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## Phytochemical and pharmacological properties of the genus *Alpinia* from 2016 to 2023

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Covering 2016 up to the end of 2023

*Alpinia* is the largest genus of flowering plants in the ginger family, Zingiberaceae, and comprises about 500 species. Many *Alpinia* are commonly cultivated ornamental plants, and some are used as spices or traditional medicine to treat inflammation, hyperlipidemia, and cancers. However, only a few comprehensive reviews have been published on the phytochemistry and pharmacology of this genus, and the latest review was published in 2017. In this review, we provide an extensive coverage of the studies on *Alpinia* species reported from 2016 through 2023, including newly isolated compounds and potential biological effects. The present review article shows that *Alpinia* species have a wide spectrum of pharmacological activities, most due to the activities of diarylheptanoids, terpenoids, flavonoids, and phenolics.

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### 1. Introduction

The genus *Alpinia* in the Zingiberaceae family is large, comprising more than 500 species. According to the work of Ma *et al.*, phytochemical and pharmacological data are available for only 35 *Alpinia* species:<sup>40</sup> *A. blepharocalyx* K.Schum, *A. bracteata* Roscoe, *A. calcarata* (Andrews) Roscoe, *A. chinensis* (Retz.)

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Roscoe, *A. conchigera* Griff., *A. coriandriodora* D. Fang, *A. densispicata* Hayata, *A. densibracteata* T. L. Wu and S. J. Chen, *A. elegans* (C.Presl) K.Schum., *A. eremochlamys* K.Schum., *A. flabellata* Ridl., *A. formosana* K.Schum., *A. gagnepainii* K.Schum., *A. galanga* (L.) Willd., *A. intermedia* Gagnep., *A. japonica* (Thunb.) Miq., *A. katsumadae* Hayata, *A. hainanensis* K.Schum., *A. malaccensis* (Burm.f.) Roscoe, *A. mutica* Roxb., *A. nantoensis* F. Y. Lu and Y. W. Kuo, *A. nigra* (Gaertn.) Burt, *A. nutans* (L.) Roscoe, *A. officinarum* Hance, *A. oxyphylla* Miq., *A. pahangensis* Ridl., *A. pinnanensis* T. L. Wu and S. J. Chen, *A. platytilus* K.Schum., *A. pricei* Hayata, *A. purpurata* (Vieill.) K.Schum., *A. rafflesiana* Wall. ex Baker, *A. sichuanensis* Z. Y. Zhu, *A. tonkinensis* Gagnep., *A. zerumbet* (Pers.) B. L. Burt and R. M. Sm, and *A. speciosa* (J.C.Wendl.) K.Schum.

The rhizomes of *A. officinarum* (Yang Gang), seeds of *A. officinarum* (Hong Du Gu), seeds of *A. katsumadae* (Cho Du Gu), and

fruits of *A. oxyphylla* (Ik Ji, bitter cardamon) have been used in traditional medicine to treat indigestion, emesis, and stomach ache.<sup>43,44</sup> *Alpinia* species are rich in diarylheptanoids, terpenoids, flavonoids, and phenolic compounds and have shown cytotoxic, anti-inflammatory, antioxidant, and anti-bacterial activities.<sup>40,47</sup> In Korea, there have been 95 studies on *Alpinia* species since 1997, and the most investigated species are *A. officinarum* (39 cases), *A. katsumadae* (25 cases), and *A. oxyphylla* (22 cases). Biological studies have been performed, with analyses of the cytotoxicity, anti-inflammation, and anti-oxidant activity of these species. In the studies performed in Korea, most of the newly found compounds are diarylheptanoids from *A. katsumadae* and *A. officinarum*.

Previous reviews have summarized phytochemistry reports of more than 500 active compounds from the genus *Alpinia*.<sup>40,47,48</sup> However, no reviews have been reported since 2017,



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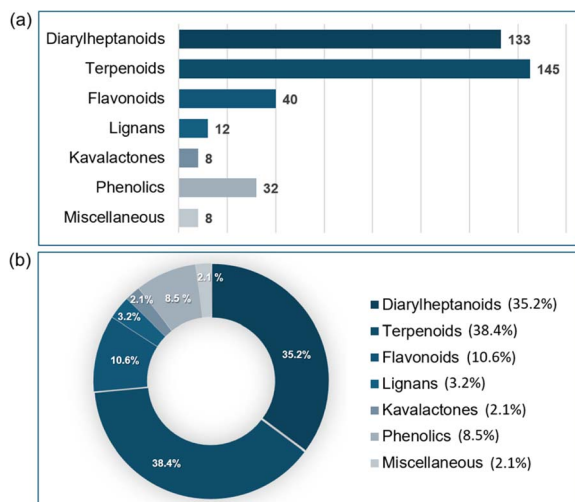


Fig. 1 (a) Number of compounds by class. (b) Percentage (%) of each class as a pie chart.

though many studies have been performed since then. Here we describe newly isolated and known compounds from the *Alpinia* species with pharmacological activity reported in 148 references published from 2016 to 2023. This review includes 378

compounds from the *Alpinia* species, comprising 133 diarylheptanoids, 145 terpenoids, 40 flavonoids, 12 lignans, 8 kavalactones, 32 phenolics, and others (Fig. 1a). The percentage of each class compared with the total number of compounds is shown in Fig. 1b. Moreover, the biological activities of frequently used compounds are reported. A literature search was conducted using online databases (PubMed, SciFinder, and Google scholar), and publications that underwent peer-review and in journals with specific impact factors were considered for this review. Scientific names were validated *via* the “International Plant Names Index” (<https://www.ipni.org/>).

## 2. Phytochemical investigation

### 2.1. Diarylheptanoids

Here, we discuss the structures of diarylheptanoid monomers, dimers, and hybrid conjugates with other structural classes. A total of 133 diarylheptanoids has been identified in *Alpinia* species since 2016.

**2.1.1. Monomers.** In total, 74 diarylheptanoid monomers were found in the genus *Alpinia* and are summarized in Fig. 2 and Table 1 based on structure. *trans*-(4*R*,5*S*)-Epoxy-1,7-diphenyl-3-heptanone (39) was isolated from the aqueous extract of *A. officinarum* and contains an epoxide ring between C-

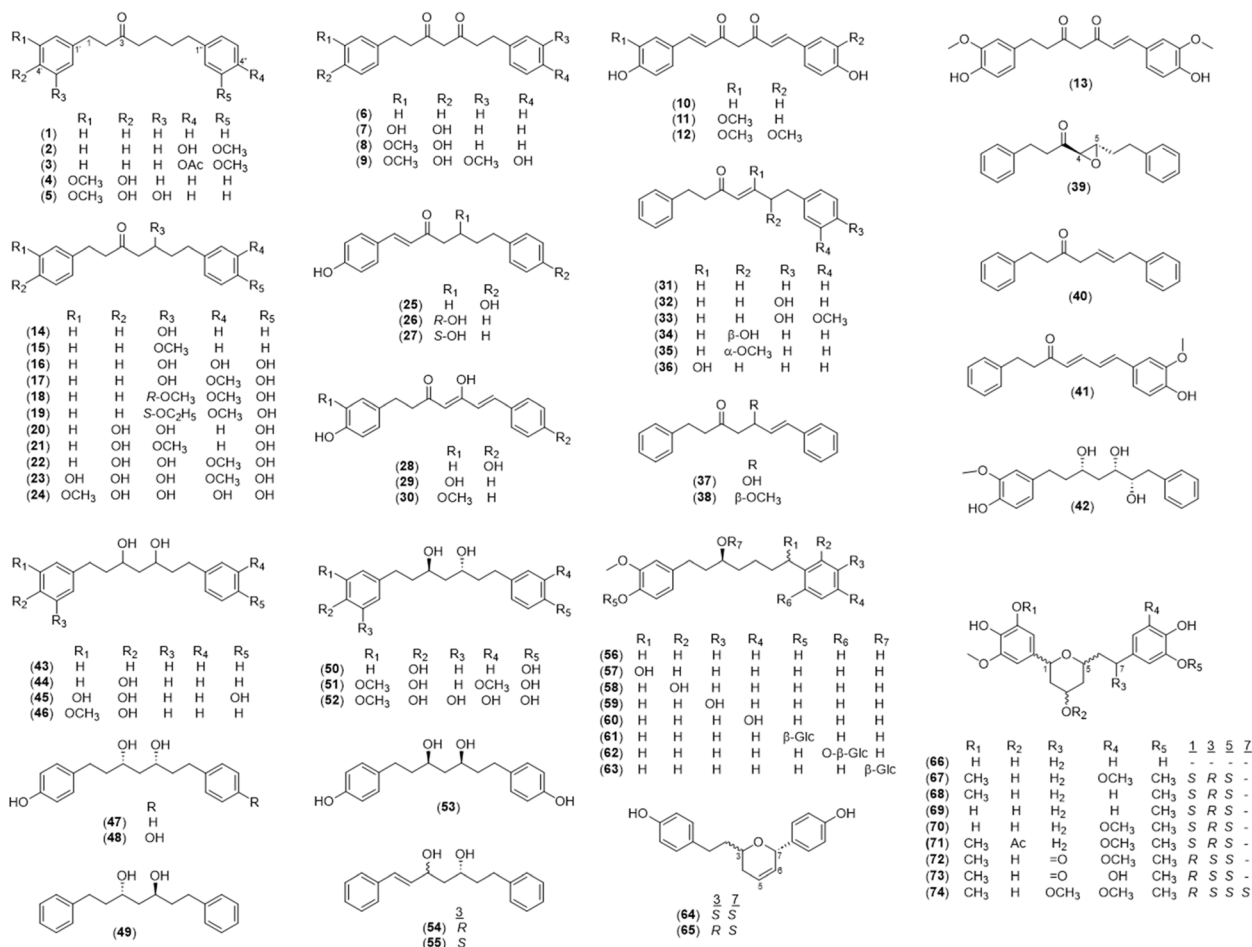


Fig. 2 Diarylheptanoid monomers in the *Alpinia* species.



Table 1 Diarylheptanoid monomers in the *Alpinia* species

| No. | Name   | No. | Name  |
|-----|--|-----|---|
| 1   | 1,7-Diphenylheptan-3-one <sup>25</sup>   | 38  | (5 <i>S</i> )-5-Methoxy-1,7-diphenylhepta-6-en-3-one <sup>22</sup>  |
| 2   | 7-(4''-Hydroxy-3''-methoxyphenyl)-1-phenylheptan-3-one <sup>41</sup>   | 39  | <i>trans</i> -(4 <i>R</i> ,5 <i>S</i> )-Epoxy-1,7-diphenylheptan-3-one <sup>45</sup>                            |
| 3   | 7-(4''-Acetoxy-3''-methoxyphenyl)-1-phenylheptan-3-one <sup>41</sup>   | 40  | 1,7-Diphenylhept-5-en-3-one <sup>45</sup>   |
| 4   | Yakuchinone A <sup>49,50</sup>   | 41  | (4 <i>E</i> ,6 <i>E</i> )-7-(4''-Hydroxy-3''-methoxyphenyl)-1-phenylhepta-4,6-dien-3-one <sup>45</sup>          |
| 5   | 5'-Hydroxyyakuchinone A <sup>50</sup>  | 42  | (3 <i>S</i> ,5 <i>S</i> ,6 <i>S</i> )-1-(4'-Hydroxy-3'-methoxyphenyl)-7-phenylheptane-3,5,6-triol <sup>25</sup> |
| 6   | 1,7-Diphenylheptane-3,5-dione <sup>25</sup>  | 43  | 1,7-Diphenylheptane-3,5-diol <sup>25,68</sup>   |
| 7   | 1-(3',4'-Dihydroxyphenyl)-7-phenylheptane-3,5-dione <sup>25</sup>  | 44  | 1-(4'-Hydroxyphenyl)-7-phenylheptane-3,5-diol <sup>25</sup>   |
| 8   | 1-(4'-Hydroxy-3'-methoxyphenyl)-7-phenylheptane-3,5-dione <sup>25</sup>  | 45  | 1-(3',4'-Dihydroxyphenyl)-7-(4'-hydroxyphenyl)heptane-3,5-diol <sup>69</sup>                                    |
| 9   | 1,7-Bis(4-hydroxy-3-methoxyphenyl)heptane-3,5-dione <sup>25</sup>  | 46  | 1-(4'-Hydroxy-3'-methoxyphenyl)-7-phenylheptane-3,5-diol <sup>25</sup>  |
| 10  | (1 <i>E</i> ,6 <i>E</i> )-1,7-Bis(4-hydroxyphenyl)hepta-1,6-diene-3,5-dione <sup>25</sup>                              | 47  | (3 <i>S</i> ,5 <i>S</i> )-Alpinikatin <sup>65</sup>   |
| 11  | (1 <i>E</i> ,6 <i>E</i> )-1-(4'-Hydroxy-3'-methoxyphenyl)-7-(4''-hydroxyphenyl)hepta-1,6-diene-3,5-dione <sup>25</sup> | 48  | (+)-Hannokinol <sup>66</sup>  |
| 12  | (1 <i>E</i> ,6 <i>E</i> )-1,7-Bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione <sup>22,23,25</sup>              | 49  | (3 <i>S</i> ,5 <i>R</i> )-1,7-Diphenylheptane-3,5-diol <sup>66,68</sup>   |
| 13  | ( <i>E</i> )-1,7-Bis(4-hydroxy-3-methoxyphenyl)hept-1-ene-3,5-dione <sup>25</sup>                                      | 50  | <i>meso</i> -Hannokinol <sup>66</sup>   |
| 14  | 5-Hydroxy-1,7-diphenylheptan-3-one <sup>16,20,41,68,69</sup>   | 51  | (3 <i>R</i> ,5 <i>S</i> )-1,7-Bis(4-hydroxy-3-methoxyphenyl)heptane-3,5-diol <sup>25</sup>                      |
| 15  | 5-Methoxy-1,7-diphenylheptan-3-one <sup>45</sup>   | 52  | Alpinin B <sup>69</sup>   |
| 16  | 5-Hydroxy-7-(3'',4''-dihydroxyphenyl)-1-phenylheptan-3-one <sup>41,69</sup>  | 53  | (3 <i>R</i> ,5 <i>R</i> )-1,7-Bis(4-hydroxyphenyl)heptane-3,5-diol <sup>25</sup>                                |
| 17  | 5-Hydroxy-7-(4''-hydroxy-3''-methoxyphenyl)-1-phenylheptan-3-one <sup>16,20,21,25,41,68,69</sup>                       | 54  | (3 <i>R</i> ,5 <i>S</i> )- <i>trans</i> -3,5-Dihydroxy-1,7-diphenyl-1-heptene <sup>66</sup>                     |
| 18  | (5 <i>R</i> )-5-Methoxy-7-(4''-hydroxy-3''-methoxyphenyl)-1-phenylheptan-3-one <sup>16,21,68</sup>                     | 55  | (3 <i>S</i> ,5 <i>S</i> )- <i>trans</i> -3,5-Dihydroxy-1,7-diphenyl-1-heptene <sup>66</sup>                     |
| 19  | (5 <i>S</i> )-5-Ethoxy-7-(4''-hydroxy-3''-methoxyphenyl)-1-phenylheptan-3-one <sup>65</sup>                            | 56  | (3 <i>S</i> )-Oxyphyllacinol <sup>49</sup>  |
| 20  | 5-Hydroxy-1,7-bis(4-hydroxyphenyl)heptan-3-one <sup>25</sup>   | 57  | (3 <i>S</i> )-7-Hydroxyoxyphyllacinol <sup>49</sup>   |
| 21  | 5-Methoxy-1,7-bis(4-hydroxyphenyl)heptan-3-one <sup>25</sup>   | 58  | (3 <i>S</i> )-2''-Hydroxyoxyphyllacinol <sup>49</sup>   |
| 22  | 5-Hydroxy-1-(4'-hydroxyphenyl)-7-(4''-hydroxy-3''-methoxyphenyl)heptan-3-one <sup>25</sup>                             | 59  | (3 <i>S</i> )-3''-Hydroxyoxyphyllacinol <sup>49</sup>   |
| 23  | 5-Hydroxy-1-(3',4'-dihydroxyphenyl)-7-(4''-hydroxy-3''-methoxyphenyl)heptan-3-one <sup>25</sup>                        | 60  | (3 <i>S</i> )-4''-Hydroxyoxyphyllacinol <sup>49</sup>   |
| 24  | 5-Hydroxy-1-(4'-hydroxy-3'-methoxyphenyl)-7-(3'',4''-dihydroxyphenyl)heptan-3-one <sup>69</sup>                        | 61  | (3 <i>S</i> )-Oxyphyllacinol-4'- <i>O</i> -β-D-glucopyranoside <sup>49</sup>                                    |
| 25  | ( <i>E</i> )-1,7-Bis(4-hydroxyphenyl)hept-1-en-3-one <sup>22</sup>   | 62  | (3 <i>S</i> )-2''-Hydroxyoxyphyllacinol-2''- <i>O</i> -β-D-glucopyranoside <sup>49</sup>                        |
| 26  | ( <i>R</i> )-4''-Hydroxyashabushiketol <sup>65</sup>   | 63  | (3 <i>S</i> )-Oxyphyllacinol-3- <i>O</i> -β-D-glucopyranoside <sup>49</sup>                                     |
| 27  | ( <i>S</i> )-4''-Hydroxyashabushiketol <sup>66</sup>   | 64  | (3 <i>S</i> ,7 <i>S</i> )-5,6-Dehydro-4''- <i>de-O</i> -methylcentrolobine <sup>65</sup>                        |
| 28  | 1,2-Dihydro-bis( <i>de-O</i> -methyl)curcumin <sup>65</sup>  | 65  | (3 <i>R</i> ,7 <i>S</i> )-5,6-Dehydro-4''- <i>de-O</i> -methylcentrolobine <sup>66</sup>                        |
| 29  | (4 <i>Z</i> ,6 <i>E</i> )-5-Hydroxy-1-(3',4'-dihydroxyphenyl)-7-phenylhepta-4,6-dien-3-one <sup>25</sup>               | 66  | Alpinin A <sup>69</sup>   |
| 30  | (4 <i>Z</i> ,6 <i>E</i> )-5-Hydroxy-1-(4'-hydroxy-3'-methoxyphenyl)-7-phenylhepta-4,6-dien-3-one <sup>25,65</sup>      | 67  | Coriandralpinin A <sup>32</sup>   |
| 31  | 1,7-Diphenylhept-4-en-3-one <sup>8,16,25,41,45,68,69,96</sup>  | 68  | Coriandralpinin B <sup>32</sup>   |
| 32  | (4 <i>E</i> )-7-(4-Hydroxyphenyl)-1-phenylhepten-3-one <sup>16,20,98</sup>   | 69  | Coriandralpinin C <sup>32</sup>   |
| 33  | (4 <i>E</i> )-7-(4''-Hydroxy-3''-methoxyphenyl)-1-phenylhept-4-en-3-one <sup>20,21,68,99</sup>                         | 70  | Coriandralpinin D <sup>32</sup>   |
| 34  | (4 <i>E</i> )-6-Hydroxy-1,7-diphenylhept-4-en-3-one <sup>25</sup>  | 71  | Coriandralpinin E <sup>32</sup>   |
| 35  | (6 <i>S</i> ,4 <i>E</i> )-6-Methoxy-1,7-diphenylhept-4-en-3-one <sup>25</sup>  | 72  | Coriandralpinin F <sup>32</sup>   |
| 36  | 5-Hydroxy-1,7-diphenylhept-4-en-3-one <sup>69</sup>  | 73  | Coriandralpinin G <sup>32</sup>   |
| 37  | 5-Hydroxy-1,7-diphenylhept-6-en-3-one <sup>25,68</sup>   | 74  | Coriandralpinin H <sup>32</sup>   |

