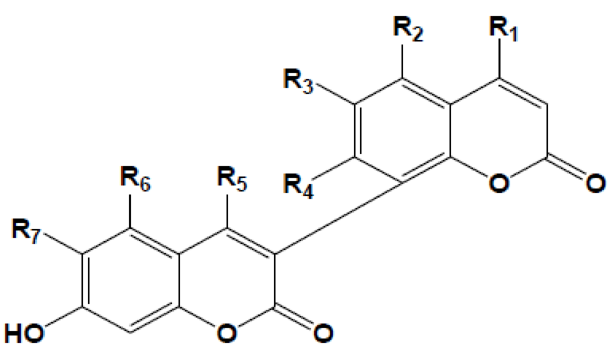
Kotanin	(41)	R_1 = CH_3	R_2 = CH_3
Desmethylkotanin	(42)	R_1 = H	R_2 = CH_3
Orlandin	(43)	R_1 = H	R_2 = H



Euphorbetin (44)

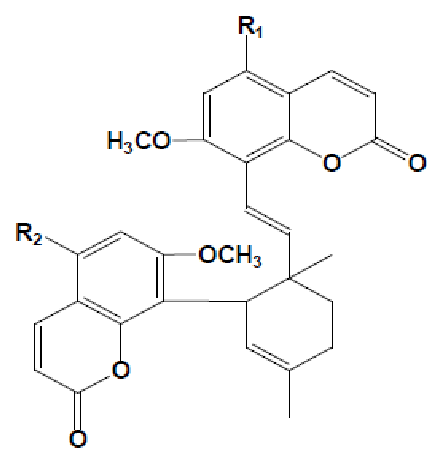


Isoeuphorbetin (45)

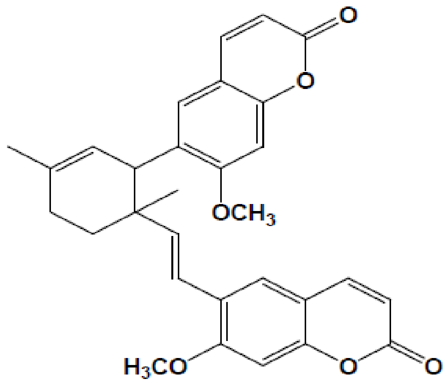


Ipomosin (46) $R_1 = R_2 = R_5 = R_6$ = H
$R_3 = R_7 = CH_3$
R_4 = OH

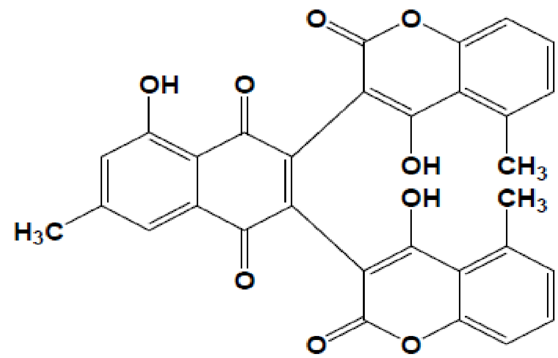
7,7'-dihydroxy-3,8'-biscoumarin (47) $R_3 = R_7$ = H
$R_2 = R_6 = CH_3$
$R_1 = R_4 = R_5 = OCH_3$



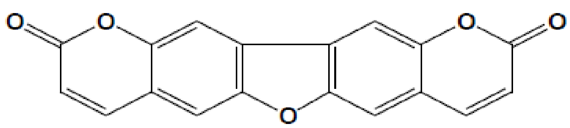
Phebalin (48), $R_1 = R_2$ = H
Toddasin (49), $R_1 = R_2 = OCH_3$



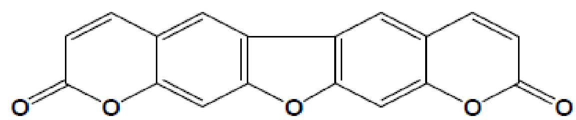
Thamnosin (50)



