A Review on Daphnane-Type Diterpenoids and Their Bioactive Studies

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Abstract: Natural daphnane diterpenoids, mainly distributed in plants of the Thymelaeaceae and Euphorbiaceae families, usually include a 5/7/6-tricyclic ring system with poly-hydroxyl groups located at C-3, C-4, C-5, C-9, C-13, C-14, or C-20, while some special types have a characteristic orthoester motif triaxially connected at C-9, C-13, and C-14. The daphnane-type diterpenoids can be classified into five types: 6-epoxy daphnane diterpenoids, resiniferonoids, genkwanines, 1-alkyldaphnanes and rediocides, based on the oxygen-containing functions at rings B and C, as well as the substitution pattern of ring A. Up to now, nearly 200 daphnane-type diterpenoids have been isolated and elucidated from the Thymelaeaceae and Euphorbiaceae families. In-vitro and in-vivo experiments of these compounds have shown that they possess a wide range of biological activities, including anti-HIV, anti-cancer, anti-leukemia, anti-hyperglycemic [2], neurotropic [3], insecticidal and cytotoxic [4] effects. A comprehensive account of the structural diversity is given in this review, along with the cytotoxic activities of daphnane-type diterpenoids, up to April 2019.

Keywords: daphnane; diterpenoid; cytotoxic activities

1. Introduction

Since the first daphnane diterpenoid characterized by a macrolactone motif was isolated from Trigonostemon reidioides [1], the daphnane diterpenoids have attracted the interest of many researchers because of their significant bioactive activities. Until now, nearly 200 natural products of daphnane-type diterpenoids have been isolated and identified, and they have shown good biological activities, including anti-HIV, anti-cancer, anti-leukemia, anti-hyperglycemic [2], neurotropic [3], insecticidal and cytotoxic [4] effects. Due to their rich pharmacological activities, especially strong anti-HIV activity and small cytotoxicity, daphnane-type diterpenoids have been employed in a range of clinical applications for a variety of clinical uses [5,6]. Studies have found that the natural daphnane-type diterpenoids usually embrace a 5/7/6-tricyclic ring system with poly-hydroxyl groups located at C-3, C-4, C-5, C-9, C-13, C-14, or C-20, while a special group also have a characteristic orthoester motif connected to C-9, C-13, and C-14. The daphnane-type diterpenoids can be categorized into five types (Figure 1): 6-epoxy daphnane diterpenoids, resiniferonoids, genkwanines, 1-alkyldaphnanes and rediocides, based on the substitution pattern of ring A and the oxygen-containing functions at rings B and C. Besides, 6-epoxy...
daphnane diterpenoids usually have a C-6α epoxy structure in ring B; resiniferonoids usually have an α-β unsaturated ketone structure in ring A; genkwanines usually have an α-β saturated ketone structure in ring A, but without a C-6α epoxy structure in ring B; 1-alkyldaphnanes usually have a saturated ring A, and a large ring between the end of the orthoester alkyl chain and C-1 of ring A; and rediocides usually have a 12-carbon macrolide structure between C-3 and C-16, and have a special C-9, C-12, and C-14 orthoester structure. The variety of daphnane-type diterpenoid structures have continued to widen with the discovery of unusual variations with the well-established skeleton. Owing to the unique skeleton and remarkable bioactive activities, daphnane-type diterpenoids have attracted many synthetic endeavors to construct a core structure. However, few papers have reported on the total synthesis of daphnane diterpenoids—isolation from natural plants is still the only source of obtaining daphnane diterpenoids. Considering the extensive interest in daphnane-type diterpenoids, we reviewed the structural and bioactive activities of daphnane-type diterpenoids, with an emphasis on the recent progress in structure identification and bioactive evaluation.

![Daphnane skeleton](image)

**Figure 1.** The kinds of daphnane-type diterpenoids skeleton.

### 2. Occurrence

Natural daphnane-type diterpenoids are mainly distributed in species belonging to the Thymelaeaceae or Euphorbiaceae families (Table 1). These plants grow mainly in tropical and subtropical regions of Asia [7]. Previous chemical investigations on such species have led to the isolation of a number of structurally diverse diterpenoids [8]. Various daphnane-type diterpenoids have been isolated from some parts of the following plants: The twigs and leaves of *Trigonostemon thyrsoideum*, the roots of *Trigonostemon reidioides*, the stems of *Trigonostemon lii*, the stems of *Trigonostemon chinensis*, the twigs and leaves of *Trigonostemon howii*, the flower buds of *Daphne giraldii*, the air-dried roots of *Euphorbia fischeriana*, the stems of *D. acutiloba*, the roots of *Lasiosiphon kraussianus*, the flower buds of *Daphne genkwa*, and the roots of *Maprounea africana* Muell. Arg., *Trigonostemon xyphophylloides*, *Wikstroemiaretusa*, *Trigonostemon howii*, and *Stellerachamaejasme* L., and so on [9].
Table 1. The species of daphnane-type diterpenoids.