4 and C-5, which is a rare functional group in diarylheptanoids.<sup>28,45</sup> Preparative scale microtransformation of yakuchinone A (4) was performed with *Mucor hiemalis* to study the structure-activity relationship of yakuchinone A derivatives

against HT-29 cancer cells.<sup>49</sup> Eight new metabolites were isolated from the sample: (3*S*)-oxyphyllacinol (56), (3*S*)-7-hydroxyoxyphyllacinol (57), (3*S*)-2''-hydroxyoxyphyllacinol (58), (3*S*)-3''-hydroxyoxyphyllacinol (59), (3*S*)-4''-hydroxyoxyphyllacinol (60),



(3*S*)-oxyphyllacinol-4'-*O*- $\beta$ -D-glucopyranoside (**61**), (3*S*)-2''-hydroxyoxyphyllacinol-2''-*O*- $\beta$ -D-glucopyranoside (**62**), and (3*S*)-oxyphyllacinol-3-*O*- $\beta$ -D-glucopyranoside (**63**). In addition, (3*S*,7*S*)-5,6-dehydro-4''-*de-O*-methylcentrolobine (**64**) and (3*R*,7*S*)-5,6-dehydro-4''-*de-O*-methylcentrolobine (**65**) were isolated from *A. katsumadae* and were shown to possess a 3,7-*O*-bridged dihydropyran ring with a conjugation at C-5 and C-6.<sup>65,66</sup> Two undescribed diarylheptanoids, alpinin A (**66**) and alpinin B (**52**), were isolated from *A. officinarum*, and alpinin A (**66**) was confirmed to have a 2,6-*cis*-configured tetrahydropyran ring between C-1 and C-5 based on 2D NMR analyses.<sup>69</sup> Coriandrinalpinins A-H (**67–74**), isolated from the rhizomes of *A. coriandriodora*, have diarylheptanoid structures closely related to that of alpinin A, with a C<sub>1</sub>–C<sub>5</sub> oxa-bridged tetrahydropyran ring with polyoxygenated aryl units.<sup>32</sup>

**2.1.2. Dimers.** Dimeric diarylheptanoids were mainly isolated from two plants: *A. katsumadae* and *A. officinarum* (Fig. 3). Ten new diarylheptanoid dimers, katsumadainols C<sub>1</sub>–C<sub>10</sub> (**75–84**), were isolated and reported as previously undescribed structures.<sup>71</sup> The planar structures of katsumadainols C<sub>1</sub>–C<sub>4</sub> (**75–78**) were similar to that of blepharocalyxin D, and katsumadainol C<sub>1</sub> (**75**) was assigned as the enantiomer of blepharocalyxin D.<sup>75</sup> Katsumadainol C<sub>5</sub> (**79**) resembled blepharocalyxin C from *A. blepharocalyx*, except for an additional acetyl group at C(B)-5 of **79**.<sup>75</sup> Katsumadainols C<sub>6</sub>–C<sub>10</sub> (**80–84**) were the conjugates of 3,7-epoxy-5-hydroxy-1,7-bis(4-hydroxyphenyl)heptane (unit A) and 1,7-bis(4-hydroxyphenyl)-3-hydroxy-5-heptene (unit B) substructures with a direct C–C bond between C(A)-6 and C(B)-7. Moreover, three novel dimeric diarylheptanoids (alpinidinoids A–C, **85–87**) were isolated from *A. officinarum*.<sup>78</sup> The substructures (units A and B) of alpinidinoid A [(±)-**85**] were linked through the C(A)-4–C(B)-3 bond and the oxygen bridge

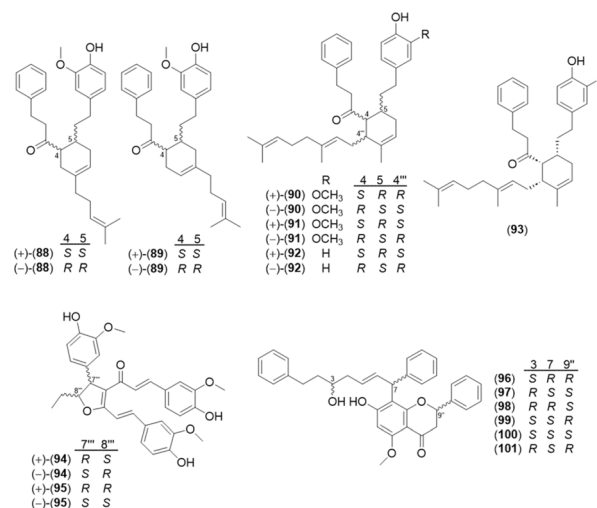


Fig. 4 Diarylheptanoid conjugates with monoterpenes, sesquiterpenes, butyrovaniolones, and flavones isolated from the *Alpinia* species.

between C(A)-5 and C(B)-5 to form a tetrahydropyran ring.<sup>78</sup> Alpinidinoid B (**86**) was a symmetrical diarylheptanoid dimer, in which the two monomeric units were connected *via* a C(A)-5–O–C(B)-5 bond. Alpinidinoid C (**87**) contains a pyridine ring connected *via* C(A)-4–C(B)-5 and C(A)-5–N–C(B)-3 bonds between two diarylheptanoid monomers and is rare in naturally occurring dimeric diarylheptanoid.

**2.1.3. Hybrids.** Undescribed diarylheptanoid–monoterpene conjugates (±)-alpininoids A and B [(±)-**88** and (±)-**89**] were isolated from *A. officinarum*, together with (±)-alpininoids C–E [(±)-**90**–(±)-**92**], and were reported as a new diarylheptanoid–sesquiterpene adduct (Fig. 4).<sup>79</sup> Moreover, alpinisin A (**93**) was isolated as a new sesquiterpene-bearing diarylheptanoid from the rhizomes of *A. officinarum*.<sup>80</sup> Alphananins A and B (**94** and **95**, Fig. 4) from *A. katsumadae* carried a 2,3-dihydrofuran motif and were confirmed as curcumin–butyrovaniolone hybrids that feature a rare structural group.<sup>22</sup> Six novel diarylheptanoid–flavone conjugate structures were isolated and named calyxin T (**96**), *ent*-calyxin T (**97**), calyxin U (**98**), *ent*-calyxin U (**99**), calyxin V (**100**), and calyxin W (**101**) (Fig. 4).<sup>81</sup>

A total of 32 diarylheptanoid–chalcone hybrid conjugates (Fig. 5) was isolated in *Alpinia*. New structures alphananins C and D (**102** and **103**) were isolated from *A. katsumadae*,<sup>22</sup> as was katsumain H (**104**).<sup>82</sup> In addition, 16 new diarylheptanoid–chalcone hybrids, katsumadainols A<sub>1</sub>–A<sub>16</sub> (**105–120**), were found in *A. katsumadae*.<sup>83</sup> In that same study, 13 known analogs were isolated: calyxin F (**121**), *epi*-calyxin F (**122**), (3*S*,5*S*,6*S*,7*R*)-6-hydroxycalyxin F (**123**), (3*S*,5*S*,6*S*,7*S*)-6-hydroxycalyxin F (**124**), calyxin L (**125**), *epi*-calyxin B (**126**), calyxin B (**127**), alpinnanin A (**128**), alpinnanin B (**129**), calyxin H (**130**), *epi*-calyxin H (**131**), katsumain C (**132**), and 7-*epi*-katsumain C (**133**).<sup>83</sup>

## 2.2. Terpenoids

**2.2.1. Monoterpenoids.** Six monoterpenoids were isolated from the *Alpinia* species (Fig. 6). An undescribed menthane-type

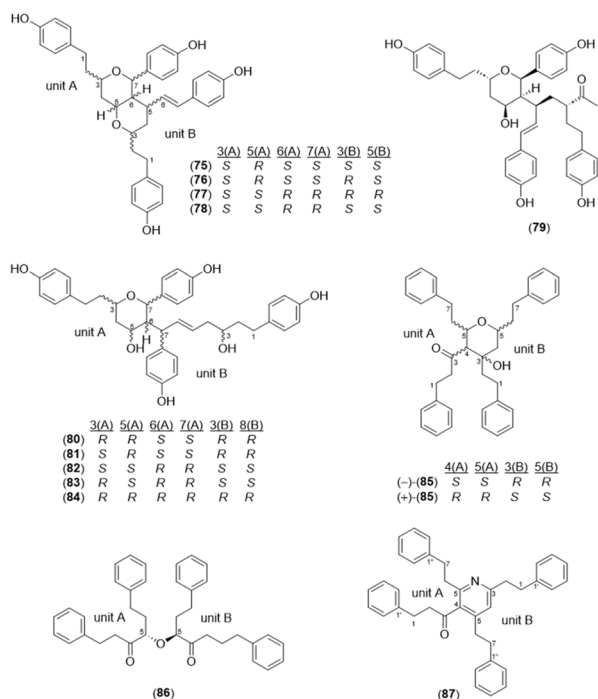


Fig. 3 Dimeric diarylheptanoids found in the *Alpinia* species.



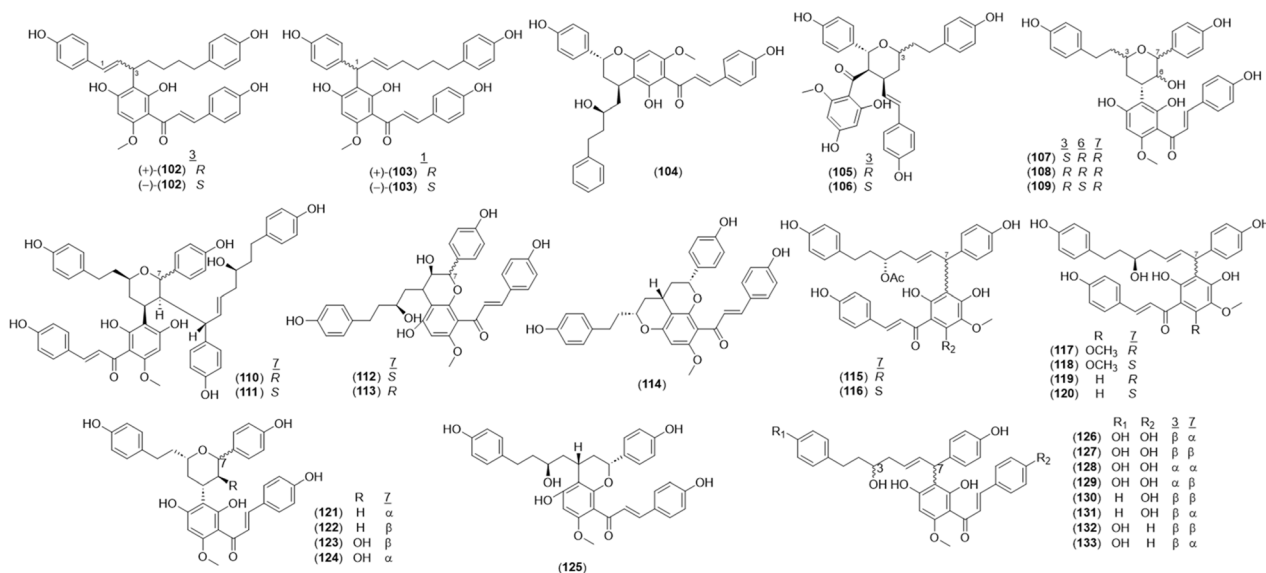


Fig. 5 Diarylheptanoid-chalcone derivatives found in the genus *Alpinia*.

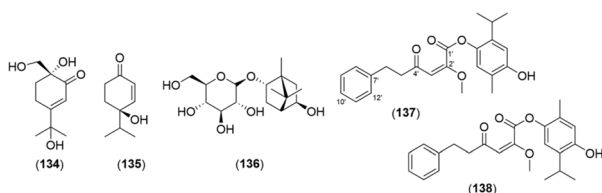


Fig. 6 Monoterpenoids in the genus *Alpinia*.