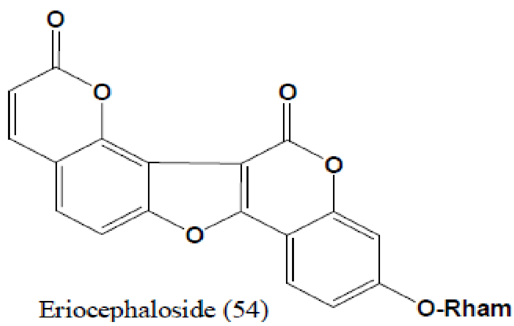
Ismailin (51)



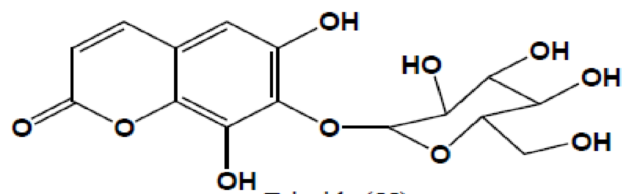
Gnidicoumarin (52)



Lasioerin (53)

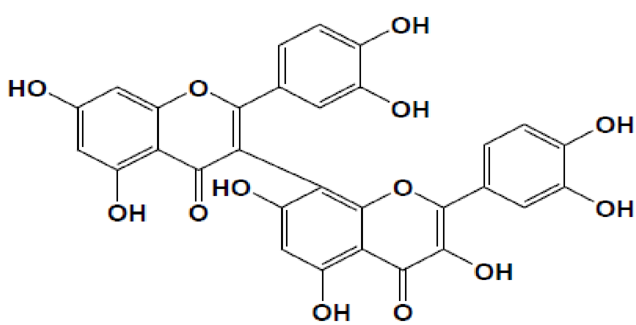


Eriocephaloside (54)

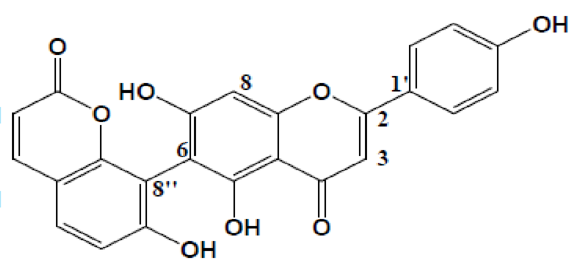


Erioside (55)

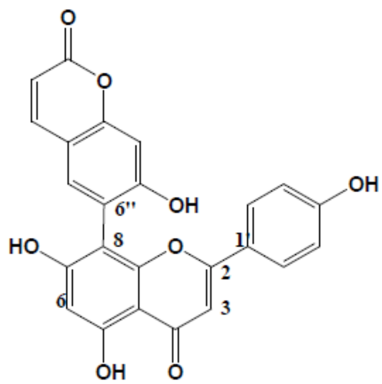
Flavonoids:



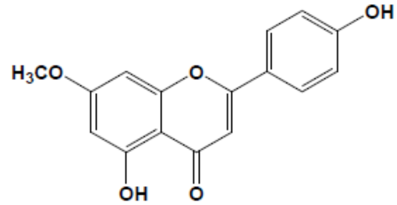
Manniflavanone (56)



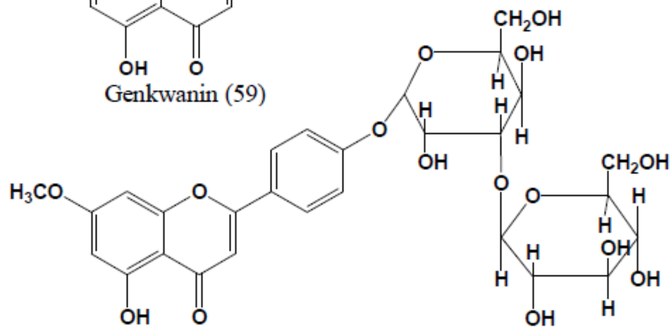
6-(8''-Umbelliferyll)-apigenin (57)



