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An overview of chemical constituents from *Alpinia* species in the last six decades†

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Alpinia species is one of the most important genera of the Zingiberaceae family. In Asia, they have been widely used as food and traditional medicines for centuries. This review focuses on their chemical constituents and their relevant biological activities with 252 references covering from 1955 to 2015. In total, 544 compounds were isolated from 35 *Alpinia* species. The major ones are terpenoids (207) and diarylheptanoids (143). The crude extracts and identified compounds exhibited a broad spectrum of bioactivities including antiemetic, antiulcer, antibacterial, anti-inflammatory, anti-amnesic, anticancer, *etc.*

1. Introduction

The genus *Alpinia* is an important member of the Zingiberaceae family. It includes *ca.* 230 species.[1] Most of them are distributed in tropical and subtropical Asia, including India, Malaysia, China, and Japan. A few are found in Australia and the Pacific Islands.[1–3] Plants of this genus have been extensively used for different purposes for centuries. For example, *A. vittata*, *A. purpurata* (Vieill.) K. Schum., *A. calcarata* Rosc., and *A. zerumbet* are cultivated as ornamental plants;[3,4] *A. blepharocalyx* K. Schum. is a natural dye;[5] *A. galanga* (L.) Willd is an important ingredient for curries and has been broadly utilized as a flavoring in the preparation of meats and soups in Southeast Asia[6–8] and in the preparation of beverages in Europe;[9] and *A. officinarum* Hance, listed as medicinal and edible food by the Chinese Ministry of Health, are used in medicinal diets,[10–15] wines,[16] sauces, and flavorings.[17–19] Moreover, *A. galanga* (L.) Willd is also applied to preserve food and fruits.[8,20] Most important of all, *Alpinia* plants are also broadly used as traditional medicines in India, China, and Japan to treat many diseases such as indigestion, gastralgia, vomiting, enterozoa *etc.*[21–23] Thus, a growing investigation on the chemical constituents and bioactivities of this genus has been carried out since 1955.[24] Consequently, *Alpinia* species were proved to have various biological activities including antiulcer,[25] antiemetic,[26–28] antibacterial,[29–31] antitumor,[32–34] hypoglycemic,[35] cardioprotection,[36] antifungi,[37] neuroprotection,[38,39] and antianxiety activities.[40]

Up to 2015, this genus contributed about 252 papers. However, only seven review articles were published, five of which were on chemical constituents and biological activities of single plant. And the rest two were on two major components of *Alpinia* species. The first review came out in 2010 regarding distributions, physiological activities and ^{13}C NMR spectroscopic data of 307 naturally occurring diarylheptanoids, which were mainly isolated from *Alpinia* species.[41] In 2011, the pharmacological and phytochemical studies of *A. galanga* (L.) Willd were summarized with 30 references. Although it was claimed to concern new phytoconstituents that have appeared in recent years for *A. galangal*, it actually collected all reported compounds including volatile oil.[42] In 2012, structural characterization and biological effects of constituents from the seeds of *A. katsumadai* was described. Sixty compounds were reported together with their structures and bioactivities with 18 references.[43] In 2013, chemical constituents in fruits of *A. oxyphylla* and their pharmacological activities were summarized. Eighty-five compounds were obtained from this species between 2001 and 2012, with the major component of sesquiterpenes (61.2%). It possessed a variety of pharmacological activities, including neuroprotection, learning and memory-improving function, anticancer, anti-aging, anti-inflammation, and anti-anaphylaxis.[44] In 2015, a comprehensive review on the ethnomedical uses, chemical constituents, and the pharmacological profile of *A. calcarata* Roscoe was published with particular attention given to the pharmacological effects of the essential oil.[45] In the same year, the phytochemistry of *A. purpurata* with pharmacological properties of antioxidant, antibacterial, larvicidal, cytotoxic, and vasodilator activities were reported together with another ornamental ginger, *Hedychium coronarium*. As a matter of fact, little research was performed on *A. purpurata*.[46] In addition, the isolation, synthesis, and characterization of dihydro-5,6-dehydrokavain, the major constituent of *A. zerumbet* were also reviewed.[47] However, so far there has been no comprehensive review for chemical constituents of this species. Herein, we describe all isolated compounds and their

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relevant bioactivities of *Alpinia* species reported in the last six decades from 1955 to 2015.