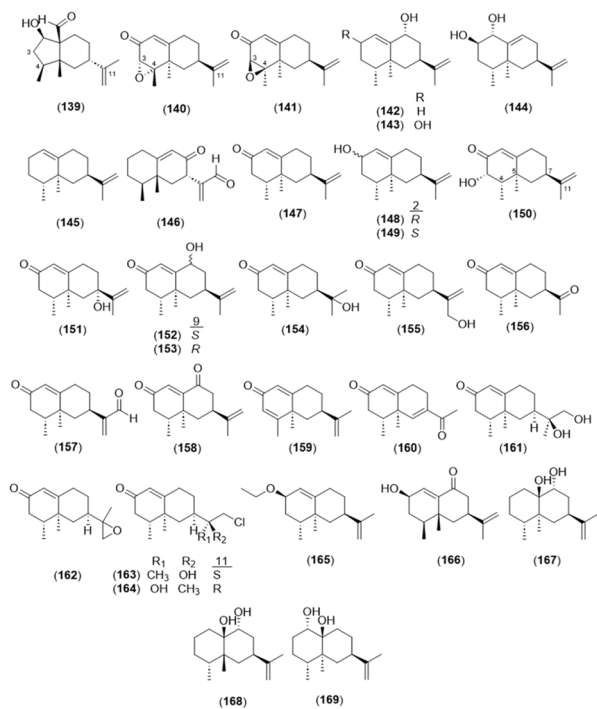


Fig. 7 Eremophilane-type sesquiterpenoids in the genus *Alpinia*.

monoterpene, alpigalanol (**134**), was isolated from *A. galanga* rhizomes,<sup>84</sup> along with (4*R*)-4-hydroxy-4-(2-methylethyl)cyclohex-2-en-1-one (**135**) and 2-*O*-β-*D*-glucopyranosyl-(+)-angelicoidenol (**136**) from the EtOAc fraction of the *A. galanga* extract.<sup>84</sup> In a later study, the monoterpene esters (2'*E*)-2'-methoxy-4'-oxo-6'-phenylhexenoic acid 4-hydroxy-2-isopropyl-5-methylphenyl ester (**137**) and (2'*E*)-2'-methoxy-4'-oxo-6'-phenylhexenoic acid 4-hydroxy-5-isopropyl-2-methylphenyl ester (**138**) were newly found in *A. zerumbet*.<sup>85</sup> The compounds were composed of a monoterpene skeleton of 5-acetyl-thymoquinol and a kavalactone moiety (C-1' to C-12') at 2-OH or 5-OH.<sup>86</sup>

## 2.2.2. Sesquiterpenoids

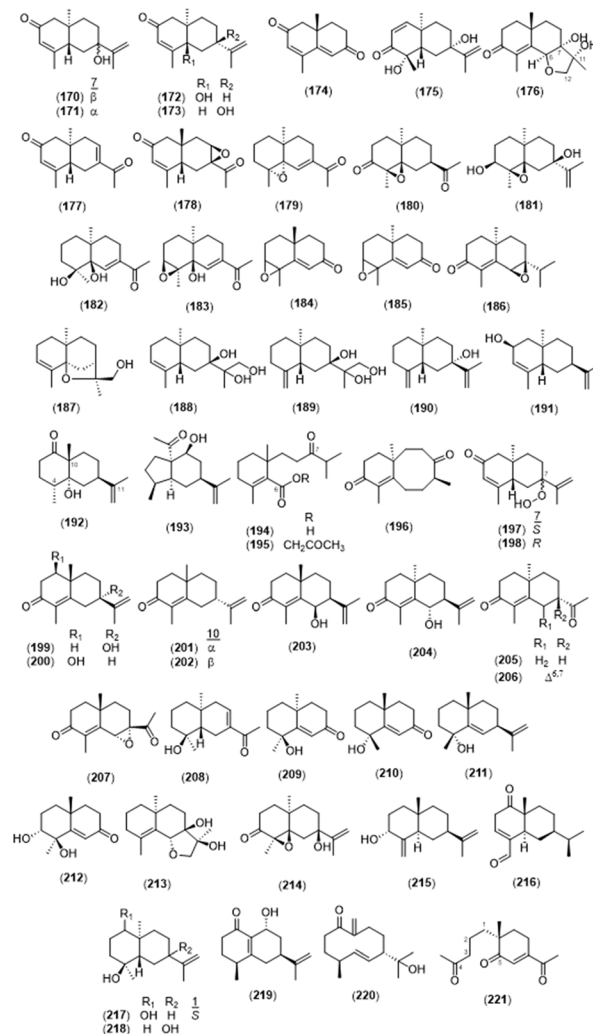
**2.2.2.1 Eremophilane type.** The basic skeleton of eremophilane-type sesquiterpenes comprises two six-membered rings and four methyl groups at C-4, 5, and 11.<sup>87</sup> The eremophilane-type sesquiterpenoids from the genus *Alpinia* are presented in Fig. 7 and Table 2. Six newly found eremophilane-type sesquiterpenes were isolated from *A. oxyphylla*: alpinoxyphyllone C (**139**); (3*S*,4*S*,5*R*,7*R*)-eremophila-3,4-epoxy-1(10),11-dien-2-one (**140**); (3*R*,4*R*,5*R*,7*R*)-eremophila-3,4-epoxy-1(10),11-dien-2-one (**141**); (4*R*,5*S*,7*S*,9*R*)-eremophila-1(10),11-dien-9-ol (**142**); (2*R*,4*R*,5*S*,7*S*,9*R*)-eremophila-1(10),11-dien-2,9-diol (**143**); and (1*R*,2*R*,4*R*,5*S*,7*R*)-eremophila-9,11-dien-1,2-diol (**144**). In addition, nootkatone and its derivatives (**147**–**155**) with a hydroxyl group at various positions are shown. 2-*O*-Ethyl-β-nootkatol (**165**), which is an ethoxy substitute of β-nootkatone, was found in *A. oxyphylla*.<sup>28</sup>

**2.2.2.2 Eudesmane type.** A total of 52 eudesmane sesquiterpenes was found in the *Alpinia* species and is summarized in Fig. 8 and Table 3. Oxyphyllins C–G (**175**–**179**) were newly isolated from *A. oxyphylla*,<sup>3,88</sup> and oxyphyllin D (**176**) and oxyphyllol D (**213**) were eudesmane-12,6-olide structures found in *A. oxyphylla*.<sup>26</sup> Compounds **193** and **196** were rare rearranged eudesmane skeletons with 5/6-fused and 6/8-fused bicyclic backbones, respectively.<sup>26</sup> Compounds **194** and **195** were 6,7-



Table 2 Eremophilane-type sesquiterpenoids in the genus *Alpinia*

| No. | Name  |
|-----|---|
| 139 | Alpinoxyphyllone C <sup>24</sup>  |
| 140 | (3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i> ,7 <i>R</i> )-Eremophila-3,4-epoxy-1(10),11-dien-2-one <sup>24</sup>      |
| 141 | (3 <i>R</i> ,4 <i>R</i> ,5 <i>R</i> ,7 <i>R</i> )-Eremophila-3,4-epoxy-1(10),11-dien-2-one <sup>24</sup>      |
| 142 | (4 <i>R</i> ,5 <i>S</i> ,7 <i>S</i> ,9 <i>R</i> )-Eremophila-1(10),11-dien-9-ol <sup>24</sup>                 |
| 143 | (2 <i>R</i> ,4 <i>R</i> ,5 <i>S</i> ,7 <i>S</i> ,9 <i>R</i> )-Eremophila-1(10),11-dien-2,9-diol <sup>24</sup> |
| 144 | (1 <i>R</i> ,2 <i>R</i> ,4 <i>R</i> ,5 <i>S</i> ,7 <i>R</i> )-Eremophila-9,11-dien-1,2-diol <sup>24</sup>     |
| 145 | Valencene <sup>51</sup>   |
| 146 | Nigriterpene F <sup>28</sup>  |
| 147 | Nootkatone <sup>3,24,61,62</sup>  |
| 148 | $\alpha$ -Nootkatone <sup>24</sup>  |
| 149 | $\beta$ -Nootkatone <sup>3,24</sup>   |
| 150 | 3 $\alpha$ -Hydroxynootkatone <sup>4</sup>  |
| 151 | 7 $\alpha$ -Hydroxynootkatone <sup>3,24</sup>   |
| 152 | 9 $\beta$ -Hydroxynootkatone <sup>4,24</sup>  |
| 153 | Oxyphyllol B <sup>3,4,24</sup>  |
| 154 | 11-Hydroxyl-eremophilane-1(10)-en-2-one <sup>3,24</sup>   |
| 155 | 13-Hydroxynootkatone <sup>3,4,7,24</sup>  |
| 156 | Diketone <sup>3,24</sup>  |
| 157 | 12-Al-nootkatone <sup>24</sup>  |
| 158 | 11(12)-Dien-2,9-dione <sup>4,24</sup>   |
| 159 | 3,4-Dehydronootkatone <sup>4,24</sup>   |
| 160 | Oxyphyllanone A <sup>3,24</sup>   |
| 161 | Nootkatone-11,12-diol <sup>4</sup>  |
| 162 | Nootkatone-11,12-epoxide <sup>4</sup>   |
| 163 | (11 <i>S</i> )-12-Chloronootkatone-11-ol <sup>14,24</sup>   |
| 164 | (11 <i>R</i> )-12-Chloronootkatone-11-ol <sup>24</sup>  |
| 165 | 2-O-Ethyl- $\beta$ -nootkatol <sup>28</sup>   |
| 166 | Oxyphyllin H <sup>3</sup>   |
| 167 | Alpinoxyphyllol A <sup>28</sup>   |
| 168 | Alpinoxyphyllol B <sup>28</sup>   |
| 169 | Oxyphyllol C <sup>24,28</sup>   |

Fig. 8 Eudesmane-type sesquiterpenoids in the genus *Alpinia*.

secoeudesmane sesquiterpenoids isolated from a plant for the first time, and 221 was a 4,5-secoeudesmane sesquiterpenoid.<sup>26</sup> 7 $\alpha$ -Hydroperoxy eudesma-3,11-diene-2-one (197) and 7 $\beta$ -hydroperoxy eudesma-3,11-diene-2-one (198) were hydrogen peroxide-substituted eudesmanes isolated from the dried fruits of *A. oxyphylla*.<sup>4</sup> In addition, (4*S*,7*S*,9*R*)-14-nor-5(10),11(12)-dien-9-ol-1-one-eudesma (219) was a 14-nor sesquiterpenoid, which is rare in eudesmane sesquiterpenoids.<sup>42</sup>

**2.2.2.3 Cadinane type.** Cadinanes constitute a large family of plant and fungal terpenes with characteristic decaline (cadinane or cadalane) scaffolds that result from the C-1/C-6 and C-5/C-10 cyclization of farnesyl pyrophosphate.<sup>89</sup> In total, 22 cadinane-type sesquiterpenoids were isolated from *A. oxyphylla*, except 4-isopropyl-6-methyl-1-naphthalenemethanol (237) from *A. officinarum* (Fig. 9 and Table 4).

Oxyspiroenes A (242) and B (243) were rare spiro[5.6]-bearing rearranged cadinanes.<sup>24</sup>

**2.2.2.4 Guaiane type.** A basic skeleton of guaiane-type sesquiterpene contains a five-membered ring, a seven-membered ring, two methyl groups at C-4 and 10, and an isopropyl group at C-7. A total of 11 guaiane-type sesquiterpenoids was found in this genus (Fig. 10 and Table 5). Among them, alpinone (248) and 11-hydroxyisohanalpinone (249) have oxygen and peroxide bridges between C-6 and C-10, respectively.<sup>3,28,42</sup> Oxyphyllin A (254) was a 7,9-*seco*-8,12-dinorguaiane-type sesquiterpenoid.<sup>3</sup>

**2.2.2.5 Others.** Along with the reported subtypes of sesquiterpenoids, acyclic sesquiterpenoid (5*S*)-5-hydroxy-*trans,trans*-farnesol (255),<sup>66</sup> humulane-type sesquiterpenoid (2*S*,3*S*,6*R*,7*R*,9*S*,10*S*)-humulene triepoxide (256),<sup>27</sup> and an oplopanone-type sesquiterpenoid oplopanone (257)<sup>24</sup> were isolated from *A. katsumadae*, *A. galanga*, and *A. oxyphylla*, respectively. In addition, four sesquiterpenes were isolated from *A. galanga*, namely, clovane-2 $\beta$ ,9 $\alpha$ -diol (258), caryolane-1,9 $\beta$ -diol (259), kobusone (260), and (–)-2-oxoisodauc-5-en-12-al (261).<sup>90</sup> Kobusone (260) was a caryophyllene-derived epoxy ketone, and (–)-2-oxoisodauc-5-en-12-al (261) was an isodaucene sesquiterpenoid, which differs from the daucanes in position C-14 and instead attaches to C-4.<sup>91</sup> The structures are shown in Fig. 11.

**2.2.3. Diterpenoids.** Labdane diterpenes are the most predominant diterpenoid type in the genus *Alpinia*, numbering 11 (Fig. 12). Intermedin A (262), intermedin B (263), and coronarin E (264) were isolated from *A. intermedia*, and 262 and 263 are C-12 diastereo-isomers and considered as artificial products from 264 reacted with EtOH.<sup>92</sup> In addition, (*E*)-labda-8(17),12-diene-15,16-dial (265) was isolated from *A. nigra*,<sup>93</sup> and (*Z*)-



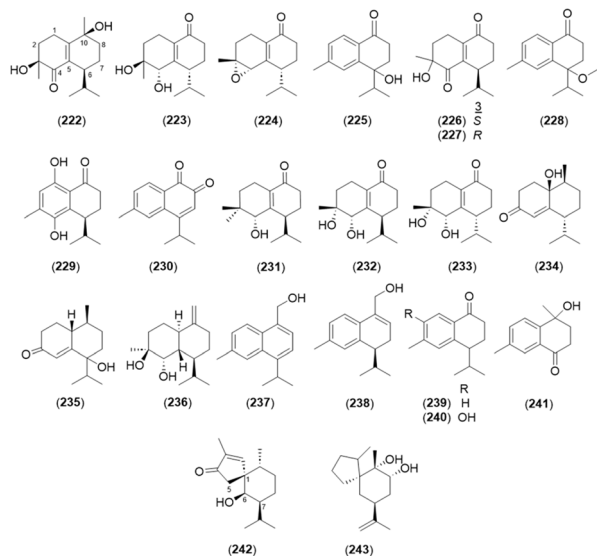
Table 3 Eudesmane-type sesquiterpenoids in the genus *Alpinia*

| No. | Name  |
|-----|---|
| 170 | Teucrenone <sup>3,4</sup>   |
| 171 | 7- <i>epi</i> -Teucrenone <sup>3,4,7</sup>  |
| 172 | Teucrenone <sup>26</sup>  |
| 173 | $\alpha$ -Rotunol <sup>26,28</sup>  |
| 174 | Oxyphyllanene B <sup>3,26</sup>   |
| 175 | Oxyphyllin C <sup>3</sup>   |
| 176 | Oxyphyllin D <sup>3</sup>   |
| 177 | Oxyphyllin E <sup>3</sup>   |
| 178 | Oxyphyllin F <sup>3</sup>   |
| 179 | Oxyphyllin G <sup>3</sup>   |
| 180 | (4 <i>R</i> ,5 <i>R</i> ,7 <i>R</i> ,10 <i>R</i> )-12-Noreudesma-4,5-epoxy-3-one <sup>26</sup>  |
| 181 | (3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i> ,7 <i>R</i> ,10 <i>S</i> )-Eudesma-4,5-epoxy-11-en-3,7-diol <sup>26</sup>   |
| 182 | (4 <i>S</i> ,5 <i>R</i> ,10 <i>S</i> )-12-Noreudesma-6-en-4,5-diol-11-one <sup>26</sup>   |
| 183 | (3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i> ,10 <i>R</i> )-12-Noreudesma-3,4-epoxy-6-en-5-ol-11-one <sup>26</sup>   |
| 184 | (3 <i>R</i> ,4 <i>S</i> ,10 <i>R</i> )-11,12,13-Trinoreudesma-3,4-epoxy-5-en-7-one <sup>26</sup>  |
| 185 | (3 <i>R</i> ,4 <i>S</i> ,10 <i>S</i> )-11,12,13-Trinoreudesma-3,4-epoxy-5-en-7-one <sup>26</sup>  |
| 186 | (6 <i>S</i> ,7 <i>S</i> ,10 <i>R</i> )-Eudesma-6,7-epoxy-4-en-3-one <sup>26</sup>   |
| 187 | (5 <i>R</i> ,7 <i>R</i> ,10 <i>S</i> ,11 <i>S</i> )-Eudesma-5,11-epoxy-3-en-12-ol <sup>26</sup>   |
| 188 | (5 <i>S</i> ,7 <i>R</i> ,10 <i>S</i> )-Eudesma-3-en-7,11,12-triol <sup>26</sup>   |
| 189 | (5 <i>R</i> ,7 <i>R</i> ,10 <i>S</i> )-Eudesma-4(15)-en-7,11,12-triol <sup>26</sup>   |
| 190 | (5 <i>R</i> ,7 <i>S</i> ,10 <i>S</i> )-Eudesma-4(15),11-dien-7-ol <sup>26</sup>   |
| 191 | (2 <i>R</i> ,5 <i>R</i> ,7 <i>S</i> ,10 <i>S</i> )-Eudesma-4,11-dien-2-ol <sup>26</sup>   |
| 192 | (4 <i>R</i> ,5 <i>R</i> ,7 <i>R</i> ,10 <i>R</i> )-Eudesma-11-en-5-ol-1-one <sup>26</sup>   |
| 193 | Epialpinol <sup>26</sup>  |
| 194 | Alpinoxphyllaone A <sup>26</sup>  |
| 195 | Alpinoxphyllaone B <sup>26</sup>  |
| 196 | Neoxyphyllanene <sup>26</sup>   |
| 197 | 7 $\alpha$ -Hydroperoxyeudesma-3,11-diene-2-one <sup>4</sup>  |
| 198 | 7 $\beta$ -Hydroperoxyeudesma-3,11-diene-2-one <sup>3,4</sup>   |
| 199 | (7 <i>S</i> ,10 <i>S</i> )-11-Hydroxyeudesmane-4(5),11(12)-diene-3-one <sup>3,26</sup>  |
| 200 | Ligucyperonol <sup>3,26</sup>   |
| 201 | (-)- $\alpha$ -Cyperone <sup>26</sup>   |
| 202 | (+)-7- <i>epi</i> - $\alpha$ -Cyperone <sup>26</sup>  |
| 203 | (4 <i>aS</i> ,7 <i>S</i> ,8 <i>R</i> )-8-Hydroxy-1,4 <i>a</i> -dimethyl-7-(prop-1-en-2-yl)-4,4 <i>a</i> ,5,6,7,8-hexahydronaphthalen-2(3 <i>H</i> )-one <sup>26</sup> |
| 204 | (6 <i>S</i> ,7 <i>S</i> ,10 <i>R</i> )-6-Hydroxyeudesmane-4(5),11(12)-diene-3-one <sup>3,28</sup>   |
| 205 | (10 <i>R</i> )-13-Noreudesma-4,6-dien-3,11-dione <sup>26</sup>  |
| 206 | 7 $\alpha$ H-12-Noreudesm-4-ene-3,11-dione <sup>26</sup>  |
| 207 | Oxyphyllanene C <sup>26</sup>   |
| 208 | Tephyllone <sup>26</sup>  |
| 209 | Teuhetenone A <sup>1,3,26</sup>   |
| 210 | (5 <i>E</i> )-(4 <i>S</i> ,10 <i>R</i> )-7-Oxo-trinoreudesm-5-en-4 $\beta$ -ol <sup>3,7</sup>   |
| 211 | Oxyphyllol A <sup>26</sup>  |
| 212 | (+)-Oxyphyllone A <sup>26</sup>   |
| 213 | Oxyphyllol D <sup>26</sup>  |
| 214 | Oxyphyllol E <sup>26</sup>  |
| 215 | Isocyperol <sup>26</sup>  |
| 216 | 1-Oxo-5 $\alpha$ ,7 $\alpha$ H-eudesm-3-en-15-ol <sup>26</sup>  |
| 217 | Lairdinol A <sup>26</sup>   |
| 218 | Teucdiol B <sup>26</sup>  |
| 219 | (4 <i>S</i> ,7 <i>S</i> ,9 <i>R</i> )-14-Nor-5(10),11(12)-dien-9-ol-1-one-eudesma <sup>42</sup>   |
| 220 | Litseagermacrane <sup>26</sup>  |
| 221 | Oxyphyllone A <sup>3,26</sup>   |