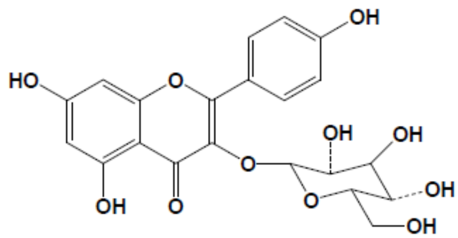
8-(6''-Umbelliferyll)-apigenin (58)



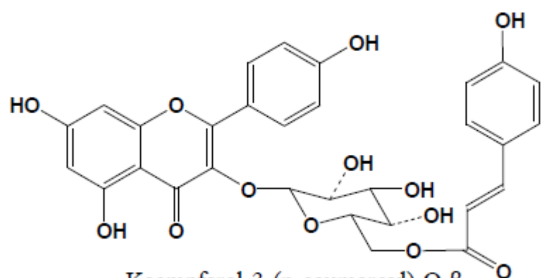
Genkwanin (59)



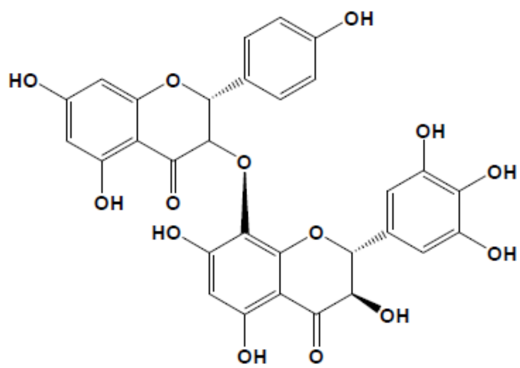
Genkwanin-4'-0-β-D-glucopyranosyl-(l-3)-D-xylopyranoside (60)



Kaempferol-3-O-glucoside (61)

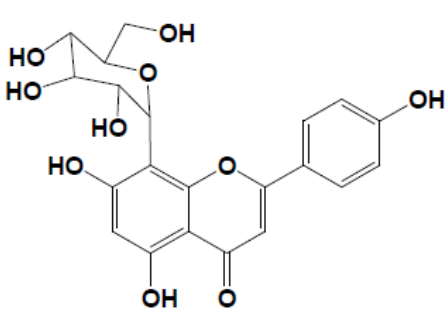


Kaempferol-3-(p-coumaroyl)-O-β-D-glucopyranoside (62)

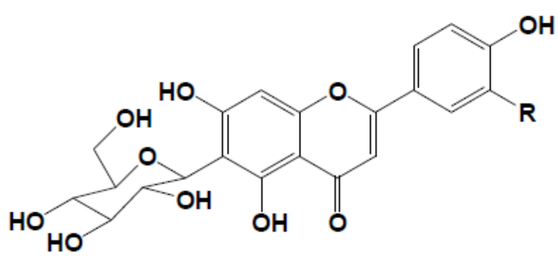


Gnidia biflavonoid 4a (63)

Glycosides:

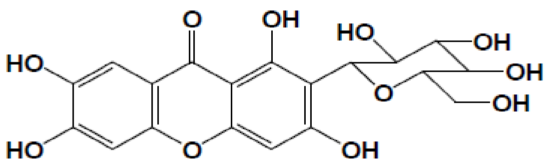


Vitexin (64)