| Types of Diterpenoids        | Species                                | Medication Site                                      |
|------------------------------|----------------------------------------|------------------------------------------------------|
| 6-epoxy daphnane diterpenoids| D. acutiloba                           | Usually their effective part is roots, stems, twigs and leaves, flower buds, fresh bark. |
|                              | Trigonostemon thyrsoideum              |                                                      |
|                              | Wikstroemiaretusa                      |                                                      |
|                              | Daphne genkwa                         |                                                      |
|                              | D. oleoides Schreber ssp. oleoides     |                                                      |
|                              | Trigonostemon xiphyophylloides         |                                                      |
|                              | Thymelaea hirsuta                     |                                                      |
|                              | Neoboutonii glabrescens                |                                                      |
|                              | S. kirkii                              |                                                      |
|                              | W. monticola                           |                                                      |
|                              | D. tangutica                           |                                                      |
|                              | Pelangata                              |                                                      |
|                              | T. xiphyophylloides                    |                                                      |
|                              | T. thyroidium                          |                                                      |
|                              | D. zschizalosum                        |                                                      |
|                              | Stellera chamaejasme L.                |                                                      |
|                              | Trigonostemon chinensis Merr           |                                                      |
| Resiniferonoids              | Euphorbia fischeriana                  | Generally, the roots and flower buds as their effective part. |
|                              | Daphne genkwa                         |                                                      |
|                              | Euphorbia pilosa                       |                                                      |
| Genkwanines                  | Trigonostemon xiphyophylloides         | Usually their effective part is roots, stems, twigs and leaves, flower buds. |
|                              | Trigonostemon thyrsoideum              |                                                      |
|                              | Trigonostemon lii                      |                                                      |
|                              | Trigonostemon chinensis Merr           |                                                      |
|                              | Daphne genkwa                         |                                                      |
|                              | Trigonostemon hauvii                   |                                                      |
| 1-alkyldaphnanes             | Wikstroemiachamaejasme                 | Usually, the flowers buds and fresh bark is their effective part. |
|                              | Wikstroemiaretusa                     |                                                      |
|                              | Stellera chamaejasme L.                |                                                      |
|                              | Daphne genkwa                         |                                                      |
|                              | Synaptoplepis kirkii                   |                                                      |
|                              | Pelangata                              |                                                      |
| Rediocides                   | Trigonostemon thyrsoideum              | Generally, their effective part is roots, twigs and leaves. |
|                              | Trigonostemon chinensis Merr           |                                                      |
|                              | Trigonostemon reidioides               |                                                      |

3. Species of Daphnane-Type Diterpenoids and Their Bioactive Activities

3.1. 6-Epoxy Daphnane Diterpenoids

6-epoxy daphnane diterpenoids feature a C-6α epoxy structure in ring B and, occasionally, an α-β unsaturated ketone structure in ring A. In most cases, there is also a C-5β hydroxyl group and a C-20 hydroxyl group in ring B (Figure 2, Table 2). Compounds acutilobins A–G (1–5, 65, 66), wikstroemia factor M1 (74), genkwanineVIII (69), gnditrin (14), gndidin (15), gndicin (13), daphnetoxin (6), yuanhuajine (50), kirkine (24), excoecaria factor O1 (8), excoecaria toxin (7), and 14′-ethyltetrahydrohuratoxin(51) have been obtained from the stems of D. acutiloba. Acutilobins A–G have been shown to exhibit significant anti-HIV-1 activities, with EC50 below 1.5 μM [10]. Trigoxyphins A (32), B (59), and trigothyroid M (63) have been isolated from the twigs and leaves of Trigonostemon thyrsoideum. These compounds have been evaluated for anti-HIV activity by an assay of the inhibition of the cytopathic effects of HIV-1 and cytotoxicity against C8166 cells. However, only trigoxyphin A expressed weak anti-HIV-1 activity [11]. Compounds huratoxin (20) and wikstroelides A–D (37–40), H–J (41–42, 56), and L–N (43, 57–58) have been obtained from the fresh bark of Wikstroemiaretusa. The orthoester compounds wikstroelides D and H, with palmitic acid at their 20-hydroxyl site, have shown the weakest cytotoxic activity [12]. Antitumor compounds genkwain I (64) and orthobenzoate 2 (70) have been isolated from the flower buds of Daphne genkwa. Genkwain I has been shown to be a potent cell growth inhibitor constituent [13]. Active ingredients genkwadane
D (9), yuanhuadine (47), yuanhuafine (45), yuanhuacine (49), yuanhuahine (44), yuanhuapine (61), genkwadaphnine (10), isoyuanhuadine (23), and genkwamine M (67) were obtained from the flower buds of *Daphne genkwa*. Among them, yuanhuadine, genkwadaphnine, yuanhuafine, yuanhuapine, and genkwamine M have exhibited the strongest cytotoxic activities against the HT-1080 cell line (IC₅₀ < 0.1 µM) [14]. Maprouneacin (76) has been isolated from the roots of *Maprounea africana* Muell. Arg. and has shown potent glucose-lowering properties when administered via the oral route. [15]. The compound trigonostempene C (71) has been obtained from the twigs and leaves of *Trigonostemon thyrsoides*, but did not show any significant activity [16]. Compounds yuanhualine (46) and yuanhuagaine (48) have been isolated from *Daphne genkwa*. In the analysis of signal transduction molecules, yuanhualine and yuanhuagaine appear to suppress the activation of Akt, STAT3 and Src in human lung cancer cells, and also exert potent antiproliferative activity against anticancer-drug resistant cancer cells [17]. Gnidilatidin (17), gnidilatidin-20-palmitate (18), 1, 2α-dihydodaphnetoxin (62), genkwadaphnin-20-palmitate (11) and gnidicin-20-palmitate (19) have successfully been obtained from the stems of *D. oleoides* Schreber from the stems of *Trigonostemon xyphophylloides*. Although these compounds have been isolated from the same plant species, they do not show any significant activity against tumor cell lines. Compounds genkwadaphnine (10) and genkwamine M have exhibited the strongest cytotoxic activities against the HT-1080 cell line (IC₅₀ > 50 µM) [17]. Genkwanine M has exhibited significant inhibitory activity against specific tumor cells (IC₅₀ > 10 µM) [19]. Genkwanine N (68) has been obtained from the dried flower buds of *Daphne genkwa*, and the compound with esterification of the 20-hydroxyl has shown weak activity [20].