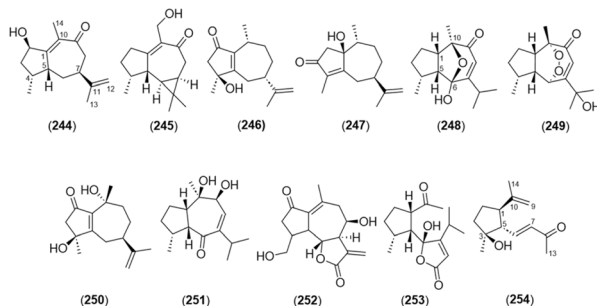
12,14-labdadien-15(16)-olide-17-oic acid (266) and (*E*)-labda-12,14-dien-15(16)-olide-17-oic acid (267) were isolated from *A. oxyphylla*.<sup>7</sup> Galangalditerpenes A–C (268–270) were isolated from *A. galanga*; galanalditerpene A (268) possesses a 5-formyl-8,10-dioxabicyclo[5.2.1]dec-4-en structure.<sup>90</sup> A bis-labdanic diterpene, pahangensin A (271), was purified from the rhizomes of *A. pahangensis*.<sup>94</sup>

**2.2.4. Triterpenoids.** Seven acyclic triterpenoids were isolated from *A. katsumadae* (Fig. 13): 2,3,6,22,23-pentahydroxy-2,6,11,15,19,23-hexamethyl-tetracos-7,10,14,18-tetraene (272),<sup>95</sup> 2,3,6,22,23-pentahydroxy-2,10,15,19,23-hexamethyl-methylenetetracos-10,14,18-triene (273),<sup>95</sup> 2,3,22,23-tetrahydroxy-2,6,10,15,19,23-hexamethyl-tetracos-6,10,14,18-tetraene (274),<sup>95</sup> and 2,3,5,22,23-pentahydroxy-2,6,10,15,19,23-hexamethyl-tetracos-6,10,14,18-tetraene (275),<sup>66,95,97</sup> (3*R*,20*S*)-

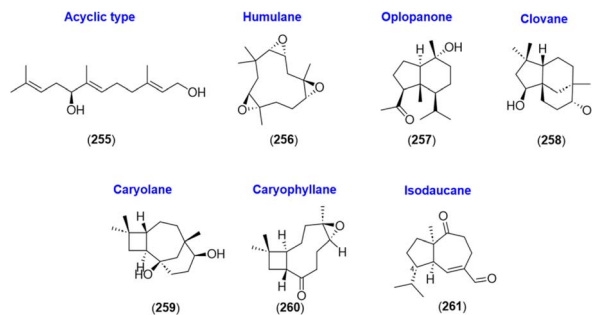
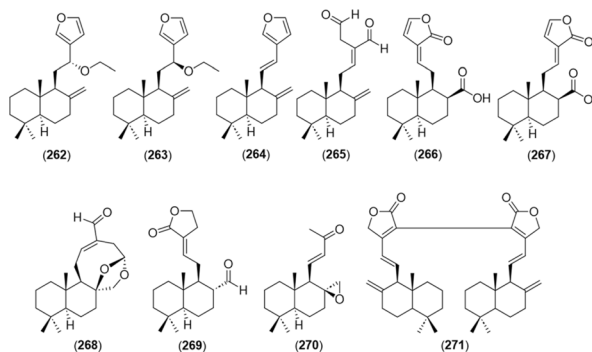


Fig. 9 Cadinane-type sesquiterpenoids in the *Alpina* species.Table 4 Cadinane-type sesquiterpenoids in the *Alpina* genus

| No. | Name  |
|-----|---|
| 222 | Oxyphyllin I <sup>3</sup>   |
| 223 | Oxyphyllin J <sup>3</sup>   |
| 224 | Oxyphyllone C <sup>24</sup>   |
| 225 | Oxyphyllone D <sup>24,28</sup>  |
| 226 | Oxyphyllone E <sup>24</sup>   |
| 227 | (3 <i>R</i> )-Oxyphyllone E <sup>24</sup>   |
| 228 | Oxyphyllone I <sup>24</sup>   |
| 229 | Oxyphyllone J <sup>24</sup>   |
| 230 | Oxyphyllone K <sup>24</sup>   |
| 231 | (6 <i>R</i> ,9 <i>S</i> ,10 <i>S</i> )-10-Hydroxyl-15-norcadinane-4(5)-ene-3-one <sup>3</sup> |
| 232 | Oxyphyllendiol A <sup>3,24</sup>  |
| 233 | Oxyphyllendiol B <sup>7</sup>   |
| 234 | (-)-(1 <i>R</i> ,7 <i>S</i> ,10 <i>R</i> )-1-Hydroxy-11-norcadinan-5-en-4-one <sup>28</sup>   |
| 235 | Oxyphyllene H <sup>28</sup>   |
| 236 | Cadin-10(14)-en-4β,5α-diol <sup>24</sup>  |
| 237 | 4-Isopropyl-6-methyl-1-naphthalenemethanol <sup>73</sup>                                      |
| 238 | (7 <i>S</i> )-Calacoren-14-ol <sup>24</sup>   |
| 239 | 3,4-Dihydro-6-methyl-4-(1-methylethyl)-1(2 <i>H</i> )-naphthalene <sup>24</sup>               |
| 240 | 2-Hydroxy-14-calamenone <sup>24</sup>   |
| 241 | 4-Hydroxy-4,7-dimethyl-1-tetralone <sup>24</sup>  |
| 242 | Oxyspirene A <sup>24</sup>  |
| 243 | Oxyspirene B <sup>24</sup>  |

Fig. 10 Guaiane-type sesquiterpenoids in the *Alpina* species.Table 5 Guaiane-type sesquiterpenoids in the *Alpina* genus

| No. | Name   |
|-----|--|
| 244 | Oxyphyllin B <sup>3</sup>  |
| 245 | Aromadendr-1(10)-ene-9-one <sup>3</sup>  |
| 246 | (4 <i>S</i> ,7 <i>S</i> ,10 <i>R</i> )-4-Hydroxyguaiane-1(5),11(12)-diene-2-one <sup>3</sup>   |
| 247 | (1 <i>S</i> ,7 <i>R</i> ,10 <i>R</i> )-1-Hydroxyguaiane-4(5),11(12)-diene-3-one <sup>3</sup>   |
| 248 | Alpinone <sup>3,42</sup>   |
| 249 | 11-Hydroxyisohanalpinone <sup>28</sup>   |
| 250 | Cyperusol A4 <sup>42</sup>   |
| 251 | [3 <i>R</i> -(3α,3αβ,7β,8β,8αβ)]-2,3,3a,7,8,8a-Hexahydro-7,8-dihydroxy-3,8-dimethyl-5-(1-methylethyl)-4(1 <i>H</i> )-azulene <sup>42</sup> |
| 252 | 3,4-Dihydrolactucin <sup>60</sup>  |
| 253 | 6-Hydroxyalpinolide <sup>28</sup>  |
| 254 | Oxyphyllin A <sup>3</sup>  |

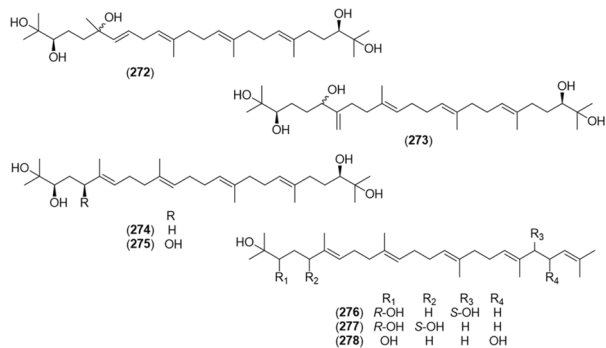
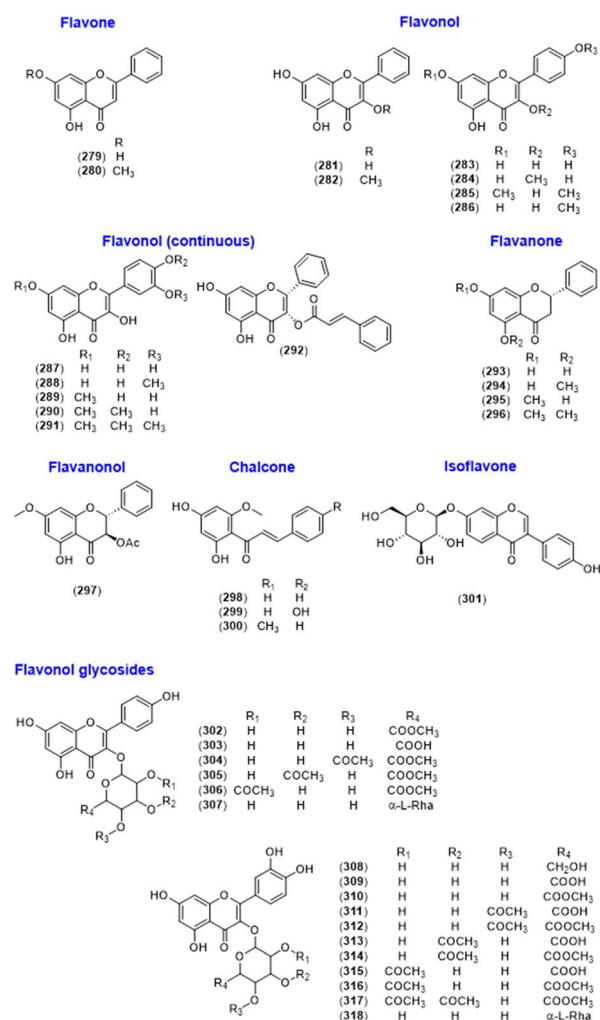
Fig. 11 Other types of sesquiterpenoids in the genus *Alpina*.Fig. 12 Diterpenoids found in the *Alpina* species.

2,3,20-trihydroxy-2,6,10,15,19,23-hexamethyl-tetracos-6,10,14,18,22-pentaene (276),<sup>66</sup> (3*R*,5*S*)-2,3,5-trihydroxy-2,6,10,15,19,23-hexamethyl-tet-racos-6,10,14,18,22-pentaene (277),<sup>66</sup> and 2,3,21-trihydroxy-2,6,10,15,19,23-hexamethyl-tetracos-6,10,14,18,22-pentaene (278).<sup>66</sup> Compounds 272, 273, and 276–278 were newly found in nature.

### 2.3. Flavonoids

Flavonoids comprise one of the main classes of the genus *Alpina*. Several flavonoid subtypes (flavone, flavonol, flavanone, flavanonol, isoflavone, chalcone, and flavonoid glycosides) were found in this genus (Fig. 14 and Table 6). Flavone derivatives



Fig. 13 Acyclic triterpenoids in the genus *Alpinia*.Fig. 14 Flavonoids isolated from the *Alpinia* species.

chrysin (279)<sup>1,2</sup> and tectochrysin (280)<sup>2,5,6</sup> are rich in *A. oxyphylla*. Various flavonol-type structures were also found in the *Alpinia* genus. Galangin (281) is a major flavonol in *A. officinarum* and *A. calcarata*,<sup>8–23</sup> and 3-methoxygalangin (282) was also isolated from *A. officinarum*.<sup>10,22</sup> Several kaempferol/quercetin compounds with various functional groups were also found in this genus: kaempferol (283),<sup>18,23</sup> 3-methoxykaempferol (284),<sup>22</sup>