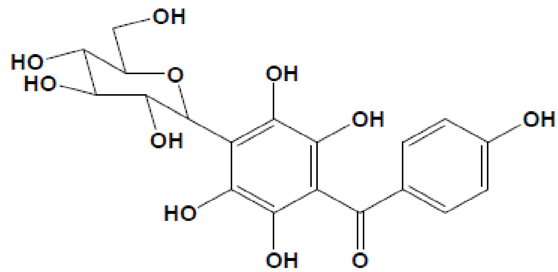


Isovitexin (Saponaretin) (65) R = H

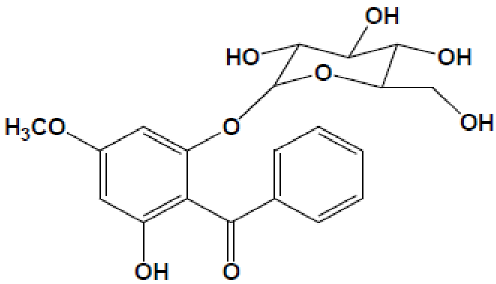
Isoorientin (66) R_1 = OH



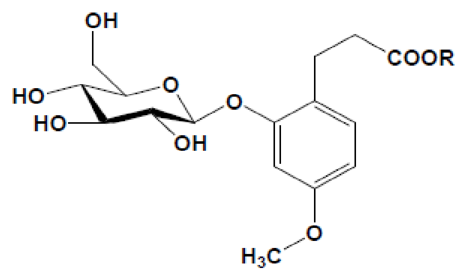
Mangiferin (67)



2,3,4',5,6-pentahydroxy benzophenone-4-C-glucoside (68)

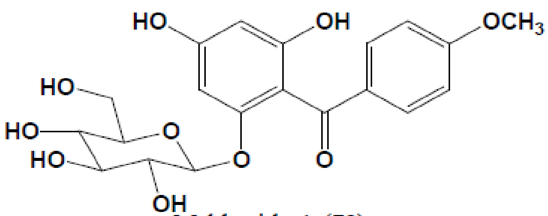


2,4',6-trihydroxy-4-ethoxy benzophenone-2-O- glucoside (69)

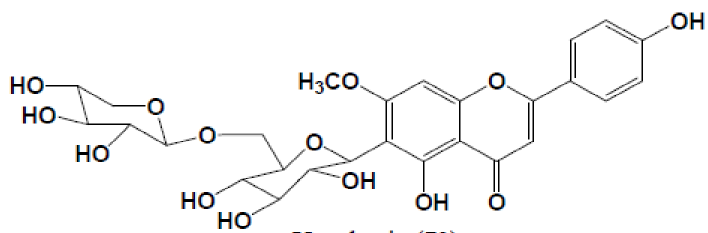


2-O-β-D-glucosyloxy-4-methoxybenzenepropanoic acid (70) R = H

Methyl-2-O-β-D-glucosyloxy-4-methoxybenzenepropanoate (71) R = CH_3

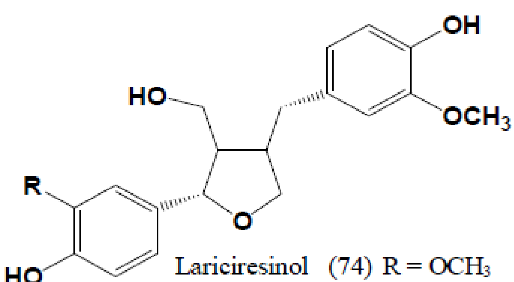


Mahkoside A (72)



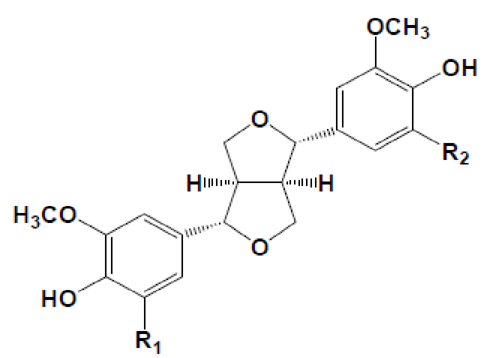
Yuankanin (73)

Lignans:



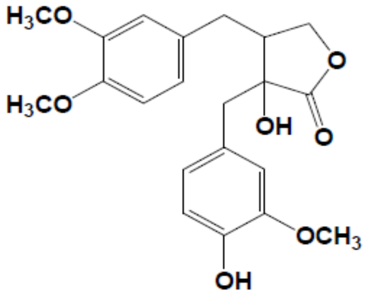
Lariciresinol (74) R = OCH_3

Taxiresinol (75) R = H

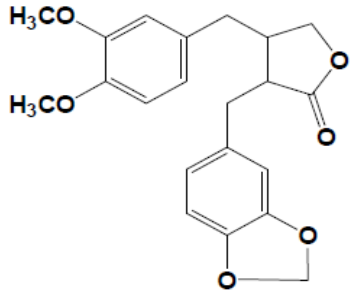


Pinoresinol (76) R_1 = H R_2 = H

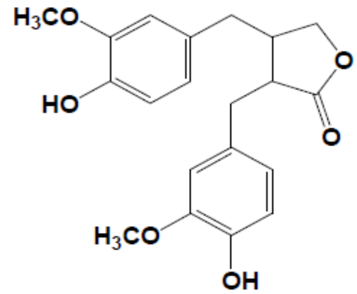
Syringaresinol (77) R_1 = OCH_3 R_2 = OCH_3



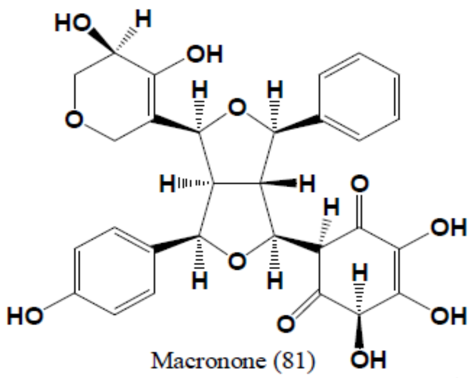
Wikstromol (78)



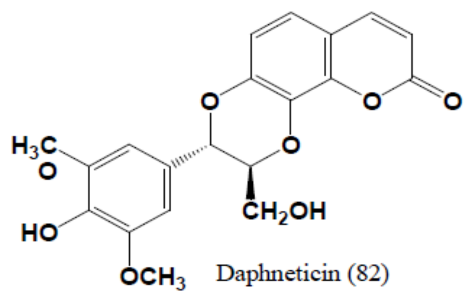
Kusunokinin (79)



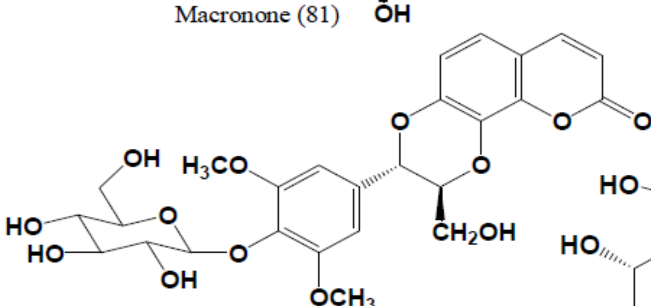
Matairesinol (80)



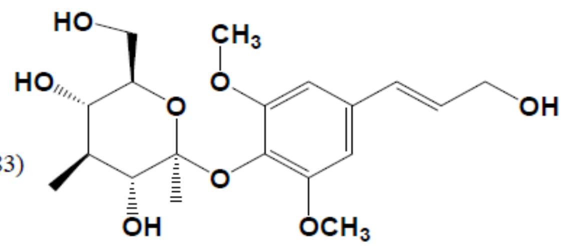
Macronone (81)



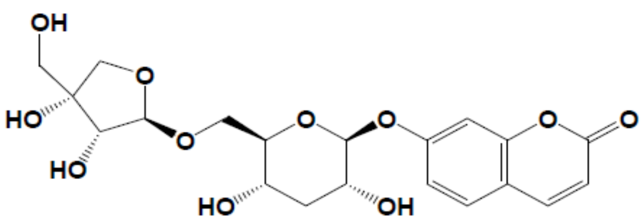
Daphneticin (82)