Trigonosin B (73) has been isolated from the roots of *Trigonostemon thyrsoides* [21], while compounds herseins A and B (21–22) have been isolated from *Thymelaeahirsuta*. Herseins A and B have shown inhibition of melanogenesis in B16 murine melanoma cells [22]. Glabrescin(12) and Montanin (26) have been obtained from *Neoboutoniaglabrescens* [23]. Kirkinine D (25) and synaptolepisfactor K₇ (28) have been isolated from the *S.kirkii* [24]. Wikstrotoxin C (35) has been isolated from *W.monticola*. The compound 2α-dihydro-20-palimoyldaphnetoxin (52) has been isolated from the *D.tangutica*, while gnidiglaucin (16) has been obtained from *P.elongata* [24]. Trigoxyphin C (60) has been obtained from *T.xyphophylloides*, and tested against HEL-7402 cells (human hepatocellular carcinoma), where in it has been shown to be inactive (IC₅₀ value > 10 µM was defined as inactive) [25]. Trigonosin A (72) has been isolated from *T.thyrsoides*, and shown to exhibit significant inhibitory activity against specific tumor cells (IC₅₀ > 10 µM) [21]. Isovesiculosin and vesiculosin (54–55) have been isolated from *D.vesiculosum* [26]. Genkwamine O (75) has been obtained from *D.genkwa*. Compound daphnegiraligin (53) has been isolated from the stem barks of *Daphne giraldii* [27]. Simplexin(27) has been obtained from *Stellerachamaejasme* L. [5]. Compounds trigochinins G–L (29–31) have been isolated from the twigs and leaves of *Trigonostemonchinensis* Merr [28].

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**Figure 2.** Eight types (A–H) of 6-epoxy daphnane skeletons.
Table 2. Reported structures of 6-epoxy daphnane skeletons.