2. Terpenoids

2.1. Monoterpenoids

A total number of 17 monoterpenoids were obtained from *Alpinia* species (Fig. 1). Rubraine (**1**), isorubraine (**2**), and sumadain C (**3**) were three new monoterpene–chalcone conjugates obtained from *A. katsumadai*.[48] They were tested for cytotoxic activities against three tumor cell lines of HepG2, MCF-7, and MAD-MB-435. Sumadain C (**3**) exhibited very weak effect with IC_{50} value of around 40.0 μM.[48] *A. katsumadai* Hayata yielded a new monoterpene–kavalactone conjugate, katsumadain (**4**) and a new (*E*)-1-(1-terpinen-4-olyl)-3-methoxystilbene (**5**).[49] While *A. densibracteata* T. L. Wu and Senjen yielded two diastereoisomers of cinnamate esters, 2α-cinnamoyl cineole (**6**) and 2β-cinnamoyl cineole (**7**).[50] From rhizomes of *A. tonkinensis* Gagnep., 2α-(*p*-hydroxycinnamoyl) cineole (**8**) was isolated.[50,51] Two endoperoxides, (1*S*,4*R*,6*R*)-1,4-epidioxy-*p*-menth-2-ene (**9**) and (1*R*,4*S*,6*R*)-1,4-epidioxy-*p*-menth-2-ene (**10**), were isolated from aerial parts of *A. densibracteata* T. L. Wu and Senjen.[50] Whilst (3*R*,4*R*,6*S*)-3,6-dihydroxy-1-menthene (**11**) and 1-terpinen-4-ol (**12**) were obtained from *A. sichuanensis* Z. Y. Zhu (a synonym of *A. jianganfeng* T. L. Wu) and *A. katsumadai* Hayata, respectively.[49,52] Fruit of *A. oxyphylla* Miq. was the source of (1*R*,2*R*)-*p*-menth-3-ene-1,2-diol (**13**).[53] And aerial parts of *A. densibracteata* T. L. Wu and Senjen yielded 3,4-dihydroxy-*p*-menth-1-ene (**14**).[50] Compounds **15**–**17** were three hydroxyl-1,8-cineole glucopyranosides, which were mainly isolated from rhizomes of *A. galanga* (L.) Willd.[54,55]

2.2. Sesquiterpenoids

To date, 132 sesquiterpenoids were reported from *Alpinia* species (Fig. 2). They were divided into acyclic sesquiterpenoids (**18** and **19**), eremophilanes (**20–40**), eudesmanes (**41–84**), cadinanes (**85–100**), guaianes (**101–117**), caryophyllanes (**118–120**), bisabolanes (**121–137**), humulanes (**138–140**), drimane (**141**), elemane (**142**), carabrane (**143**), oplopanane (**144**), and others (**145–149**).

Seeds of *A. katsumadai* Hayata produced an acyclic sesquiterpenoid, *trans*,*trans*-farnesol (**18**), which exerted weak neuraminidase inhibitory activity *in vitro* (IC_{50} = 81.4 μM).[56] Nerolidol (**19**), another acyclic sesquiterpene, was obtained from rethizoms of *A. japonica*.[57]

Investigations on fruits of *A. oxyphylla* Miq. afforded 16 eremophilanes (**20–35**). Epinootkatol (**29**) and nootkatone (**30**) displayed insecticidal activities against larvae and adults of *Drosophila melanogaster* with IC_{50} values of 11.5 μM and 96 μg per adult, respectively.[58] While 9β-hydroxynootkatone (**31**), (11*S*)-12-chloronootkaton-11-ol (**32**), and (11*R*)-12-chloronootkaton-11-ol (**33**) displayed anti-acetylcholinesterase (AChE) activities by TLC-bioautographic assays.[59,60] 12-Nornootkaton-6-en-11-one (**35**) was a novel nor-eremophilane. It showed potent anti-AChE bioactivity at 10 nM using the same TLC-bioautographic assay.[59] The rest of five eremophilanes (**36–40**) were isolated from three different species. Eremophilen-10β-ol (**36**) and eremophilen-11-ol (**37**) were obtained from *A. intermedia* Gagnep. and *A. japonica* (Thunb.) Miq., respectively,[61,62] whilst nootkatene (**38**), valencene (**39**), and dehydro-nootkatone (**40**) were all identified from *A. oxyphylla* Miq.[59,63–65]