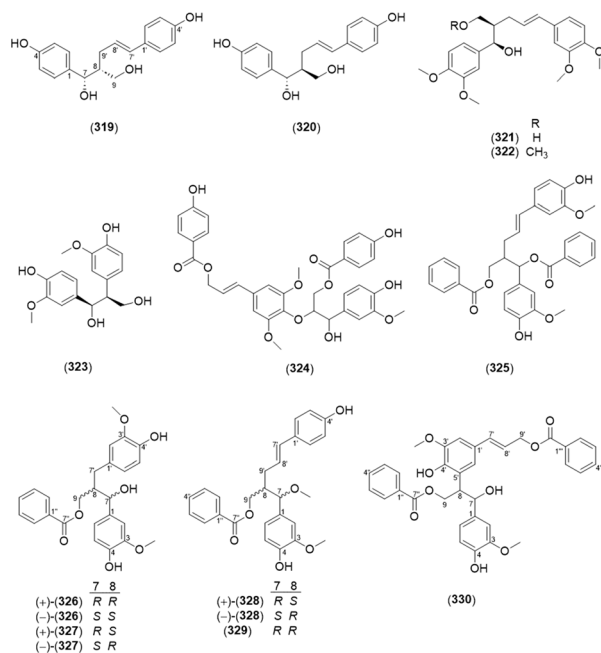
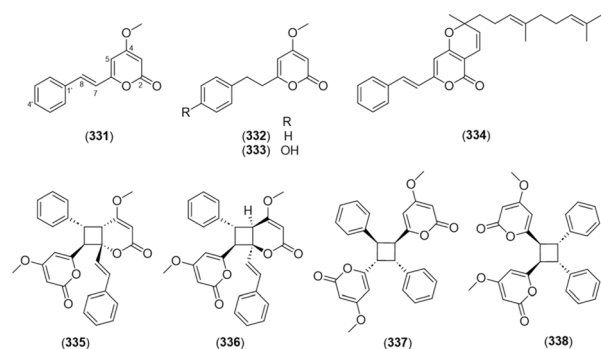
Table 6 Flavonoids isolated from the *Alpinia* species

| No. | Name   |
|-----|--|
| 279 | Chrysin <sup>1,2</sup>   |
| 280 | Tectochrysin <sup>2,5,6</sup>  |
| 281 | Galangin <sup>8–23</sup>   |
| 282 | 3-Methoxygalangin <sup>10,22</sup>   |
| 283 | Kaempferol <sup>18,23</sup>  |
| 284 | 3-Methoxykaempferol <sup>22</sup>  |
| 285 | 7,4'-Dimethoxykaempferol <sup>32</sup>   |
| 286 | Kaempferide, (3,5,7-trihydroxy-4'-methoxyflavone) <sup>8,10,11,14,16,18,20,21</sup>                            |
| 287 | Quercetin <sup>23</sup>  |
| 288 | Isorhamnetin <sup>20,21</sup>  |
| 289 | 7-Methoxyquercetin <sup>32</sup>   |
| 290 | 7,4'-Dimethoxyquercetin <sup>32</sup>  |
| 291 | 7,3',4'-Trimethoxyquercetin <sup>32</sup>  |
| 292 | (2 <i>R</i> ,3 <i>S</i> )-Pinobanksin-3-cinnamate <sup>52</sup>  |
| 293 | Pinocembrin <sup>20,53–55</sup>  |
| 294 | Alpinetin <sup>56–59</sup>   |
| 295 | Pinostrobin <sup>54</sup>  |
| 296 | 5,7-Dimethoxyflavanone <sup>54</sup>   |
| 297 | Alpinone 3-acetate <sup>64</sup>   |
| 298 | Cardamonin <sup>67</sup>   |
| 299 | Helichrysetin <sup>22,54,55</sup>  |
| 300 | Flavokawain B <sup>22</sup>  |
| 301 | Genistein 7- <i>O</i> -β- <i>D</i> -glucoside <sup>58,70</sup>   |
| 302 | Kaempferol 3- <i>O</i> -β- <i>D</i> -glucuronide-6''-methyl ester <sup>67</sup>                                |
| 303 | Kaempferol 3- <i>O</i> -β- <i>D</i> -glucuronide <sup>67</sup>   |
| 304 | Oxyphyllonide A <sup>67,72</sup>   |
| 305 | Oxyphyllonide B <sup>67</sup>  |
| 306 | Oxyphyllonide C <sup>67</sup>  |
| 307 | Kaempferol 3- <i>O</i> -β- <i>D</i> -(6- <i>O</i> -α- <i>L</i> -rhamnopyranosyl)-glucopyranoside <sup>67</sup> |
| 308 | Quercetin 3- <i>O</i> -β- <i>D</i> -glucoside <sup>32,67</sup>   |
| 309 | Quercetin 3- <i>O</i> -β- <i>D</i> -glucuronide <sup>32,67</sup>   |
| 310 | Quercetin 3- <i>O</i> -β- <i>D</i> -glucuronide-6''-methyl ester <sup>67</sup>                                 |
| 311 | Oxyphyllonide G <sup>67</sup>  |
| 312 | Oxyphyllonide D <sup>67</sup>  |
| 313 | Quercetin 3- <i>O</i> -β-(3''- <i>O</i> -acetyl-β- <i>D</i> -glucuronide) <sup>67</sup>                        |
| 314 | Oxyphyllonide E <sup>67</sup>  |
| 315 | Quercetin 3- <i>O</i> -β-(2''- <i>O</i> -acetyl-β- <i>D</i> -glucuronide) <sup>67</sup>                        |
| 316 | Oxyphyllonide F <sup>67</sup>  |
| 317 | Oxyphyllonide H <sup>67</sup>  |
| 318 | Quercetin 3- <i>O</i> -β- <i>D</i> -(6- <i>O</i> -α- <i>L</i> -rhamnopyranosyl)-glucopyranoside <sup>67</sup>  |

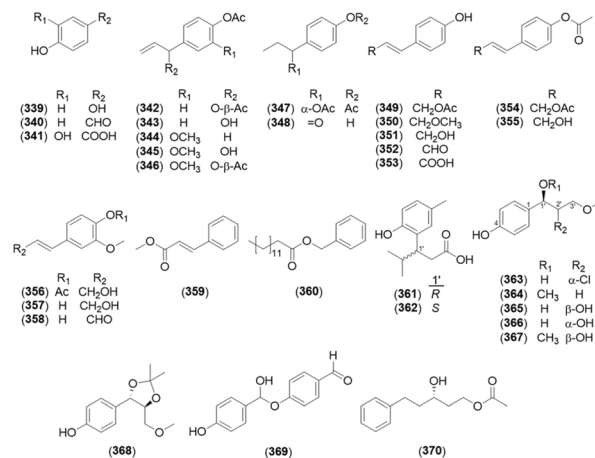
7,4'-dimethoxykaempferol (285),<sup>32</sup> kaempferide (3,5,7-trihydroxy-4'-methoxyflavone) (286),<sup>8,10,11,14,16,18,20,21</sup> quercetin (287),<sup>23</sup> isorhamnetin (288),<sup>20,21</sup> 7-methoxyquercetin (289),<sup>32</sup> 7,4'-dimethoxyquercetin (290),<sup>32</sup> and 7,3',4'-trimethoxyquercetin (291).<sup>32</sup> (2*R*,3*S*)-Pinobanksin-3-cinnamate (292) was isolated from *A. galanga* as a flavonol-type conjugated with a cinnamic acid.<sup>100</sup> A flavanone derivative, pinocembrin (293), was found in *A. zerumbet*,<sup>20,53–55</sup> and alpinetin (294) is the main active ingredient in *A. katsumadae* and *A. mutica*.<sup>56–59</sup>

Pinostrobin (295) and 5,7-dimethoxyflavanone (296) were obtained by methylating 293 in a structure–activity study.<sup>54</sup> Alpinone-3-acetate (297), the acetylated form of 295, was isolated from *A. japonica*.<sup>64</sup> In addition, chalcone derivatives were found in this species including cardamonin (298),<sup>22,54,55</sup> helichrysetin (299),<sup>22</sup> and flavokawain B (300).<sup>58,70</sup> An isoflavone



Fig. 15 Lignans from the *Alpinia* species.Fig. 16 Kavalactones from the *Alpinia* species.

glycoside, genistein 7-*O*- $\beta$ -D-glucoside (301), was isolated from *A. oxyphylla*.<sup>67</sup> Flavonol glycosides were isolated from *A. coriandriodora*, *A. oxyphylla*, and *A. zerumbet*: kaempferol 3-*O*- $\beta$ -D-

Fig. 18 Phenolic compounds from the *Alpinia* species.

glucuronide-6''-methyl ester (302),<sup>67</sup> kaempferol 3-*O*- $\beta$ -D-glucuronide (303),<sup>72</sup> oxyphyllonides A–C (304–306),<sup>67</sup> kaempferol 3-*O*- $\beta$ -D-(6-*O*- $\alpha$ -L-rhamnopyranosyl)glucopyranoside (307),<sup>32,67</sup> quercetin 3-*O*- $\beta$ -D-glucoside (308),<sup>32,67</sup> quercetin 3-*O*- $\beta$ -D-glucuronide (309),<sup>67</sup> quercetin 3-*O*- $\beta$ -D-glucuronide-6''-methyl ester (310),<sup>67</sup> oxyphyllonide G (311),<sup>67</sup> oxyphyllonide D (312),<sup>67</sup> quercetin 3-*O*- $\beta$ -(3''-*O*-acetyl- $\beta$ -D-glucuronide) (313),<sup>67</sup> oxyphyllonide E (314),<sup>67</sup> quercetin 3-*O*- $\beta$ -(2''-*O*-acetyl- $\beta$ -D-glucuronide) (315),<sup>67</sup> oxyphyllonide F (316),<sup>67</sup> oxyphyllonide H (317),<sup>67</sup> and quercetin 6-*O*- $\alpha$ -L-rhamnosyl- $\beta$ -D-glucoside (318).<sup>67</sup>

#### 2.4. Lignans

Lignans are compounds in which two phenylpropanoids are connected by the central ( $\beta$ ) carbons of each propyl chain.<sup>101</sup> Neolignan refers to structures in which the two phenylpropanoids are not linked by a  $\beta$ - $\beta'$  bond,<sup>102</sup> and the neolignans isolated from the *Alpinia* species are shown in Fig. 15. Two 8-9' linked neolignans, galanganol A (319) and galanganol B (320), were isolated from *A. galanga*.<sup>31</sup> Morinol G (321), (1*R*,2*R*,4*E*)-1,5-bis(3,4-dimethoxyphenyl)-2-(methoxymethyl)-pent-4-en-1-ol (322), 1,2-bis(3-methoxy-4-hydroxyphenyl)-1,3-propanediol (323), quique-lignan H (324), and 1,5-bis(3'-methoxyphenyl-4'-

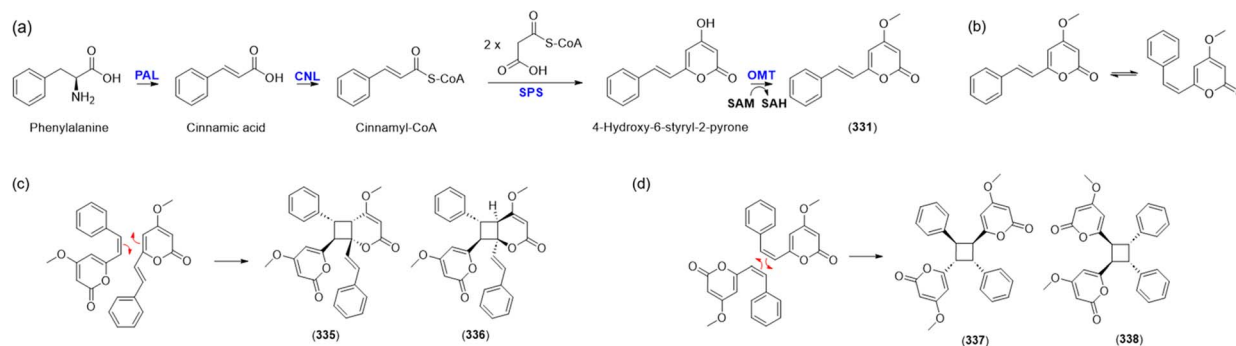
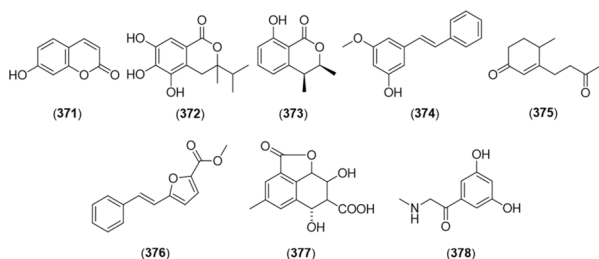


Fig. 17 Biogenetic pathways related with kavalactones. (a) Biosynthesis of 331 from phenylalanine. PAL, phenylalanine ammonia-lyase; CNL, cinnamate-CoA ligase; SPS, styrylpyrone synthase; OMT, *O*-methyltransferase; SAM, *S*-adenosyl-L-methionine; SAH, *S*-adenosyl-L-homocysteine. (b) Isomerization of 331 in light for dimerization, (c) Biodimerization of 335 and 336 from 331, (d) Biodimerization of 337 and 338 from 331.



Table 7 Phenolic compounds from the *Alpinia* species

| No. | Name   |
|-----|--|
| 339 | Hydroquinone <sup>27</sup>   |
| 340 | <i>p</i> -Hydroxybenzaldehyde <sup>29–31</sup>   |
| 341 | Protocatechuic acid <sup>2</sup>   |
| 342 | (1' <i>S</i> )-1'-Acetoxychavicol acetate <sup>29–31,33–39</sup>                               |
| 343 | (1' <i>S</i> )-1'-Hydroxychavicol acetate <sup>29,30,36,39</sup>                               |
| 344 | Eugenyl acetate <sup>30</sup>  |
| 345 | (1' <i>S</i> )-1'-Hydroxyeugenol acetate <sup>36</sup>   |
| 346 | (1' <i>S</i> )-1'-Acetoxyeugenol acetate <sup>28,30,31,36,46</sup>                             |
| 347 | (1' <i>S</i> )-1'-Acetoxylidihydrochavicol acetate <sup>36</sup>                               |
| 348 | 1'-(4-Hydroxyphenyl)-1'-propanone <sup>36</sup>  |
| 349 | <i>trans-p</i> -Coumaryl acetate <sup>29,30,36,48</sup>  |
| 350 | <i>trans-p</i> -Coumaryl alcohol $\gamma$ - <i>O</i> -methyl ether <sup>36</sup>               |
| 351 | <i>trans-p</i> -Coumaryl alcohol <sup>31,36,39</sup>   |
| 352 | <i>trans-p</i> -Coumaryl aldehyde <sup>30,31,36,39</sup>                                       |
| 353 | <i>trans-p</i> -Coumaric acid <sup>63</sup>  |
| 354 | <i>trans-p</i> -Coumaryl diacetate <sup>29,30,39</sup>   |
| 355 | <i>trans-p</i> -Acetoxycinnamoyl alcohol <sup>30,31,36,39</sup>                                |
| 356 | <i>trans</i> -Coniferyl alcohol 4- <i>O</i> -acetate <sup>36</sup>                             |
| 357 | <i>trans</i> -Coniferyl alcohol <sup>36</sup>  |
| 358 | <i>trans</i> -Coniferyl aldehyde <sup>36</sup>   |
| 359 | ( <i>E</i> )-Methylcinnamate <sup>74</sup>   |
| 360 | Benzyl myristate <sup>76</sup>   |
| 361 | ( <i>R</i> )-Oxyphylla A <sup>1,77</sup>   |
| 362 | ( <i>S</i> )-Oxyphylla A <sup>77</sup>   |
| 363 | 4-[ <i>erythro</i> -2'-Chloro-1'-hydroxy-3'-methoxypropyl]phenol <sup>27</sup>                 |
| 364 | 4-(1',3'-Dimethoxypropyl)phenol <sup>27</sup>  |
| 365 | <i>threo</i> -1-(4-Hydroxyphenyl)-3'-methoxypropane-1',2'-diol <sup>27</sup>                   |
| 366 | <i>erythro</i> -1-(4-Hydroxyphenyl)-3'-methoxypropane-1',2'-diol <sup>27</sup>                 |
| 367 | 4-( <i>threo</i> -2'-Hydroxy-1',3'-dimethoxypropyl)phenol <sup>27</sup>                        |
| 368 | 4-( <i>threo</i> -5'-(Methoxymethyl)-2',2'-dimethyl-1',3'-dioxolan-4''-yl)phenol <sup>27</sup> |
| 369 | 4-Hydroxy(4-hydroxyphenyl)methoxybenzaldehyde <sup>27</sup>                                    |
| 370 | ( <i>S</i> )-1-Acetoxy-5-phenyl-3-pentanol <sup>66</sup>                                       |

Fig. 19 Miscellaneous compounds isolated from the genus *Alpinia*.

hydroxy)-2-[(benzyloxy)methyl]-pent-4-en-1-yl benzoate (325) were previously identified.<sup>65</sup> Additionally, 7,8-*threo*-9-benzoyloxy-3,3'-dimethoxy-8',9'-dinor-7',8-neoligane-4,4',7-triol (326) and 7,8-*erythro*-9-benzoyloxy-3,3'-dimethoxy-8',9'-dinor-7',8-neoligane-4,4',7-triol (327) have an 8',9'-dinorneolignan skeleton with a 7'-8 linkage, which is rare in the lignan family. In addition, 7,8-*erythro*-9-benzoyloxy-3,7-dimethoxy-8,9'-neoligane-4,4'-diol (328) and (-)-7*R*,8*R*-9-benzoyloxy-3,7-dimethoxy-8,9'-neoligane-4,4'-diol (329) are 8'-9' linked neolignans. The compound 7,8-*erythro*-3,3-dimethoxy-9,9'-dibenzoyloxy-5',8-neoligane-4,4',7-triol (330) was a racemic mixture, in which two phenylpropanoid units were connected *via* a linkage from C-8 to C-5' and possessed a benzoyloxy group at C-9 and C-9'.<sup>65</sup>

## 2.5. Kavalactones

Kavalactones are lactones with an arylethylene-pyrone skeleton.<sup>103</sup> Kavalactone monomers 5,6-dehydrokawain (331),<sup>66,104–107</sup> 7,8-dihydro-5,6-dehydrokawain (332),<sup>66,106,107</sup> and 4'-hydroxy-7,8-dihydro-5,6-dehydrokawain (333)<sup>103</sup> were found in *Alpinia*. A kavalactone-sesquiterpene conjugate, malakavalactone (334), was newly found in *A. malaccensis*.<sup>104</sup>

Asymmetrical cyclobutane dimers of 5,6-dehydrokawain were found in *A. zerumbet*, namely, aniba dimer A (335),<sup>66,103,106</sup> aniba dimer C (336),<sup>103,106</sup> 6,6'-((1 $\alpha$ ,2 $\alpha$ ,3 $\beta$ ,4 $\beta$ )-2,4-diphenylcyclobutane-1,3-diyl)bis(4-methoxy-2*H*-pyran-2-one) (337),<sup>103,106</sup> and 6,6'-((1*R*,2*S*,3*R*,4*S*)-3,4-diphenylcyclobutane-1,2-diyl)bis(4-methoxy-2*H*-pyran-2-one) (338).<sup>66,103,106</sup> The compounds are shown in Fig. 16.