| No. | Name                                      | \( R_1 \) | \( R_2 \) | \( R_3 \) | \( R_4 \) | \( R_5 \) | Type |
|-----|-------------------------------------------|-----------|-----------|-----------|-----------|-----------|------|
| 1   | Acutilobin A                              | H         | OH        | Ph        | OCO(CH=CH)\(_2\)COC(CH\(_2\))\(_2\)CH\(_3\) | –         | A    |
| 2   | Acutilobin B                              | H         | OH        | Ph        | OCO(CH=CH)\(_2\)CH\(_2\)CH\(_2\)OH | –         | A    |
| 3   | Acutilobin C                              | H         | OH        | (CH=CH)\(_2\)(CH\(_2\))\(_2\)CH\(_3\) | OCOCH=CPhCH\(_2\)OH | –         | A    |
| 4   | Acutilobin D                              | H         | OH        | (CH=CH)\(_2\)(CH\(_2\))\(_2\)CH\(_3\) | OCOCH=CPhCH\(_2\)OH | –         | A    |
| 5   | Acutilobin E                              | H         | OH        | Ph        | OCOCH=CPhCH\(_2\)OH | –         | A    |
| 6   | Daphnetoxin                               | H         | OH        | Ph        | H        | –         | A    |
| 7   | Excoecaria toxin                         | H         | OH        | (CH=CH)\(_2\)(CH\(_2\))\(_2\)CH\(_3\) | H        | –         | A    |
| 8   | Excoecaria factor \( \Omega \)           | H         | OH        | (CH=CH)\(_2\)(CH\(_2\))\(_2\)CH\(_3\) | H        | –         | A    |
| 9   | Genkwadane D                             | H         | OH        | (CH=CH)\(_2\)(CH\(_2\))\(_2\)CH\(_3\) | OCOCH(CH\(_2\))\(_2\) | –         | A    |
| 10  | Genkwadaphnine                            | H         | OH        | Ph        | OAc      | –         | A    |
| 11  | Genkwadaphnin-20-palmitate               | H         | OCO(CH\(_2\))\(_4\)CH\(_3\) | Ph | OCOPh | – A |
| 12  | Glabrescin                                | H         | OCO(CH\(_2\))\(_2\)(CH\(_3\)) | (CH\(_2\))\(_2\)CH\(_3\) | H | – A |
| 13  | Gnidicin                                  | H         | OH        | Ph        | OCOCH=CPh | – A |
| 14  | Gniditinin                                | H         | OH        | Ph        | OCO(CH=CH)(CH\(_2\))\(_2\)CH\(_3\) | – A |
| 15  | Gnididin                                  | H         | OH        | Ph        | OCO(CH=CH)(CH\(_2\))\(_2\)CH\(_3\) | – A |
| 16  | Gnidiglaucin                              | H         | OH        | (CH\(_2\))\(_2\)CH\(_3\) | OAc | – A |
| 17  | Gnidilatidin                              | H         | OH        | (CH=CH)(CH\(_2\))\(_2\)CH\(_3\) | OCOPh | – A |
| 18  | Gnidilatidin-20-palmitate                | H         | OCO(CH\(_2\))\(_4\)CH\(_3\) | (CH=CH)(CH\(_2\))\(_2\)CH\(_3\) | OCOPh | – A |
| 19  | Gnidicen-20-palmitate                     | H         | OCO(CH\(_2\))\(_2\)(CH\(_3\)) | Ph | OCOCH=CPh | – A |
| 20  | Huratoxin                                 | H         | OH        | (CH=CH)(CH\(_2\))\(_2\)CH\(_3\) | H | – A |
| 21  | Hirsein A                                 | H         | OH        | CH=CH(CH\(_2\))\(_2\)CH\(_3\) | OCOCH=CPh | – A |
| 22  | Hirsein B                                 | H         | OH        | CH=CH(CH\(_2\))\(_2\)CH\(_3\) | OCOCH=CPhOH | – A |
| 23  | Isoyuanhuadine                            | H         | OH        | (CH=CH)(CH\(_2\))\(_2\)CH\(_3\) | OAc | – A |
| 24  | Kirkinine                                 | H         | OH        | CH=CH(CH\(_2\))\(_2\)CH\(_3\) | OAc | – A |
| 25  | Kirkinine D                               | H         | OH        | (CH=CH)(CH\(_2\))\(_2\)CH\(_3\) | OAc | – A |
| 26  | Montanin                                  | H         | OH        | (CH\(_2\))\(_2\)CH\(_3\) | H | – A |
| 27  | Simplexin                                 | H         | OH        | (CH\(_2\))\(_2\)CH\(_3\) | H | – A |
| 28  | Synaptolepisfactor \( \text{K}_{7} \)   | H         | OH        | CH=CH(CH\(_2\))\(_2\)CH\(_3\) | H | – A |
| 29  | Trigochinin G                             | H         | H         | Ph        | OCOCH\(_2\)CH(CH\(_3\))\(_2\) | – A |
| 30  | Trigochinin H                             | H         | H         | Ph        | OCO\(_6\)H\(_4\)(4-OH) | – A |
| 31  | Trigochinin I                             | H         | H         | Ph        | OCO\(_6\)H\(_2\)(5-OH)(4-OH) | – A |
| 32  | Trigoxiphyphin A                          | H         | H         | Ph        | OAc | – A |
| 33  | Trigoxiphyphin G                          | H         | OH        | CH\(_3\) | OCO(CH\(_2\))\(_2\)CH\(_3\) | – A |
| 34  | Trigoxiphyphin K                          | H         | H         | Ph        | OAc | – A |