Among 44 eudesmane sesquiterpenoids, oxyphyllones A and B (**41** and **42**) were isolated from *A. oxyphylla*. They were the first two examples of 4,5-secoeudesmanes in the Zingiberaceae family.[66] Oxyphyllone A displayed moderate anti-AChE activity.[59] Also obtained from *A. oxyphylla* Miq. were compounds **43–63**.[67,68] *A. intermedia* Gagnep. was the source of intermedeol (**64**) and β-selinene (**65**).[61] Investigations of *A. japonica* (Thunb.) Miq. led to the identification of **66–75**.[21,57,69,70] Two novel trinoreudesmanes, oxyphyllanenes A (**76**) and B (**77**) were obtained from *A. oxyphylla*, together with four known ones (**78–81**).[71,72] Investigation on *A. oxyphylla* Miq. provided three nor-eudesmane sesquiterpenoids, oxyphyllanene C (**82**), (5*R*,7*S*,10*S*)-5-hydroxy-13-noreudesma-3-en-2,11-dione (**83**), and 4-methoxy-oxyphyllenone A (**84**).[67,71,73]

A new 1,10-seco-15-norcadinane sesquiterpene nominated oxyphenol A (**85**) was isolated from *A. oxyphylla*.[65] Fruits of *A. oxyphylla* Miq. also provided one tricyclic sesquiterpene, mustakone (**86**), nine nor-cadinanes, **87–94** and 2β-hydroxy-δ-cadinol (**95**).[53,59,68,74] *A. oxymitra* K. Schum. was the source of (−)-(1*R*,4*S*)-8-hydroxy-13-calamenenoic acid (**96**).[75] Alpiniaterpene A (**97**) was provided by *A. officinarum* Hance,[76] while 4(15)-cadinene-6,10-diol (**98**) by *A. tonkinensis* Gagnep.[51] Two new compounds (**99** and **100**) were isolated from fruits of *A. oxyphylla* Miq. And **100** exhibited moderate hypoglycemic activity with inhibitory rate of 11.5%, compared to 41.9% of the positive control acarbose (41.9%) at 90 μM.[77]

Rhizomes of *A. japonica* (Thunb.) Miq. produced alpinenone (**101**), an inhibitor of AChE.[59,60] Hanamyol (**102**), containing a cyclic ether linkage, was also isolated from *A. japonica* (Thunb.) Miq.[78] Rhizomes of *A. intermedia* Gagnep. provided hanalpinol peroxide (**103**), isohanalpinol (**104**), and aokumanol (**105**).[61] While *A. intermedia* Gagnep. and *A. japonica* (Thunb.) Miq. produced hanalpinol (**106**), hanalpinone (**107**), and isohanalpinone (**108**).[61,79] From *A. japonica* (Thunb.) Miq. and *A. intermedia* Gagnep., furopelargones A (**109**) and B (**110**) were obtained.[61,78,80] Later on, **110** was also found from *A. formossana*.[81] Compounds **111–114** were four secoguaiane-type sesquiterpenes with an α,β-unsaturated butenolide. *A. intermedia* Gagnep. produced epialpinolide (**111**), whilst *A. japonica* (Thunb.) Miq. yielded alpinolide peroxide (**112**), 6-hydroxy-alpinolide (**113**), and alpinolide (**114**).[61,78,79] A 1,10-secoguaiane sesquiterpene, (+)-mandassidion (**115**), and two 1,10-seco-15-norguaiane sesquiterpenes, mandassions A (**116**) and B (**117**) were obtained from fruits of *A. oxyphylla* Miq.[65]