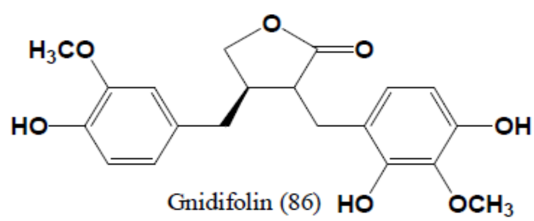
Daphneticin-4''-O-α-D-glucopyranoside (83)



Syringin (85)

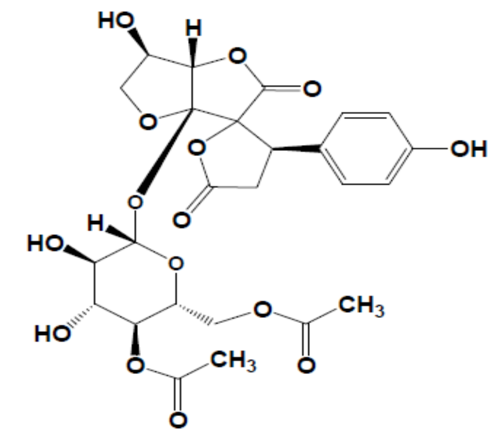


Adicardin (84)

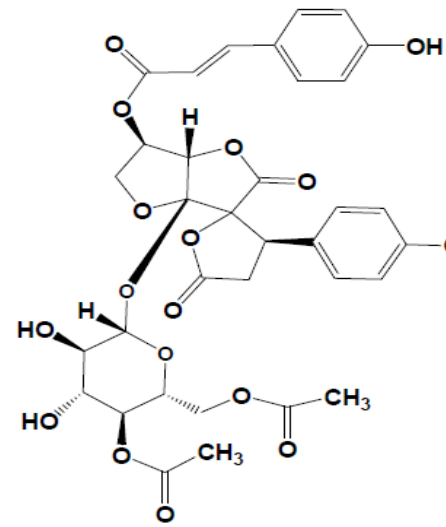


Gnidifolin (86)

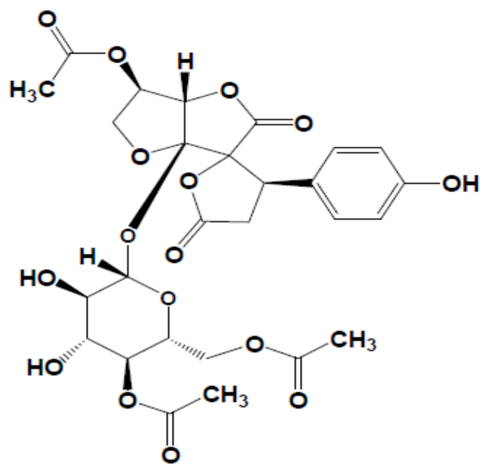
Spiro-bis-γ-lactone:



4',6'-Diacetyl-viburnolide A (73)

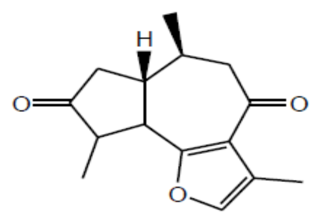


4',6'-Diacetyl-12-coumaroyl-viburnolide A (74)



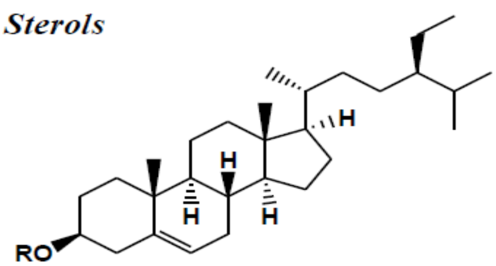
Tetraacetylviburnolide A (75)

Sesquiterpenes (Guanine-type):



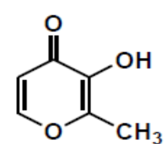
Gnididione (90)

Sterols



β- Sitosterol (96) R =H
β- Sitosterol-β-Dglucoside (97) R = Glu

γ-Pyrone



Maltol (98)

Acknowledgements:

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