| 35  | Wikstrotoxin C                           | H         | OH        | (CH=CH)(CH\(_2\))\(_2\)CH\(_3\) | OAc | – A |
| 36  | Wikstrotoxin D                           | H         | OH        | n-C\(_{18}\)H\(_{37}\) | H | – A |
| No. | Name                        | R₁      | R₂ | R₃                              | R₄   | R₅ | Type |
|-----|-----------------------------|---------|----|---------------------------------|------|----|------|
| 37  | Wikstroelide A              | H       | OH | (CH=CH₂(CH₃)₂CH₃)              | OAc  | –  | A    |
| 38  | Wikstroelide B              | H       | OH | (CH=CH₂(CH₃)₂CH₃)              | OAc  | –  | A    |
| 39  | Wikstroelide C              | H       | OH | O-trans-5-pentadecenoic acid   | OAc  | –  | A    |
| 40  | Wikstroelide D              | H       | OH | (CH=CH₂(CH₃)₂CH₃)              | OAc  | –  | A    |
| 41  | Wikstroelide H              | H       | OH | (CH=CH₂(CH₃)₂CH₃)              | OAc  | –  | A    |
| 42  | Wikstroelide I              | H       | OH | (CH=CH₂(CH₃)₂CH₃)              | OAc  | –  | A    |
| 43  | Wikstroelide L              | H       | OH | (CH=CH₂(CH₃)₂CH₃)              | OAc  | –  | A    |
| 44  | Yuanhuahine                 | H       | OH | (CH=CH₂(CH₃)₂CH₃)              | OAc  | –  | A    |
| 45  | Yuanhuafine                 | H       | Ph | OAc                            | –    | A  |      |
| 46  | Yuanhuamine                 | H       | OH | (CH=CH₂(CH₃)₂CH₃)              | OCO(CH₂)CH₃ | – | A    |
| 47  | Yuanhuadine                 | H       | OH | (CH=CH₂(CH₃)₂CH₃)              | OAc  | –  | A    |
| 48  | Yuanhuagine                 | H       | OH | (CH=CH₂(CH₃)₂CH₃)              | OCOCH₃ | – | A    |
| 49  | Yuanhuacine                 | H       | OH | (CH=CH₂(CH₃)₂CH₃)              | OAc  | –  | A    |
| 50  | Yuanhuajine                 | H       | OH | (CH=CH₂(CH₃)₂CH₃)              | OAc  | –  | A    |
| 51  | 14′-ethyltetrahydrouratoxin | H       | OH | (CH=CH₂CH₃)                   | –    | A  |      |
| 52  | 2α-dihydro-20-palimoyldaphnetoxin | H   | OH | CH=CH(C₃H₅)CH₃ | OAc  | –  | A    |
| 53  | Daphneigaladin              | H       | OH | COPh                           | H    | H  | B    |
| 54  | Isovesiculosin              | Ac      | Ac | CO(CH=CH₂(CH₃)₂CH₃)            | H    | H  | B    |
| 55  | Vesculosin                  | H       | H  | CO(CH=CH₂(CH₃)₂CH₃)            | H    | H  | B    |
| 56  | Wikstroelide J              | H       | H  | CO(CH=CH₂(CH₃)₂CH₃)            | H    | OAc| B    |
| 57  | Wikstroelide M              | H       | H  | CO(CH=CH₂(CH₃)₂CH₃)            | H    | H  | B    |
| 58  | Wikstroelide N              | H       | H  | CO(CH=CH₂(CH₃)₂CH₃)            | H    | H  | B    |
| 59  | Trigoyphin B                | H       | OAc| –                             | –    | C  |      |
| 60  | Trigoyphin C                | Ac      | H  | OAc                           | –    | C  |      |
| 61  | Yuanhuapine                 | H       | OH | OAc                           | –    | C  |      |
| 62  | 1,2α-dihydrodaphnetoxin     | H       | OH | H                             | –    | C  |      |
| 63  | Trigothyroid M              | –       | –  | –                             | –    | D  |      |
| 64  | Genkwanin I                 | –       | –  | –                             | –    | E  |      |
| 65  | Acutilobin F                | –       | –  | –                             | –    | F  |      |
| 66  | Acutilobin G                | CO(CH=CH₃(CH₂)₂CH₃) | OH | H                             | –    | F  |      |
| 67  | Genkwamine M                | H       | OAc| –                             | –    | F  |      |
| 68  | Genkwamine N                | Bz      | OH | H                             | –    | F  |      |
| 69  | Genkwamine VIII              | COPh    | OH | H                             | –    | F  |      |
| 70  | Orthobenzoate 2             | H       | OH | H                             | –    | F  |      |
| 71  | Trigonostempene C           | H       | OH | H                             | –    | F  |      |
| 72  | Trigonosin A                | H       | OAc| –                             | –    | F  |      |
| 73  | Trigonosin B                | H       | OAc| –                             | –    | F  |      |
| 74  | Wikstroemia factor M₁       | CO(CH=CH₂(CH₂)₂CH₃) | OH | H                             | –    | F  |      |
| 75  | Genkuanime O                | –       | –  | –                             | –    | G  |      |
| 76  | Maprouneacin                | –       | –  | –                             | –    | H  |      |
3.2. Resiniferonoids