Caryophyllene oxide (**118**), caryophyllenol-I (**119**), and caryophyllenol-II (**120**) were caryophyllanes from *A. galanal*. In addition, caryophyllene oxide was also distributed in rhizomes of *A. conchigera* Griff.[24,82]

Investigation of the aerial parts of *A. densibracteata* T. L. Wu and Senjen led to the isolation of two bisabolane endoperoxides (**121** and **122**), three bisabolane hydroperoxides (**123–125**), and one 3,4-dihydroxy-bisabola-1,10-diene (**126**).[50] Compounds **127–137** were reported from rhizomes of *A. japonica* (Thunb.) Miq.[83]

A. oxyphylla Miq. was the source of 3(12),7(13),9(*E*)-humulatriene-2,6-diol (**138**).[84] While *A. formossana* and *A. japonica* produced humulene epoxideII (**139**).[57,81] (9*E*)-Humulene-2,3;6,7-diepoxide (**140**) was reported from the fruits of *A. oxyphylla* Miq. However, its relative configuration remained undetermined. It

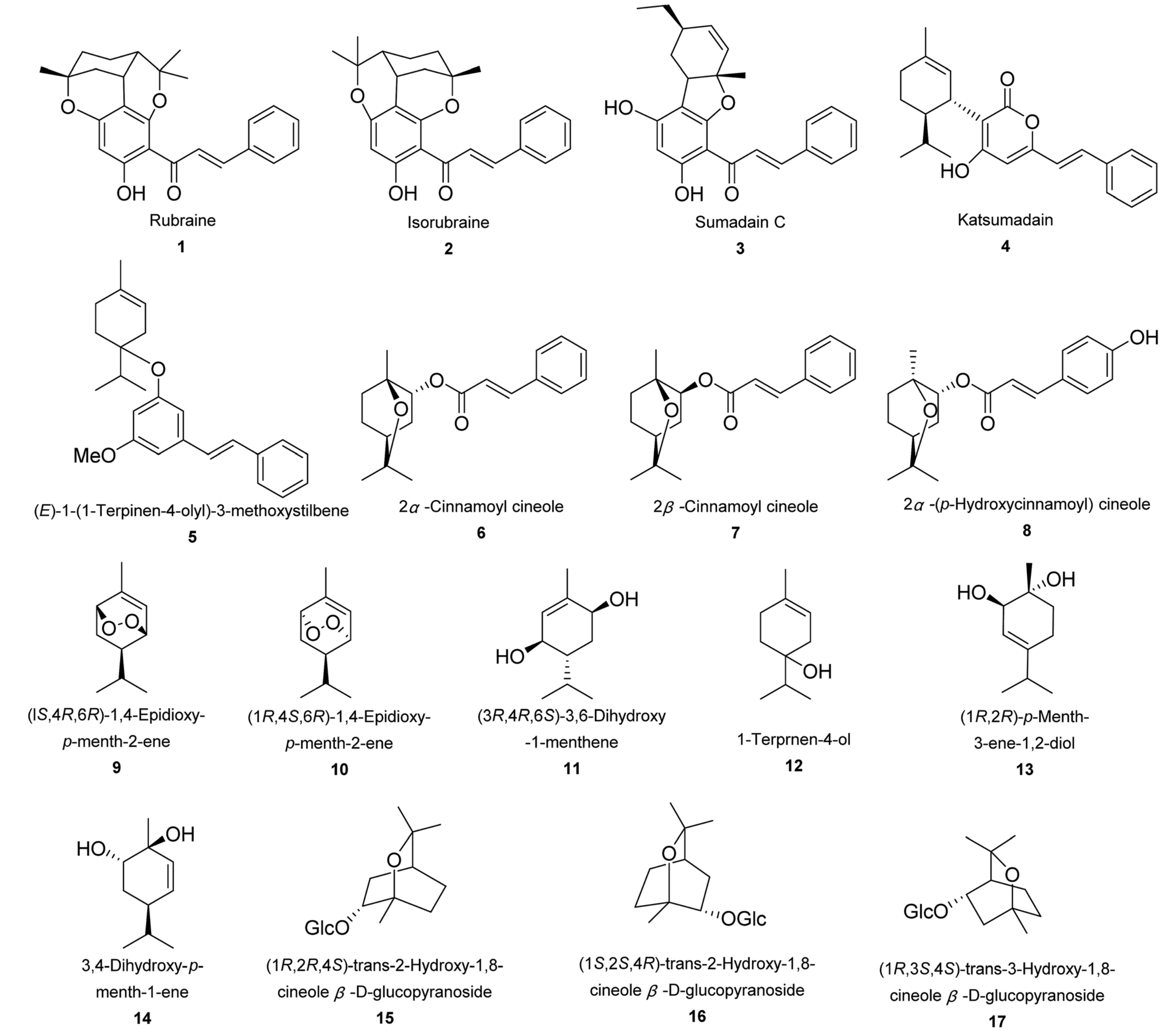


Fig. 1 Monoterpenoids from *Alpinia* species.

exhibited moderate anti-AChE activity in bioautographic assay at 10 nM.[59,84] Interestingly, the structure and molecular formula for **140** (CAS Registry Number: 21956-93-4) provided by Scifinder were not correct. It should be $C_{15}H_{24}O_2$ instead of $C_{14}H_{21}O_2$.

Rhizomes of *A. calcarata* Rosc. afforded a drimane-type sesquiterpene (γ-bicyclohomofarnesal, **141**),[85] and an elemane one (shyobunone, **142**).[83] Pubescone (**143**) was isolated from *A. oxyphylla* Miq. and showed weak anti-AChE activity at the concentration of 100 μM.