Kavalactones, also known as styrylpyrones, have been found not only in kava root (*Piper methysticum*), but also in fungi such as *Phellinus* and *Inonotus* spp.<sup>108,109</sup> Recently, the key enzymes in the biosynthetic pathway of kavalactones were elucidated (Fig. 17a): phenylalanine ammonia-lyase (PAL); cinnamate-CoA ligase (CNL); styrylpyrone synthase (SPS); *O*-methyltransferase (OMT); *S*-adenosyl-*L*-methionine (SAM); and *S*-adenosyl-*L*-homocysteine (SAH).<sup>86</sup> Kavalactones undergo phyto-isomerization in nature, and oligomeric kavalactones can be produced (Fig. 17b).<sup>110</sup> Nishidono *et al.* proposed a biosynthesis of 335 and 336 by a [2 + 2] photo-



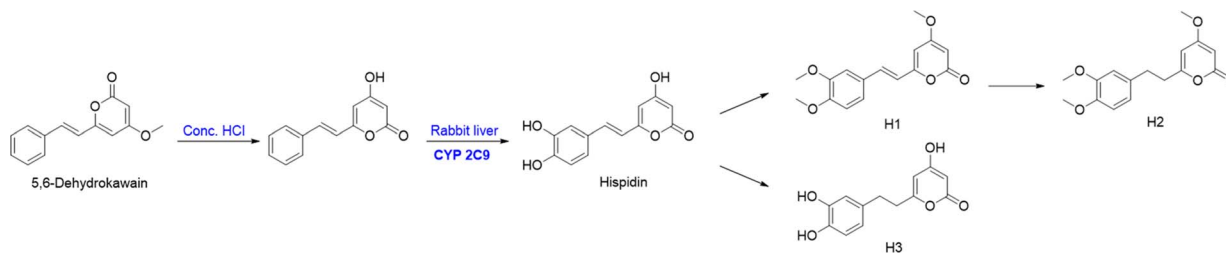


Fig. 20 The bioconversion of hispidin and its derivatives (H1–H3) from the 5,6-dehydrokawain.

cycloaddition from the *trans-trans* form of **331** (Fig. 17c).<sup>106</sup> Dimerization of **337** and **338** from **331** was contrived from a previous study on 5-substituted-2-styryl-4-pyrones (Fig. 17d).<sup>110</sup>

## 2.6. Phenolics

Oxyphylla A was elucidated in 2016,<sup>1</sup> and its chiral separation yielded (*R*)-oxyphylla A (**361**) and (*S*)-oxyphylla A (**362**), with neuroprotective activity against Parkinson's disease.<sup>77</sup> Six phenylpropanoids were newly identified from the chemically converted extract of *A. galanga*: 4-[*erythro*-2'-chloro-1'-hydroxy-3'-methoxypropyl]phenol (**363**), 4-(1',3'-dimethoxypropyl)phenol (**364**), *threo*-1-(4-hydroxyphenyl)-3'-methoxypropane-1',2'-diol (**365**), *erythro*-1-(4-hydroxyphenyl)-3'-methoxypropane-1',2'-diol (**366**), 4-(*threo*-2'-hydroxy-1',3'-dimethoxypropyl)phenol (**367**), and 4-(*threo*-5'-(methoxymethyl)-2',2'-dimethyl-1',3'-dioxolan-4'-yl)phenol (**368**).<sup>27</sup> The isolated phenolic compounds from the *Alpinia* species are shown in Fig. 18 and Table 7.

## 2.7. Miscellaneous compounds

A coumarin structure, umbelliferone (**371**), was isolated from *A. galanga*,<sup>60</sup> and (3*R*)-5,6,7-trihydroxy-3-isopropyl-3-methylisochroman-1-one (**372**) was identified as a novel antioxidant coumarin from *A. katsumadae*.<sup>111,112</sup> In addition, 4-hydroxymelein (**373**) was an isocoumarin identified in *A. galanga*.<sup>27</sup> Furthermore, 3-methoxy-5-hydroxystilbene (**374**),<sup>22,113</sup> oxyphyllone F (**375**),<sup>3</sup> 5-styrylfuran-2-carboxylic acid methyl ester (**376**),<sup>22</sup> 3-methyl-6 $\alpha$ , 8 $\beta$ -diol-7-carboxylic acid tetralin-11, 9 $\beta$ -olide (**377**),<sup>76</sup> and 1-(3,5-dihydroxyphenyl)-2-(methylamino)ethan-1-one (**378**)<sup>114</sup> were found in *Alpinia*. Their structures are shown in Fig. 19.

# 3. Pharmacological and toxicological aspects

## 3.1. Cytotoxicity and anti-tumor effects

Alpinisin A (**93**), a diarylheptanoid–sesquiterpene conjugate isolated from the rhizomes of *A. officinarum*, inhibited the growth of human gastric carcinoma (SGC-7901, IC<sub>50</sub> = 11  $\mu$ M), human breast cancer (MCF-7, IC<sub>50</sub> = 15  $\mu$ M), and epidermoid cervical carcinoma (CaSki, IC<sub>50</sub> = 15  $\mu$ M) cell lines.<sup>80</sup> Microbial transformation of yakuchinone A (**4**) using the fungus *M. hienalis* KCTC 26779 produced nine metabolites. Among them, compound **63** showed the most selective cytotoxic activities against murine melanoma (B16F1 and B16F10) and human melanoma (A375P) cell lines (IC<sub>50</sub> values: 6.1–9.7  $\mu$ M).<sup>49</sup>

Terpenoid derivatives also exhibited cytotoxic activity. 3,4-Dihydrolactucin (**252**), a guaiane-type sesquiterpenoid, showed cytotoxicity against MDA-MB-231 and HeLa cells, with IC<sub>50</sub> values of 37 and 75  $\mu$ g mL<sup>-1</sup>, respectively.<sup>60</sup> In addition, a labdane diterpene from *A. intermedia*, intermedin A (**262**), at 30  $\mu$ g mL<sup>-1</sup> suppressed the growth of human leukemia cells (HL-60) and prolonged the life of P-388D<sub>1</sub> tumor-bearing CDF<sub>1</sub> mice by 49% at 20 mg kg<sup>-1</sup>.<sup>92</sup>

The cytotoxic and anti-tumor effects of some flavonoids have also been reported. Flavokawain B (**300**) and alpinetin (**294**) isolated from *A. mutica* inhibited the UCK2 enzyme and suppressed the growth of HT-29 cells, with IC<sub>50</sub> values of 28  $\mu$ M and 44  $\mu$ M, respectively.<sup>115</sup> Helichrysetin (**299**), a chalcone isolated from *A. katsumadae*, inhibited the growth of human gastric cancer cells (MGC803) with an IC<sub>50</sub> value of 16  $\mu$ M and gastric cancer growth *in vivo* through mTOR/p70S6K/c-Myc/PDHK1-mediated energy metabolism reprogramming.<sup>116</sup> The rates of growth inhibition in an MGC803-xenografted mouse model were 63% (3 mg kg<sup>-1</sup>), 46% (10 mg kg<sup>-1</sup>), and 51% (30 mg kg<sup>-1</sup>). A synergistic cytotoxic effect of tectochrysin (**280**) with cetuximab (an anti-epidermal growth factor receptor (EGFR) monoclonal antibody) was observed in the human colon cancer cell lines HCT116 and SW480.<sup>5</sup> The underlying mechanism involved inhibition of the EGFR pathway, followed by suppression of NF- $\kappa$ B and AP-1 activity. Atwa *et al.* investigated the combination cancer therapy of galangin (**281**) and luteolin (100 mg kg<sup>-1</sup> each) with doxorubicin in a chemically induced hepatocellular carcinoma (HCC) rat model and observed significant decreases of HCC markers compared to healthy rats.<sup>117</sup>

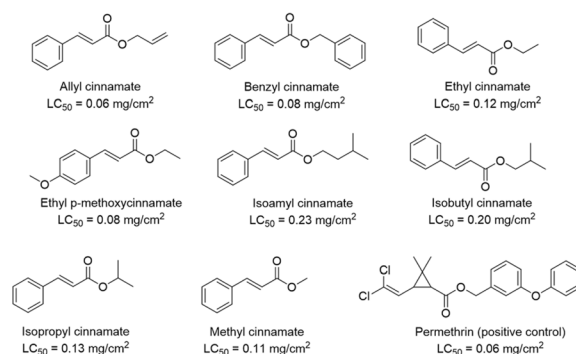


Fig. 21 LC<sub>50</sub> values of the commercial cinnamate derivatives against *H. longicornis* nymphs.



Hispidin and its derivatives H1–H3 were synthesized from 5,6-dehydrokawain (331) by CYP2C9 in the liver microsomes of rabbit.<sup>118</sup> The bioconversion pathway of hispidin and H1–H3 are shown in Fig. 20,<sup>118</sup> and the IC<sub>50</sub> values of hispidin and H1–H3 against A549 cancer cells were 25, 17, 21, and 17 μM, respectively (IC<sub>50</sub> of the positive control resveratrol = 23 μM).<sup>119</sup>

### 3.2. Anti-bacterial effects

Several diarylheptanoids (2, 3, 14, 17, and 31) isolated from the rhizomes of *A. officinarum* showed inhibitory activity against *Mycobacterium tuberculosis* H37Ra and *M. bovis* BCG.<sup>41</sup> Among them, 2 showed the strongest activity against *M. buterculosis* (IC<sub>50</sub> = 4.2 μg mL<sup>-1</sup>) and *M. bovis* (IC<sub>50</sub> = 4.7 μg mL<sup>-1</sup>). Additionally, 3,4-dihydrolactucin (252) showed inhibitory activity against *Bacillus cereus*, *B. subtilis*, *Staphylococcus aureus*, and methicillin-resistant *S. aureus*, with a minimum inhibitory concentration (MIC) of 16–32 μg mL<sup>-1</sup>.<sup>60</sup> Compound 265 induced death of *Escherichia coli* and *S. paratyphi* cells at a concentration of 50 μg mL<sup>-1</sup>.<sup>93</sup> The kavalactone derivative malakavalactone (334) from *A. malaccensis* exhibited weak antibacterial activity (MIC = 60 μM) against four gram-negative bacteria: *Enterobacter aerogenes*, *E. coli*, *Pseudomonas aeruginosa*, and *Shigella dysenteriae*.<sup>104</sup> Compound 378 alleviated the swarming mobility of *P. aeruginosa* at a minimum concentration of 12.5 μg mL<sup>-1</sup> and reduced the virulence of *P. aeruginosa*.<sup>114</sup>

### 3.3. Anti-parasitic and insecticidal effects

Various phenolic compounds showed anti-parasitic activities. The most active compound was hydroquinone (339), with IC<sub>50</sub> values of 0.4 ± 1.4 μg mL<sup>-1</sup> (*Leishmania major*), 3.2 ± 0.1 (*Trypanosoma brucei gambiense*), and 3.3 ± 0.3 (*T. brucei rhodesiense*).<sup>27</sup> Compound 363 was also confirmed as a significant active component, with IC<sub>50</sub> values of 4.2 ± 0.8 (*T. brucei gambiense*) and 5.6 ± 1.5 (*T. brucei rhodesiense*). Kang *et al.*<sup>120</sup> observed potent acaricidal activities of the cinnamate derivatives derived from *A. galanga* oil and conducted a structure-activity relationship (SAR) study of commercial cinnamate derivatives against *Haemaphysalis longicornis* nymphs (Fig. 21). Allyl cinnamate showed the most potent toxicity (LC<sub>50</sub> = 0.06 mg cm<sup>-2</sup>),<sup>120</sup> and the mode of action was inhibition of acetylcholinesterase (AChE) of *H. longicornis* nymphs.

(1'S)-1'-Acetoxychavicol acetate (342, LD<sub>50</sub> = 1.6 μg per larva, 24 h) and *trans-p*-coumaryl diacetate (354, LD<sub>50</sub> = 2.4 μg per larva, 24 h) showed insecticidal effects against *Spodoptera litura*.<sup>39,121</sup>

### 3.4. Anti-virus activities

Yoo *et al.* performed structure-based virtual screening to find inhibitors of neuraminidase, which is a key enzyme of the influenza viruses.<sup>25</sup> By virtual screening of 6149 compounds in the drug library, a diarylheptanoid structure was selected as a promising scaffold. Thirty diarylheptanoids were isolated from *A. officinarum*, and 9, 13, 16, 22, 23, and 51 (10 μM each) showed strong relative inhibitory activity compared with mangiferin (1.9, 0.9, 1.0, 0.9, 2.1, and 0.9, respectively).

The viral protein R (Vpr) is found in HIV-1 and 2 and influences G2 cell cycle arrest and apoptosis.<sup>122</sup> Monoterpenoids such as 134, 135, and 136 showed dose-dependent anti-Vpr

activity in TReX-HeLa-Vpr cells (concentrations: 0.3–5.0 μM) without cytotoxicity.<sup>84</sup>

### 3.5. Anti-inflammatory effect

Diarylheptanoids have shown anti-inflammatory activities. In particular, 14, 17, 18, 31, 33, and 37 showed anti-inflammatory activities against lipopolysaccharide (LPS)-induced macrophages (RAW 264.7).<sup>68,123</sup> Moreover, 17 and 33 down-regulated the gene expressions of interleukin (IL)-1β, IL-6, and tumor necrosis factor alpha (TNF-α) in LPS-treated HepG2 cells, and the *in silico* docking simulation revealed that the compounds interact with p38 mitogen-activated protein kinase (MAPK).<sup>21</sup> Compound 17 (10 mg kg<sup>-1</sup>) inhibited right paw edema induced by carrageenan-induced inflammation in a rat model.<sup>8</sup> The compound (10 and 20 mg kg<sup>-1</sup>) also inhibited paw volume, joint diameter, thermal hyperalgesia, and tactile allodynia in mice with Freund's complete adjuvant (FCA)-induced arthritis and oxido-inflammatory markers such as SOD, GSH, MDA, and TNF-α.<sup>124</sup> Compound 64 inhibited nitric oxide (NO) release in LPS-induced RAW 264.7 cells (IC<sub>50</sub> = 8.3 μM).<sup>65</sup> Coriandrinalpinin C (69) and E (71) isolated from the rhizomes of *A. coriandriodora* inhibited NO release in LPS-treated RAW 264.7 cells.<sup>32</sup> Compounds 12, (-)-94, and (-)-102 significantly inhibited the production of NO, IL-1β, IL-6, and TNF-α *via* the NF-κB signaling pathway in LPS-treated RAW 264.7 cells.<sup>22,23</sup>

Compound 137, a monoterpene isolated from the pericarps of *A. zerumbet*, inhibited IL-1β-induced production of NO in primary cultured rat hepatocytes (IC<sub>50</sub> = 18 μM).<sup>85</sup> Eremophilane-type (147, 149, 153, and 158) and cadinane-type (238, 239, and 240) sesquiterpenoids inhibited cytokine release (NO, TNF-α, and IL-6) in LPS-treated BV-2 cells, and compound 158 further suppressed the mRNA levels and protein expressions of TNF-α, IL-6, COX-2, and iNOS.<sup>24</sup> Compound 219, a eudesmane-type sesquiterpenoid isolated from the fruits of *A. oxyphylla*, inhibited PGE2 release in LPS-treated RAW 264.7 cells with an IC<sub>50</sub> value of 90 μM (IC<sub>50</sub> of hydrocortisone, a positive control = 48 μM).<sup>42</sup> Compound 275, an acyclic triterpenoid from the *A. katsumadae* seed, inhibited the release of iNOS and COX-2 and suppressed the gene expressions of IL-1β, IL-6, and NF-κB in LPS-treated J774 cells, and oral administration of 275 (50 mg kg<sup>-1</sup>) attenuated paw thickness and volume in a mouse model.<sup>97</sup>