Relative to 6-epoxy daphnane diterpenoids, there is no C-6α epoxy structure in ring B for resiniferonoids. However, resiniferonoids do possess an α-β unsaturated ketone structure in ring A (Figure 3, Table 3). Compounds 4β, 9α, 20- trihydroxy-13, 15- seco- squalene-1,6- diene-3,13-dione 20-O-β-D-glucopyranoside (86) and euphopiloside A (84) have been isolated from the air-dried roots of *Euphorbia fischeriana*, and display moderate inhibitory effects against α-glucosidase in in-vitro bioassays [29]. Yuanhuatine (78) has been isolated from the flower buds of *Daphne genkwa* [14]. Compounds daphneresiniferins A and B (80–81) have been obtained from the flower buds of *Daphne genkwa*. A study found that daphneresiniferin A was able to dependently inhibit melanin production [30]. Genkwadane L (77) has been isolated from the bud of *Daphne genkwa* [31]. Euphopiloside B (83), langduin A (85) and phorbol (87) have been obtained from the *Euphorbia Pilosa* [32], while compounds genkwadane A (79) and yuanhuaoate B (82) have been isolated from the flower buds of *Daphne genkwa* [14].

![Figure 3. Seven types (I-O) of resiniferonoids skeletons.](image)

**Table 3.** Reported structures of resiniferonoids skeletons.

| No. | Name           | R         | Type |
|-----|----------------|-----------|------|
| 77  | Genkwadane L   | OAc       | I    |
| 78  | Yuanhuatine    | OBz       | I    |
| 79  | Genkwadane A   | –         | J    |
| 80  | Daphneresiniferin A | Me | K    |
| 81  | Daphneresiniferin B | Ph | K    |
| 82  | Yuanhuaoate B  | –         | L    |
| 83  | Euphopiloside B| –         | M    |
| 84  | Euphopiloside A| –         | N    |
| 85  | Langduin A     | H         | N    |
| 86  | 4β,9α,20-trihydroxy-13,15-secotigla-1,6-diene-3,13-dione20-O-β-D-glucopyranoside | – | N |
| 87  | Phorbol        | –         | O    |

3.3. Genkwadanes

Relative to 6-epoxy daphnane diterpenoids and resiniferonoids, genkwadanes have an α-β saturated ketone structure in ring A, but do not possess a C-6α epoxy structure in ring B (Figure 4, Table 4). Compound trigoxyphin H (100) has been isolated from the twigs of *Trigonostemon xyphophylloides* [33]. The active ingredients trigothysoydis A–L (122–124, 96–99, 139–141, 131,128), trigochinins A–E (145–146, 130,
Trigonostemon chinensis and Trigonostemon howii have been isolated from the flower buds and leaves of Trigonostemon chinensis and Trigonostemon howii, respectively [33]. Among them, trigochinins A, B, and D expressed weak anti-HIV-1 activity [11]. Trigolins A–G have been shown to exhibit modest anti-HIV-1 activity with EC₅₀ values of 20.4, 9.17, 11.42, and 9.05 µg/mL, respectively [34]. Compound trigochinin F has been obtained from the twigs and leaves of Trigonostemon chinensis [30]. Trigochinins A and D have been shown to exhibit moderate cytotoxic activity against the HL-60 tumor cell line [28]. Trigonothyrins A–C have been isolated from the flower buds of Trigonostemon howii, and has shown strong inhibition of HL-60 tumor cell lines [28]. Trigonothyrins A–C have been isolated from the stems of Trigonostemon howii and Trigonostemonthyrsoidum [6]. Among them, trigonothyrin F has shown significant activity to prevent the cytotoxic effects of HIV-1 in C8166 cells, with an EC₅₀ value of 2.19 µg/mL [35]. Compounds genkwanines F, I, and J have been isolated from the flower buds of Daphne genkwa [14]. Genkwanine H has been obtained from the flower buds of Daphne genkwa, and the compound has been shown to dependently inhibit melanin production [30]. Compounds trigonostempenes A and B have been isolated from the twigs and leaves of Trigonostemonthyrsoidum [6]. Studies have shown that the discovery of these NO inhibitory daphnane diterpenoids—including compound trigonostempe A—which possess IC₅₀ values comparable to positive controls may have the potential to be developed as anti-neuroinflammatory agents for Alzheimer disease (AD) and other related neurological disorders [16]. Most inhibitors of acetylcholinesterase (AChE) are alkaloids that often possess several side effects, whereas these daphnane-type diterpenoids do not belong to the class of alkaloids, and therefore they may constitute novel active AChE inhibitors with fewer side effects. It is important to search for new AChE inhibitors not belonging to this structural class [36,37]. Genkwanines A–E, G, I, and K have been obtained from the twigs and leaves of Trigonostemonthyrsoid. Studies have shown that the discovery of these NO inhibitory daphnane diterpenoids—including compound trigonostempe A—which possess IC₅₀ values comparable to positive controls may have the potential to be developed as anti-neuroinflammatory agents for Alzheimer disease (AD) and other related neurological disorders [16]. Most inhibitors of acetylcholinesterase (AChE) are alkaloids that often possess several side effects, whereas these daphnane-type diterpenoids do not belong to the class of alkaloids, and therefore they may constitute novel active AChE inhibitors with fewer side effects.

Figure 4. Eight types (P–W) of genkwanines skeletons.
Table 4. Reported structures of genkwanines skeletons.

| No. | Name          | R₁ | R₂ | R₃ | R₄ | R₅ | R₆ | R₇ | R₈ | Type            |
|-----|---------------|----|----|----|----|----|----|----|----|-----------------|
| 88  | Genkwanine A  | H  | H  | H  | OH | CH₂OH | H | Ph | H | P               |
| 89  | Genkwanine B  | CH₂(CH₂)₃ CH₃ | H  | H  | OH | CH₂OH | H | Ph | H | P               |
| 90  | Genkwanine C  | CH₂(CH₂)₂ CH₃ | H  | H  | OH | CH₂OH | H | Ph | H | P               |
| 91  | Genkwanine D  | Bz | H  | H  | OH | CH₂OH | H | Ph | H | P               |
| 92  | Genkwanine E  | H  | H  | H  | OH | CH₂OH | H | Ph | H | P               |
| 93  | Genkwanine F  | H  | H  | H  | OH | CH₂OH | H | Ph | H | P               |
| 94  | Genkwanine G  | H  | H  | H  | OH | CH₂OH | H | Ph | H | P               |
| 95  | Genkwanine H  | H  | H  | H  | OH | CH₂OBz | H | Ph | H | P               |
| 96  | Trigothysoid I| OAc OH Bz OAc OH | – | – | – | – | – | – | Q               |
| 97  | Trigothysoid J| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 98  | Trigothysoid K| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 99  | Trigothysoid L| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 100 | Trigothysoid M| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 101 | Trigothysoid N| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 102 | Trigothysoid O| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 103 | Trigothysoid P| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 104 | Trigothysoid Q| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 105 | Trigothysoid R| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 106 | Trigothysoid S| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 107 | Trigothysoid T| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 108 | Trigothysoid U| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 109 | Trigothysoid V| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 110 | Trigothysoid W| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 111 | Trigothysoid X| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 112 | Trigothysoid Y| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 113 | Trigothysoid Z| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 114 | Trigothysoid A| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 115 | Trigothysoid B| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 116 | Trigothysoid C| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 117 | Trigothysoid D| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 118 | Trigothysoid E| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 119 | Trigothysoid F| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 120 | Trigothysoid G| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 121 | Trigothysoid H| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 122 | Trigothysoid I| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 123 | Trigothysoid J| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 124 | Trigothysoid K| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 125 | Trigothysoid L| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 126 | Trigothysoid M| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 127 | Trigothysoid N| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 128 | Trigothysoid O| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 129 | Trigothysoid P| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 130 | Trigothysoid Q| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 131 | Trigothysoid R| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 132 | Trigothysoid S| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 133 | Trigothysoid T| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 134 | Trigothysoid U| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 135 | Trigothysoid V| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 136 | Trigothysoid W| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 137 | Trigothysoid X| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 138 | Trigothysoid Y| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 139 | Trigothysoid Z| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 140 | Trigochinin A| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 141 | Trigochinin B| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 142 | Trigochinin C| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 143 | Trigochinin D| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 144 | Trigochinin E| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 145 | Trigochinin F| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 146 | Trigochinin G| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 147 | Trigochinin H| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 148 | Trigochinin I| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 149 | Trigochinin J| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
| 150 | Trigochinin K| Ac Ac Me Ac Ac | Me | Ac | H Bz | H Bz | OH | – | – | Q               |
3.4. 1-Alkyldaphnanes