[59] (−)-Oplopanone (**144**) and oxyphyllone F (**145**) were obtained from fruits of *A. oxyphylla* Miq.[84] (*Z*)-4-(2,6-Dimethylhepta-1,5-dien-1-yl)-1-methyl-cyclobut-1-ene (**146**) was a novel nor-sesquiterpene incorporating cyclobutene ring from *A. oxyphylla* Miq.[74] Seeds of *A. galanga* (L.) Willd produced caryolane-1,9β-diol (**147**), which suppressed the proliferation of four cancer cell lines of HeLa, A549, HepG2, and SMMC-7721 with IC_{50} values ranged from 252 to 378 μM.[86] *A. japonica* (Thunb.) Miq. yielded alpiniol (**148**).[87] Compound 2-ethyl-6-isopropyl-7-hydroxymethyl naphthalene (**149**) was a noval naphthalene from *A. oxyphylla*.[77] It showed bioactive activity with the inhibitory rates of 10.3%, compare to 41.9% of the positive control acarbose at 0.9 mM.[77]

Noteworthily, compounds **22–31**, **34**, **48–56**, **58–63**, **79–82**, **87–89**, **117**, and **129–136** exerted NO production inhibitory activities at different levels.[58–60,65,67,71,73,83,88–90] While (10*R*)-13-noreudesma-4,6-dien-3,11-dione (**46**), (5*S*,8*R*,10*R*)-2-oxoeudesma-3,7(11)-dien-12,8-olide (**47**), (5*R*,7*S*,10*S*)-5-hydroxy-13-noreudesma-3-en-2,11-dione (**83**), and (4*S*)-10-nor-calamenen-10-one (**90**) showed potent auxo-action of NO production at 10 μM induced by lipopolysaccharide (LPS) in microglia.[71]

2.3. Diterpenoids

Labdane diterpenes is undoubtedly predominant in Zingiberaceae family, notably in *Alpinia* genus. Almost all diterpenes are