Tectochrysin (280, 2.5 and 5.0 mg kg<sup>-1</sup>) alleviated allergic airway inflammation by regulating the Th2 response and oxidative stress in a shrimp tropomyosin-induced mouse asthma model.<sup>125</sup> Compounds 281, 283, 284, 286, 287, 288, and 299 suppressed the production of IL-1β, IL-6, and TNF-α.<sup>21–23</sup> In addition, 281 (10 mg kg<sup>-1</sup>) inhibited paw edema in the carrageenan-induced mouse inflammation model.<sup>8</sup> Compound 297, a flavanolol from the seeds of *A. japonica*, mitigated the symptoms of ear edema in a 12-O-tetradecanoylphorbol 13-acetate-induced mouse inflammation model with an ID<sub>50</sub> value (50% inhibitory dose) of 176 μg per ear.<sup>64</sup> Compound 298 inhibited the IL-1β-induced production of NO in primary cultured rat hepatocytes (IC<sub>50</sub> = 10 μM).<sup>85</sup>

A previous study showed that (+)-326, (-)-326, (+)-327, and (-)-327, neolignans with an 8',9'-dinorneolignan skeleton,



reduced NO production in LPS-induced RAW 264.7 cells with IC<sub>50</sub> values of 3.6, 7.6, 6.5, and 5.6 μM, respectively (the IC<sub>50</sub> of dexamethasone, a positive control, was 30 nM).<sup>65</sup> As the pericarps of *A. zerumbet* significantly inhibited NO production in IL-1β-treated hepatocytes, the kavalactone derivatives from this plant were subjected to an anti-inflammatory assay, and the IC<sub>50</sub> value of each compound on NO suppression was 27 (331), 28 (332), 34 (335), 25 (336), 34 (337), and 26 μM (338).<sup>106</sup> (*E*)-Methylcinnamate (359) alleviated the symptoms of colitis through the MAPK pathway.<sup>126</sup> Compound 372 also showed protective effects of H9c2 cells against lipoteichoic acid-induced toxicity through anti-inflammatory and oxidative responses.<sup>112</sup>

### 3.6. Anti-oxidant effects

Several compounds from *A. oxyphylla* exhibited anti-oxidant activity. For example, diarylheptanoids yakuchinone A (4) and 5'-hydroxyakuchinone A (5) scavenged reactive oxygen species (ROS) in HepG cells.<sup>50</sup> Moreover, 13-hydroxynootkatone (155) and nootkatone-11,12-epoxide (162) from *A. oxyphylla* effectively repaired the damage from *tert*-butyl hydroperoxide-induced oxidative stress in adipose-derived mesenchymal stem cells in a dose-dependent manner.<sup>4</sup> Coriandrinalpinins A–H (67–74) isolated from *A. coriandriodora* also exerted ROS inhibition in a dose-dependent manner.<sup>32</sup> Compounds 372 (5 mg kg<sup>-1</sup>) from *A. katsumadae* and 292 (15 mg kg<sup>-1</sup>) from *A. galanga* significantly reduced oxidative stress and improved retinal function in an rd10 mouse model of retinitis pigmentosa.<sup>100,111</sup>

### 3.7. Neuroprotective effects

The neuroprotective effects of the compounds from *Alpinia* species have been reported in several studies. Compound 32 has been reported to improve amyloid β (Aβ) 42-induced neuronal damage, apoptosis, and oxidative stress.<sup>98</sup> Alpinin A (66, 10 μM) and alpinin B (52, 10 μM) were tested for their effects on the aggregation of α-synuclein (α-syn), a protein mainly expressed in neurons of Parkinson's disease (PD) patients.<sup>69,127</sup> The two compounds inhibited α-syn aggregation by 66% and 67%, respectively. Moreover, a diarylheptane–monoterpene conjugate, (–)-alpininoid B (89), inhibited AChE with an IC<sub>50</sub> of 2.6 μM.<sup>16</sup>

Qiu *et al.* observed that the sesquiterpenoids (153, 154, 175, 204, 221, 244, 246, and 247) from the fruits of *A. oxyphylla* improved the cell viability (≥80%) of a neuroblastoma cell line (SH-SY5Y) in conditions of H<sub>2</sub>O<sub>2</sub>-induced oxidation with serial concentrations of the compounds (5, 10, and 20 μM).<sup>3</sup> Moreover, 175, 221, 247, and 375 (20 and 100 μM) also reduced the production of ROS.

The protective effects of (*R*)-oxyphylla A (361) and (*S*)-oxyphylla A (362) against PD have been reported in several studies. Zhou *et al.* demonstrated elevated α-syn degradation by 361 *in vitro* (10, 30, and 100 μM) and *in vivo* (30 mg kg<sup>-1</sup>).<sup>128</sup> The compound induced the PKA/Akt/mTOR pathway and reduced α-syn accumulation. Li *et al.* also reported that 361 (5, 10, and 20 mg kg<sup>-1</sup>) protected against neuron loss and improved neurobehavioral changes of PD mice *via* Nrf2 signal transduction. The efficacy of 361 at 20 mg kg<sup>-1</sup> for the survival of neurons was similar to that of rasagiline (a positive control).<sup>1</sup> Both 361 and

362 at low doses (1.3, 2.5, and 5.0 μM) exerted mild neuroprotective activities in the MPTP-induced PD zebrafish model, whereas high doses (5, 13, and 25 μM) did not show comparable toxicities in zebrafish larvae.<sup>77</sup> Additionally, 361 and 362 (10 and 20 mg kg<sup>-1</sup>) inhibited the expression levels of amyloid precursor protein (APP) and Aβ protein and attenuated cognitive decline in SAMP8 mice *via* antioxidative effects through the Akt-GSK3β and Nrf2-Keap1-HO-1 pathways.<sup>129</sup>

Ischemic stroke is caused by reduced blood supply to the brain, and the current therapy is thrombolytic treatment with a limited time window (4.5 to 6 h after the incident). Therefore, the need for neuroprotection in stroke treatment is urgent. A previous study showed that (+)-85 (alpinidinoid A) alleviated oxygen-glucose deprivation and reoxygenation (OGD/R) damage in primary cortical neurons by inducing the PI3K/AKT/mTOR signaling pathway.<sup>78</sup> *p*-Coumaric acid (353) activated the BDNF/TrkB/AKT signaling pathway to proliferate neural stem cells *in vitro*.<sup>63</sup> In addition, the compound (50, 100, and 200 mg kg<sup>-1</sup>) improved neuronal proliferation and spatial/memory functions in a transient middle cerebral artery occlusion rat model.

As neuroprotective effects of *A. galanga* have been reported in several studies, the aqueous stability and gastro-intestinal/blood–brain barrier (GI/BBB) permeability of the main compounds in the extract were investigated.<sup>31</sup> The phenolics (340, 342, 346, 351, 352, and 355) showed good permeability, which contributes to the neuroprotective effects of *A. galanga*. Four compounds with neuroprotective activity in *A. oxyphylla* were tested for BBB permeability,<sup>2</sup> and the order of permeability was 341, 147, 279, and 280.

### 3.8. Anti-diabetic effects

Insulin resistance (IR) indicates decreased responses of insulin-target tissues to insulin stimulation,<sup>130</sup> and it causes several metabolic disorders such as nonalcoholic fatty liver disease and type 2 diabetes.<sup>131</sup> Compounds 14 and 31 alleviated oxidative stress and glucose metabolism by regulating the PI3K/AKT-Nrf2-GSK3β pathway, improving the IR of HepG2 cells.<sup>96,132</sup> Li *et al.* reported that 33 improves IR through the PI3K/AKT and TNF-α signaling pathways.<sup>99</sup> Among the diarylheptanoid dimers isolated from *A. katsumadae*, katsumadainols C<sub>1</sub>–C<sub>4</sub> (75–78) and C<sub>7</sub>–C<sub>10</sub> (81–84) showed significant stimulation of glucagon-like peptide-1 receptor (GLP-1) secretion. Additionally, 75–78 significantly inhibited glycogen phosphorylase (GPa) (IC<sub>50</sub> values of 18–31 μM), and 75–79 inhibited α-glucosidase (IC<sub>50</sub> values of 6.9–18 μM) and protein tyrosine phosphatase 1B (PTP1B, IC<sub>50</sub> values of 36 to 80 μM).<sup>71</sup> He *et al.* revealed that the *A. katsumadae* EtOH extract (200 mg kg<sup>-1</sup>) reduced blood glucose level in a db/db mouse model; the authors identified 29 diarylheptanoid-chalcone hybrids (105–133) from *A. katsumadae* to test α-glucosidase and PTP1B inhibition.<sup>83</sup> All the isolated compounds exhibited α-glucosidase inhibition with IC<sub>50</sub> values of 2.9–30 μM, and 105–107, 109–111, 115–118, 125–129, and 131 showed PTP1B selective inhibition with IC<sub>50</sub> values ranging from 22 to 97 μM.

Sesquiterpenoids isolated from the fruits of *A. oxyphylla* were also tested for anti-diabetic activity.<sup>28</sup> The results showed that 173 and (6*R*)-235 (20–100 μM) stimulated GLP-1 by 151–1242%



and 421–1090%, respectively, *via* Ca<sup>2+</sup>/CaMKII and PKA pathways. Compound **346** (2.5, 5.0, and 10 μM) from *A. galanga* improved glucose-stimulated insulin secretion and inhibited α-glucosidase activity in rat pancreatic β-cells.<sup>30</sup> Moreover, **335** (135 μM) and **338** (25 μM) increased the viability of human umbilical vein endothelial cells damaged by high glucose by 83% and 75%, respectively.<sup>103</sup>

### 3.9. Osteoblast-protective effects

Mesenchymal stem cells differentiate into osteoblasts *via* the Smad- and Runt-related transcription factor 2 (RUNX2) pathways by osteogenic factors, *e.g.*, bone morphogenetic protein (BMP). Apoptosis and migration/differentiation of osteoblasts are important mechanisms by which osteoblasts maintain bone physiology and mitigate bone-related diseases.<sup>74</sup> Pinocembrin (**293**) isolated from the leaves of *A. zerumbet* improved osteoblast differentiation of pre-osteoblasts (MC3T3-E1) by inducing BMP-2 expression *via* endoplasmic reticulum (ER) stress and mineralization through the Smad and RUNX2 pathways.<sup>53</sup> (*E*)-Methylcinnamate (**359**) inhibited the migration of pre-osteoblasts and induced their differentiation.<sup>74</sup> In addition, 5,6-dehydrokawain (**331**) and 7,8-dihydro-5,6-dehydrokawain (**332**) stimulated alkaline phosphatase activity and mineralization in MC3T3-E1 cells.<sup>107</sup> As **331** improved osteoblastogenesis of MC3T3-E1, semi-synthesis was performed for 5,6-dehydrokawain analogs (Fig. 22). The synthesized compounds (*E*)-6-(4-ethylstyryl)-4-methoxy-2*H*-pyran-2-one and (*E*)-6-(4-butylstyryl)-4-methoxy-2*H*-pyran-2-one significantly stimulated osteoblastic expression of RUNX2 and Osterix genes and showed preventive effects on osteoblasts.<sup>133</sup>

### 3.10. Miscellaneous activities

Compounds **14**, **15**, **31**, **39**, and **41** (10–80 μM), isolated from *A. officinarum*, induced differentiation of 3T3-L1 preadipocytes in a dose-dependent manner, which may help protect against obesity.<sup>45</sup> Compounds **276** and **277**, acyclic triterpenoids isolated from *A. katsumadae*, suppressed the mRNA and protein levels of proprotein convertase subtilisin/kexin type 9 (PCSK9), which regulates low-density lipoprotein cholesterol (LDL-C) levels in the blood.<sup>66</sup>

Melanogenesis is the production of melanin, which protects the skin from UV damage. However, excessive melanin production leads to dermatological disorders. Melanogenesis inhibitory activities (IC<sub>50</sub>) of compounds from *A. galanga* were investigated using theophylline-stimulated murine B16 melanoma 4A5 cells:<sup>90</sup> **257** (IC<sub>50</sub> = 18 μM), **258** (IC<sub>50</sub> = 9.4 μM), **259** (IC<sub>50</sub> = 30 μM), **260** (IC<sub>50</sub> = 2.9 μM), **268** (IC<sub>50</sub> = 4.4 μM), **269** (IC<sub>50</sub> = 8.6 μM), and **270** (IC<sub>50</sub> = 4.6 μM). These activities were more potent than that of arbutin (174 μM), a positive control.

Tectochrysin (**280**, 0–500 μM) extended the lifespan of *Caenorhabditis elegans* by up to 21% and protected worms against Aβ<sub>1-42</sub>-induced toxicity by regulating FOXO/DAF-16 and HSF-1.<sup>134</sup> Flavonoid glycosides (**301**, **303**, **309**, **311**, **313**, **315**, **317**, and **318**) isolated from *A. oxypphylla* exhibited anti-renal fibrosis activity at concentrations of 10, 20, and 40 μM in TGF-β<sub>1</sub>-induced kidney proximal tubular cells, a reno-protective activity.<sup>67</sup>

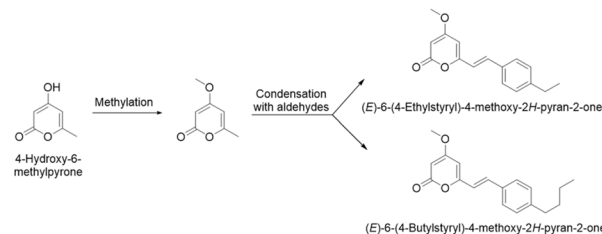


Fig. 22 Semi-synthesis of (*E*)-6-(4-ethylstyryl)-4-methoxy-2*H*-pyran-2-one and (*E*)-6-(4-butylstyryl)-4-methoxy-2*H*-pyran-2-one.

## 4. Compounds with various activities

### 4.1. Nootkatone

Nootkatone (**147**, 0.02 and 0.2 mg kg<sup>-1</sup>) showed protective effects in an Alzheimer's disease (AD) mouse model by decreasing malondialdehyde, Aβ, and AChE and dramatically enhanced the performance of the mice in the Y-maze and Morris water maze tests.<sup>62</sup> Nootkatone (5 and 10 mg kg<sup>-1</sup>) also improved learning and memory impairment in mice, and this may be related with attenuated inflammatory cytokines (IL-1β, IL-6, TNF-α, and NF-κB p65) in the hippocampus.<sup>135</sup> Moreover, **147** showed modest BBB permeability in human brain microvascular endothelial cells co-cultured with astrocytes with passive diffusion, which supports the compounds as a good candidate for CNS-related illnesses.<sup>2</sup> In addition, administration of nootkatone (10 μM) with schisandrin (50 μM) showed a synergistic neuroprotective activity in Aβ<sub>1-42</sub>-induced differentiated PC12 cells.<sup>136</sup> The underlying mechanism involves the PI3K/AKT/Gsk-3β/mTOR pathway and decreased pro-inflammatory cytokines including NF-κB, IKK, IL-1β, IL-6, and TNF-α.