1-alkyldaphnanes have a large ring between the end of the orthoester alkyl chain and C-1 of ring A (Figure 5, Table 5). Pimela factors S₀ (168) and S₇ (169) have been isolated from the flower buds of *Wikstroemia chamaedaphne* and have shown moderate cytotoxic activities against human myeloid leukemia HL-60, hepatocellular carcinoma SMMC-7721, lung cancer A549, breast cancer MCF-7, and colon cancer SW480 [1]. Compound pimela factor P₂ (155) has been obtained from the fresh bark of *Wikstroemia retusa*, and has been shown to exhibit cytotoxicity in 10 cell lines (including HeLa, HepG2, HT-1080, HCT116, A375-S2, MCF-7, A549, U-937, K562 and HL60 cell lines) [14]. Wikstroelides E–G, K and O (163–167) have been isolated from the fresh bark of *Wikstroemia retusa*. Among them, compound wikstroelide E has been shown to exhibit the highest activity against cell lines PC-6 (human lung cancer cell line) and P388 (mouse leukaemia cell line), followed by wikstroelides A and J, which have the orthoester group without a fatty acid at the 20-hydroxyl [12]. Compounds stelleralides A–C (151–152, 174) and gnidimacrin (153) have been isolated from the *Stellera chamaejasme* L. [5]. Genkwadane B (154), pimelotides A and C (170, 172), and genkwadane C (156) have been isolated from the flower buds of *Daphne genkwa* [14]. Compounds wikstroelides R–T (157–159) have been obtained from the flower buds of *Wikstroemia retusa*. Wikstroelide R has been shown to have moderate cytotoxic activities against human cancer cell lines [1]. Compounds kirkinines B, C, and E (160–162) were isolated from *Synaptolepis kirkii*. Pimelotides B and D (171, 173) have been obtained from *Pelongata* [40].

![Figure 5. Four types (X₁–X₄) of 1-alkyldaphnanes skeletons.](image-url)

**Table 5.** Reported structures of 1-alkyldaphnanes skeletons.

| No. | Name             | R₁   | R₂   | R₃   | R₄   | R₅   | R₆   | Type |
|-----|------------------|------|------|------|------|------|------|------|
| 151 | Stelleralide A   | CH₂OAc | OH   | OBz  | OH   | –    | –    | X₁   |
| 152 | Stelleralide B   | CH₂OBz | H    | OBz  | OH   | –    | –    | X₁   |
| 153 | Gnidimacrin     | CH₂OBz | H    | OBz  | OH   | –    | –    | X₁   |
| 154 | Genkwadane B     | Me    | H    | OH   | OBz  | –    | –    | X₁   |
| 155 | Pimelea factor P₂| CH₂OH | H    | OBz  | OH   | –    | –    | X₁   |
| 156 | Genkwadane C     | H     | benzoyl | H | H | Me | – | X₂ |
| 157 | Wikstroelide R   | H     | benzoyl | OH | H | Me | – | X₂ |
| 158 | Wikstroelide S   | benzoyl | H | H | Me | H | – | X₂ |
| 159 | Wikstroelide T   | H     | trans-cinnamoyl | H | H | Me | – | X₂ |
| 160 | Kirkinine B      | H     | CH=CH(CH₂)₅ | Me | H | Me | X₃ |
| 161 | Kirkinine C      | H     | CH=CH(CH₂)₅ | Me | H | Me | OAc | X₃ |
| 162 | Kirkinine E      | H     | CH=CH(CH₂)₅ | Me | OH | Me | H | X₃ |
| 163 | Wikstroelide E   | H     | CH₂ | Me | H | Me | H | X₃ |
| 164 | Wikstroelide F   | H     | CH₂ | CH₂OBz | H | Me | H | X₃ |
| 165 | Wikstroelide G   | palmitic acid | CH₂ | CH₂OBz | H | Me | H | X₃ |
| 166 | Wikstroelide K   | CO(CH₂)₂₄CH₃ | CH₂ | CH₂OBz | Me | H | H | X₃ |
| 167 | Wikstroelide O   | H     | CH₂ | CH₂OBz | Me | H | H | X₃ |
| 168 | Pimelea factor S₈| OH    | CH₂ | Me | H | Me | H | X₃ |
| 169 | Pimelea factor S₇| H     | H    | Me | H | – | – | X₄ |
| 170 | Pimelotide A     | H     | H    | Me | H | – | – | X₄ |
| 171 | Pimelotide B     | OAc   | H    | H | Me | – | – | X₄ |
| 172 | Pimelotide C     | H     | H    | Me | H | – | – | X₄ |
| 173 | Pimelotide D     | OAc   | H    | H | Me | – | – | X₄ |
| 174 | Stelleralide C   | H     | OBz  | Me | H | – | – | X₄ |
3.5. Rediocides