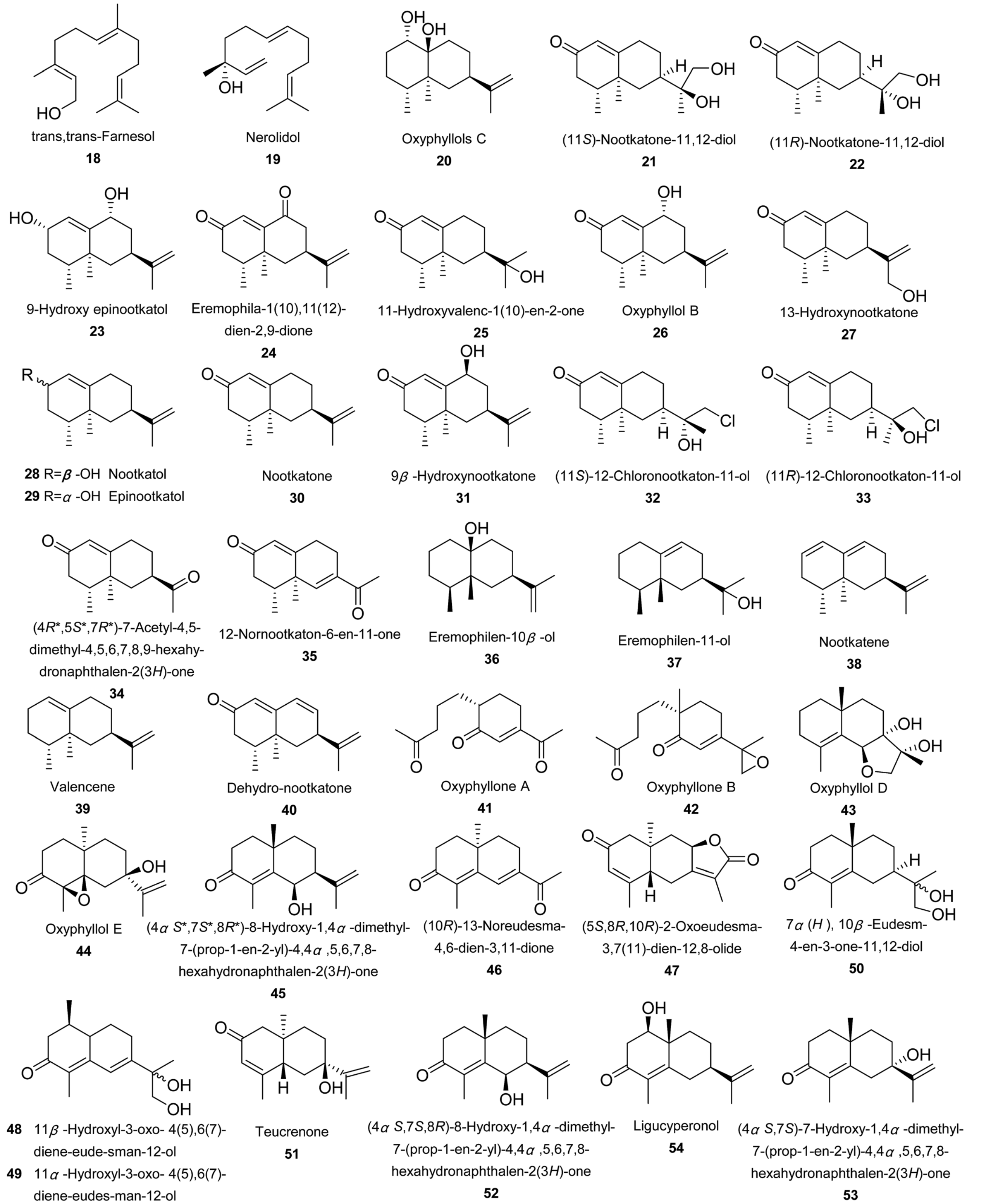


Fig. 2 Sesquiterpenoids from *Alpinia* species.

labdanes (**150–205**). Only one grayanane diterpene was found (**206**) (Fig. 3).

(*E*)-Labda-8(17),12-diene-15,16-dial (**150**) is widely distributed in *Alpinia*. It exhibited a number of bioactivities, such as antibacterial,[91] α-glucosidase inhibition,[92] NO production inhibition,[88] antifungal,[93] antiglycation,[94] HIV-1 integrase, and neuraminidase inhibitory activities.[95] *A. katsumadai* Hayata, *A. galanga* (L.) Willd, and *A. nigra* yielded (*E*)-8β,17-epoxylabd-12-