Compound **147** (5, 10, and 20 mg kg<sup>-1</sup>) showed anti-oxidant and anti-inflammatory activities through NOX4, NF-κB, and Nrf2/HO-1 pathways in kidneys of mice exposed to CCl<sub>4</sub>.<sup>137</sup> It (10 mg kg<sup>-1</sup>) also protected an obstructive nephropathy mouse model from oxidative stress and the inflammatory response, reduced cell apoptosis, and attenuated renal fibrosis.<sup>138</sup>

Another study showed that **147** (25 and 50 mg kg<sup>-1</sup>) improved body weight, liver weight/index elevation, glycolipid metabolism, glucose tolerance, and hepatic lipid accumulation in high fat diet-induced metabolic-associated fatty liver disease (MAFLD) mice.<sup>61</sup> Additionally, **147** down-regulated NAG-1 induction and cyclin D and showed cytotoxic activities in colorectal cancer cells (HCT-116 and SW480).<sup>139</sup> It reduced NO production in LPS-treated RAW 264.7 cells and exhibited anti-inflammatory activity.<sup>51</sup>

### 4.2. Galangin

Galangin (**258**) is a natural flavonoid mainly isolated from *A. officinarum* and *A. galanga*, and it has been reported to show cytotoxic and anti-tumor effects. For example, it prevented the growth of renal cell lines (789-0 and Caki-1) by controlling epithelial/mesenchymal markers (*e.g.*, E-cadherin, N-cadherin, and vimentin) and suppressing cell invasion.<sup>9</sup> It also inhibited the proliferation of human laryngeal cancer cells through p38



and AKT/NF- $\kappa$ B/mTOR pathways,<sup>140</sup> and activated apoptosis of bladder cancer cells by promoting the p53 signaling pathway.<sup>141</sup> Galangin inhibited a human gastric carcinoma cell line (MGC 803) by regulating the STAT3/ROS axis.<sup>142</sup> Co-treatment of 258 (30  $\mu$ M) and berberine (90  $\mu$ M) suppressed the growth of esophageal carcinoma cells (ECa9706) by modulating anti-apoptotic proteins Bcl-2, Mcl-1, and XIAP and the pro-apoptotic protein Bax.<sup>143</sup> Compound 258 (2, 5, and 10  $\mu$ M) also mitigated the drug resistance of cisplatin (2  $\mu$ M) in human lung cancer cells by dose-dependent suppression of cell proliferation and apoptosis induction.<sup>144</sup> This combination therapy (10 mg kg<sup>-1</sup> of 258 and 5 mg kg<sup>-1</sup> of cisplatin) also attenuated tumor growth in a mouse xenograft model to a greater extent compared with that of 258 or cisplatin treatment alone.

One study reported that 258 shows beneficial effects with cardioprotective properties. It (15 mg kg<sup>-1</sup>) attenuated cardiac myofibril damage and infarction size, improved cardiac function, and inhibited mitochondrial injury for myocardial ischemic reperfusion injury in a mouse model.<sup>145</sup> In hypertensive rats, 258 (30 and 60 mg kg<sup>-1</sup>) attenuated hypertension, cardiorenal damage, and oxidative stress by modulating the expression of AT1R, TGF- $\beta$ 1, and Collagen I (Col-I) protein in the heart and AT1R/Nox-4 and Nrf2/HO-1 protein in renal tissue.<sup>146</sup> The compound (1 mg kg<sup>-1</sup>) also showed preventive effects against isoproterenol-induced myocardial fibrosis in male albino Wistar rats.<sup>17</sup>

Another report found that 258 showed osteoprotective effects in LPS-stimulated bone marrow-derived dendritic cells and promoted osteogenic differentiation through activation of AKT/mTOR signaling.<sup>147</sup> It also improved the osteogenic differentiation in human amniotic mesenchymal stromal cells by regulating the JAK2/STAT3 signaling pathway.<sup>148</sup> In addition, 258 regulated lipid metabolism by reducing lipid accumulation in HepG2 liver cells and improving lipid destruction by increasing the expressions of beclin1, LC3-II/LC3-I, Atg3, AMPK $\alpha$ 1, and phosphorylated AMPK $\alpha$ 1 proteins.<sup>12</sup> Administration of 258 (4, 8, and 16 mg kg<sup>-1</sup>) also reduced hyperlipidemia in a streptozotocin-induced hyperglycemia rat model.<sup>15</sup>

Compound 258 has shown protective effects against hepatic fibrogenesis by downregulating the levels of  $\alpha$ -smooth muscle actin and Col-I in LX-2 cells.<sup>13</sup> It (100 mg kg<sup>-1</sup>) alleviated the virulence of *S. aureus* in a mouse model with *S. aureus*-induced pneumonia.<sup>149</sup> The antioxidant activity of 258 was confirmed against DPPH, with an IC<sub>50</sub> value of 4.2  $\mu$ M.<sup>14</sup>

#### 4.3. Alpinetin

As a main active flavonoid from *A. katsumadae*, alpinetin (271) has been reported to have cytotoxicity in several cell lines. For example, 271 induced tumor regression *via* inhibition of the NF- $\kappa$ B signaling pathway in breast cancer cells.<sup>57</sup> It also inhibited uridine-cytidine kinase 2 enzyme (UCK2), which is related with uncontrolled cell proliferation, at the concentration of 50  $\mu$ M.<sup>58</sup> Compound 271 also attenuated the viability of the SKOV3 ovarian cancer cell line by inhibiting the STAT3 signaling pathway.<sup>150</sup> 271 showed preventive effects against cancer cachexia caused by chemotherapy.<sup>151</sup> It reduced myotube atrophy in carcinoma-conditioned murine myoblasts (25–100

$\mu$ M) and markedly mitigated the losses of body weight and skeletal muscle in the mouse model (25 and 50 mg kg<sup>-1</sup>).

Compound 271 has been shown to have anti-inflammatory effects in several studies. It down-regulated acute pancreatitis-induced acute lung injury (ALI) by promoting aquaporin-1 and decreasing TNF- $\alpha$  expression in a HPMVEC cell line (0.01, 0.1, 1.0, and 10  $\mu$ g mL<sup>-1</sup>) and in a rat model (40, 80, 160, and 320  $\mu$ g mL<sup>-1</sup>).<sup>56</sup> Two research teams revealed that the progression of dextran sulfate sodium (DSS)-induced colitis in mice was relieved by 271 (25, 50, and 100 mg kg<sup>-1</sup>) through the toll-like receptor 4 (TLR4)/NF- $\kappa$ B/NOD-like receptor protein 3 (NLRP3) signaling and the Nrf2/HO-1 signaling pathways.<sup>152,153</sup> It (13, 25, and 50 mg kg<sup>-1</sup>) also improved LPS/D-galactosamine-induced liver injury in the mouse model by recruiting the NF- $\kappa$ B and Nrf2 signaling pathways.<sup>59</sup> In a septic mouse model, the inflammatory symptoms and the release of proinflammatory cytokines were alleviated by 271 (50 mg kg<sup>-1</sup>).<sup>154</sup> Compound 271 (50 mg kg<sup>-1</sup>) also enhanced Nrf2-mediated redox homeostasis, inhibited macrophage infiltration, and decelerated atherosclerotic plaque development in an ApoE<sup>-/-</sup> mouse model.<sup>155</sup>

#### 4.4. Cardamonin

Cardamonin (276) is a chalcone mainly found in *A. katsumadae* and *A. conchigera* and was demonstrated to exhibit anti-inflammatory and anti-oxidant activities in several studies. Treatment with 276 (50 and 100 mg kg<sup>-1</sup>) significantly relieved acetaminophen (APAP)-induced hepatotoxicity in APAP-stimulated mice by suppressing high mobility group box 1 (HMGB1), TLR4, and NLRP3.<sup>156</sup> Wang *et al.* also observed that 276 (2.5 mg kg<sup>-1</sup>) significantly reduced IL-1 $\beta$  secretion and caspase-1 activity by inhibiting NLRP3 inflammasome activation in a monosodium urate-induced gouty arthritis rat model.<sup>157</sup> Oral administration of 276 (15, 30, and 60 mg kg<sup>-1</sup>) in a DSS- and 2,4,6-trinitrobenzene sulfonic acid-induced colitis mouse model mitigated the symptoms of the disease, and the underlying mechanism involves AhR/Nrf2/NQO1 and NLRP3 inflammasome pathways.<sup>158</sup> It (1 mg kg<sup>-1</sup>) also exhibited critical anti-inflammatory effects for lung injury through the regulation of the TLR2,4-MyD88 and mTOR pathways in a mouse model.<sup>159</sup> Additionally, 276 (25, 50, and 100  $\mu$ M) inhibited the expression of COX-2, iNOS, NO, TNF- $\alpha$ , and IL-6 in rat nucleus pulposus cells, and it (20 mg kg<sup>-1</sup>) showed protective effects in a puncture-induced intervertebral disc degeneration (IVDD) mouse model through the Nrf2/HO-1 signaling pathway.<sup>160</sup> In addition, it (0.8–200  $\mu$ M) exhibited neuroprotective effects by exerting anti-oxidant and anti-inflammatory activities in LPS-treated BV-2 microglial cells.<sup>161</sup> The mechanism of action may involve Nrf2/Keap1, NF- $\kappa$ B, and antioxidant-related enzymes (*e.g.*, SOD, CAT, and GSSH). The application of doxorubicin (DOX) is limited in cancer treatment due to its cardiotoxicity. Notably, 276 (20, 40, and 80 mg kg<sup>-1</sup>) exerted cardioprotective activity by suppressing oxidative stress and inflammatory response through the Nrf2 signaling pathway in a DOX-treated mouse model.<sup>162</sup>

Compound 276 exerted cytotoxic effects on HepG2 cells, with an IC<sub>50</sub> value of 15  $\mu$ M after 72 h of treatment.<sup>163</sup> It induced pro-apoptotic proteins (*e.g.* FADD, FAS, TRIAL, and HIF-1) and



downregulated anti-apoptotic proteins like heat shock proteins (HSP) 60, 27, and 70. Moreover, 276 (0–20  $\mu\text{M}$ ) sustained cell proliferation and stimulated apoptosis of pancreatic cancer (PC) cells (PANC-1 and SW1990) by regulating the FOXO3a-FOXO1 axis and improved chemosensitivity of PC cells to gemcitabine, a chemotherapy drug.<sup>164</sup> 276 (1 and 5  $\text{mg kg}^{-1}$ ) also improved immune responses on WEHI-3 cell-generated leukemia mice by fortifying the phagocytic ability of macrophages and reducing the populations of CD3 (T cells), CD11b (monocytes), and Mac-3 (macrophages).<sup>165</sup>

Another study showed that 276 (10  $\text{mg kg}^{-1}$ ) exerted an anti-nociceptive effect by up-regulating the serotonin 1A receptor (5-HT<sub>1A</sub>) in the central nervous system (CNS) of a neuropathic pain mouse model.<sup>166</sup> Moreover, 276 showed selective inhibitory activity ( $\text{IC}_{50} = 454 \text{ nM}$ ) against transient receptor potential ankyrin 1 (TRPA1), a receptor involved in pain.<sup>167</sup> In addition, it suppressed the cytopathic property induced by the human coronavirus (HCoV-OC43) in human lung cells (MRC-5), with an  $\text{IC}_{50}$  value of 3.6  $\mu\text{M}$ , and showed anti-virus activity through the p38 MAPK pathway.<sup>168</sup>

#### 4.5. 1'S-1'-Acetoxychavicol acetate

1'S-1'-Acetoxychavicol acetate (342) can be easily found in *A. galanga* and exhibits various biological activities. In particular, 342 inhibited the growth of colorectal adenocarcinoma cells (SW480,  $\text{IC}_{50} = 80 \mu\text{M}$ ) by regulating apoptosis and the G0/G1 cell cycle check point with significant DNA damage.<sup>33</sup> Phuah *et al.* revealed that miR-629 is a key microRNA that enhances sensitivity of cancer cells toward 342.<sup>169</sup> Moreover, over-expression of Ras suppressor-1 (RSU1), which is regulated by miR-629, improved the cytotoxicity of 342. Sok *et al.* demonstrated the autophagy-inducing ability of 342 in A549 and SK-LU-1 with  $\text{IC}_{50}$  values of 29 and 25  $\mu\text{M}$ , respectively.<sup>170</sup> Compound 342 exhibited cytotoxic activity by regulating the human epidermal growth factor receptor 2 (HER2) signaling pathway in breast cancer cells (MCF7,  $\text{IC}_{50} = 12 \mu\text{M}$ ) and HER2-overexpressed MCF7 cells ( $\text{IC}_{50} = 5.9 \mu\text{M}$ ).<sup>37</sup>

Another study showed that 342 significantly inhibited larval growth of *S. frugiperda* by 34% at the concentration of 20  $\text{mg L}^{-1}$  and showed cytotoxicity in ovarian tissue of *S. frugiperda* ( $\text{IC}_{50} = 1.9 \mu\text{M}$ ).<sup>35</sup> It also showed anti-microbial activity against methicillin-resistant *S. aureus* ( $\text{MIC} = 0.5 \text{ mg mL}^{-1}$ ).<sup>29,121</sup> 342 showed anti-tuberculosis activity with an MIC of 0.2  $\mu\text{g mL}^{-1}$  (*M. tuberculosis* H37Ra ATCC 25177) and 0.7  $\mu\text{g mL}^{-1}$  (*M. tuberculosis* H37Rv ATCC 27294).<sup>38</sup>

While protein degradation by proteasomes is important to maintain protein homeostasis, the age-related reduction of proteasome activity leads to neurodegenerative processes. One study showed that 342 (0.02% of the diet) improved the spatial and memory performance of mice in the Y maze and Morris water maze tests and increased the serum concentrations of  $\beta$ -hydroxybutyric acid and palmitic acid, which help maintain cognitive function.<sup>171</sup> 342 also improved proteasome activity in neuronally differentiated murine pheochromocytoma (PC12) cells by stimulating the cAMP/PKA pathway.<sup>172</sup> It also showed good GI/BBB permeability in the artificial membrane

permeability assay and thus has potential for the treatment for neurodegenerative diseases.<sup>31</sup>

One study showed that 342 (5  $\text{mg kg}^{-1}$ ) inhibited the releases of proinflammatory cytokines, such as IL-6 and TNF- $\alpha$ , and also relieved lung inflammation in the LPS-challenged mouse model by regulating NF- $\kappa\text{B}$  and MAP kinases.<sup>173</sup> In addition, it (0.03 and 0.05% of food intake) acted as a TRPA1 agonist and stimulated lipolysis of adipose tissue in a diet-induced obesity mouse model.<sup>174</sup> In a drug metabolism study of 342, the compound showed moderate inhibition against CYP1A2 ( $\text{IC}_{50} = 4.5 \mu\text{M}$ ), CYP2D6 ( $\text{IC}_{50} = 7.5 \mu\text{M}$ ), and CYP3A4 ( $\text{IC}_{50} = 9.5 \mu\text{M}$ ). Drug-drug interactions were observed when 342 was co-administered with drugs metabolized by CYP1A2, CYP2D6, or CYP3A4 enzymes.<sup>34</sup>

## 5. Conclusions

The family Zingiberaceae is composed of approximately 47 genera and 1400 species. *Alpinia* is a largest genus in Zingiberaceae, followed by *Globba*, *Amomum*, and *Zingiber*.<sup>175</sup> Chemical profiles of *Alpinia* genus demonstrated that diarylheptanoid is the most abundant structure; terpenoids and flavonoids are commonly isolated compounds in the genus *Amomum*, *Hedychium*, and *Zingiber*.<sup>175–177</sup> As the largest genus in the family, *Alpinia* has been investigated for potential pharmacological activities, and evidence has indicated *Alpinia* as a promising treatment for various diseases, including neurodegenerative disorders, cancers, and metabolic diseases.

In this review, the compounds isolated in *Alpinia* species were categorized and the characteristics related to structures were discussed. Compounds usually found in *Alpinia* included diarylheptanoids, terpenoids, flavonoids, lignans, kavalactones, and phenolic compounds. Diarylheptanoid-chalcone conjugates are unique structures exclusively found in the genus *Alpinia*.<sup>178,179</sup> The sesquiterpenoids found in this genus were mainly eremophilane, eudesmane, cadinane, and guaiane types. Moreover, the pharmacological properties of the compounds from *Alpinia* genus included cytotoxic/anti-tumor, anti-bacterial, anti-parasitic/insecticidal, anti-virus, anti-inflammatory, anti-oxidant, neuroprotective, anti-diabetic, and osteoblast-protective activities. Phenylpropanoid from the shikimic acid pathway including cinnamate derivatives showed anti-parasitic and insecticidal effects.

This article provides newly updated structural information of the unique substances isolated from various species of the genus *Alpinia* and biological activities from the compounds. As the life expectancy of people is increasing, these findings will help researchers find treatments for metabolic syndromes including obesity, type-2 diabetes, and cardiovascular diseases, and for neurodegenerative diseases such as AD and PD.

## 6. Author contributions

Conceptualization, A. R. H. and E. K. S.; formal analysis, I. Y. and A. R. H.; investigation, D. P., H. L., H. K., and Y. L.; writing-original draft preparation, I. Y. and A. R. H.; writing-review and editing, I. Y., J. W. N., and E. K. S.; visualization, I. Y.; supervision, E. K. S.; project administration, E. K. S.; funding



acquisition, I. Y. and E. K. S. All authors have read and agreed to the published version of the manuscript.

## 7. Conflicts of interest

There are no conflicts to declare.

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