Rediocides usually have a 12-carbon macrolide structure between C-3 and C-16, and have a special C-9, C-12, and C-14 orthoester structure (Figure 6, Table 6). The active compounds trigothysoids N–P (182–184), rediocides A, C, and F (176–177, 179), and trigonosin F (181) have been obtained from the twigs and leaves of *Trigonostemon thyrsoides*. Amongst them, compounds trigothysoid N, rediocides A, C, and F, and trigonosins F have shown potent anti-HIV-1 activity, with EC₅₀ values ranging from 0.001 to 0.015 nM. Additionally, trigothysoid O has been shown to exhibit moderate anti-HIV-1 activity [11], while rediocide A has shown potent activities against mosquito larvae in an in-vitro assay study and against fleas (Ctenocephalides felis) in an artificial membrane feeding system, exhibiting LD₉₀ values of 0.25 and 0.5 ppm, respectively [39]. Trigochilide A and B (175, 186) have been isolated from the twigs and leaves of *Trigonostemon chinensis* Merr. Trigochilide A has shown modest cytotoxicity against HL-60 (human leukemia) and BEL-7402 (human hepatoma), with demonstrated IC₅₀ values of 3.68 and 8.22 μM, respectively, whereas compound trigochilide B has only been shown to exhibit weak cytotoxicity against two tumor cell lines, with IC₅₀ values of 33.35 and 54.85 μM [1]. Compound rediocide E (178) has been obtained from the roots of *Trigonostemon reidioides* Merr. Trigonostemone E and has shown significant acaricidal activity on D. pteronyssinus [40]. Trigonosin E (180) and trigonostemone D (185) have been isolated from the twigs and leaves of *Trigonostemon thyrsoides* [16,21]. Rediocides B, G, and D (187–189) have been isolated from the *Trigonostemon reidioides*, and have been evaluated for their insecticidal properties in an anti-flea artificial membrane feeding assay (as detailed earlier). In this assay, rediocides B and D exhibited LD₉₀ values of 0.25 and 0.5 ppm, respectively, and thus were equipotent with rediocide A (LD₉₀ 0.25 ppm) [41].

**Figure 6.** Five types (Y1–Y5) of rediocides skeletons.

**Table 6.** Reported structures of rediocides skeletons.

| No. | Name               | R₁    | R₂               | R₃    | Type |
|-----|--------------------|-------|-----------------|-------|------|
| 175 | Trigochilide A     | –     | –               | –     | Y1   |
| 176 | Rediocide A        | Me    | COCH₂CH(CH₃)₂   | OH    | Y2   |
| 177 | Rediocide C        | Me    | Bz              | OH    | Y2   |
| 178 | Rediocide E        | H     | COCH₂CH(CH₃)₂   | OH    | Y2   |
| 179 | Rediocide F        | H     | Bz              | OH    | Y2   |
| 180 | Trigonosin E       | Me    | COPh            | OH    | Y2   |
| 181 | Trigonosin F       | Me    | COPh            | OH    | Y2   |
4. Conclusions

It can be concluded that the bioactive activities of daphnane-type diterpenoids is obviously related to structure types. The most important points of them are the following: (1) The orthoester groups at C-9, C-13 and C-14 are essential to the cytotoxic activity. Daphnane-type diterpenoids with orthoester groups at C-9, C-13, and C-14 usually have stronger activity than daphnane-type diterpenoids with orthoester groups at C-9, C-12, and C-14 or C-12, C-13 and C-14. The absence of the orthoester group is unhelpful to the cytotoxic activity. (2) Specific to the 6-epoxyl groups, free 20-hydroxyl and 3-carbonyl are important for their activities. (3) Side chains at C-10 are crucial for cytotoxic activities. Generally speaking, long C-10 alkyl chains are more important than phenyl at C-10. Interestingly, the structure with macro-lactones exhibited much stronger activity than the others. Due to the rich activities of daphnane-type diterpenoids, researchers have not stopped exploring and researching such compounds and their bioactive activities from plants.

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Sample Availability: Samples of the compounds are available from the authors.

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