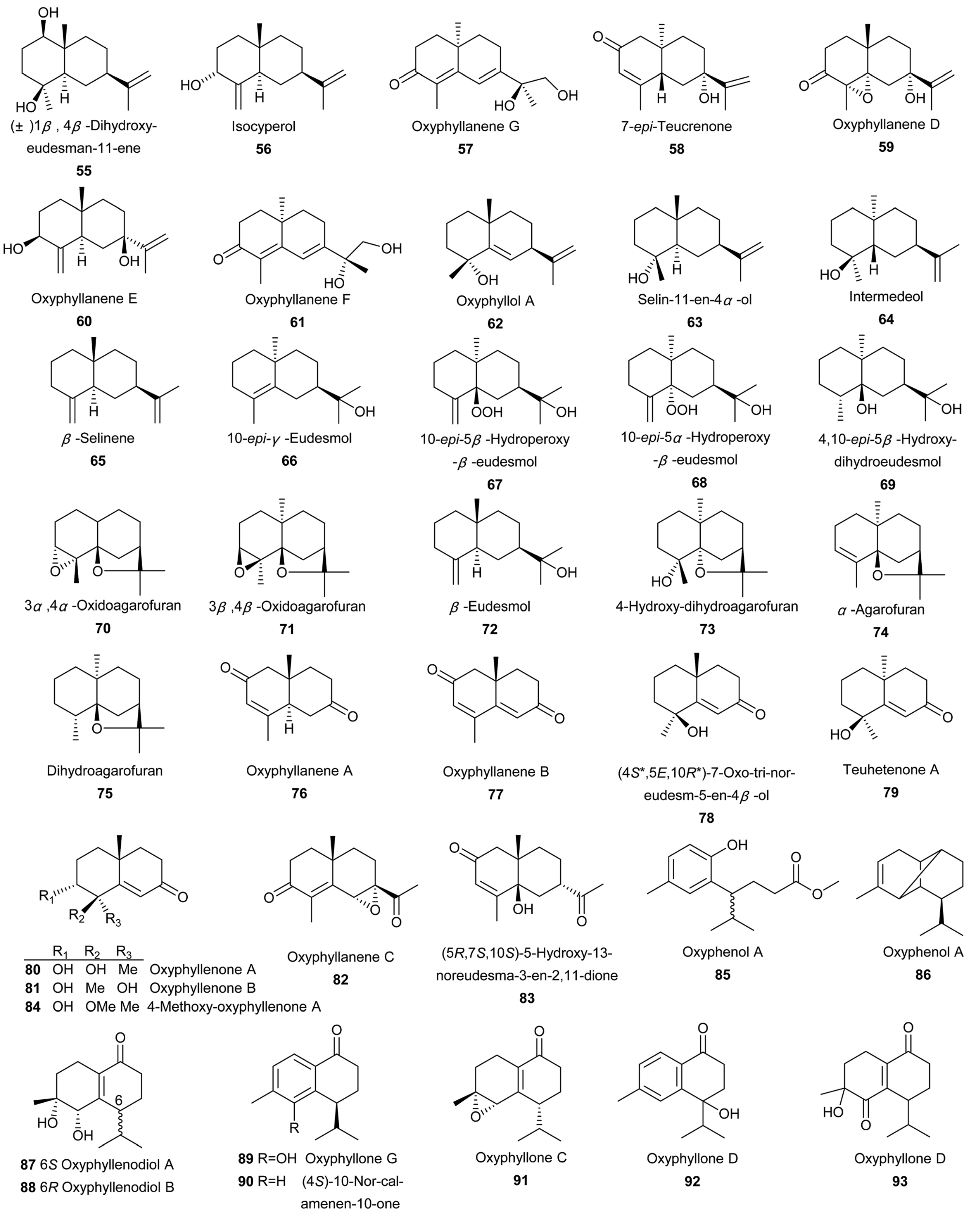


Fig. 2 Sesquiterpenoids from *Alpinia* species (continued).

ene-15,16-dial (**151**). It exhibited extensive antibacterial activities, especially against *Candida guilliermondii* and *Candida tropicalis*.[49,91,93,96] Moreover, **151** also showed α-glucosidase inhibitory activity with IC_{50} value between 5 μM and 10 μM.[70] The α-glucosidase inhibitory activity of **151** was even much higher than the positive control, acarbose (IC_{50} = 400 μM),

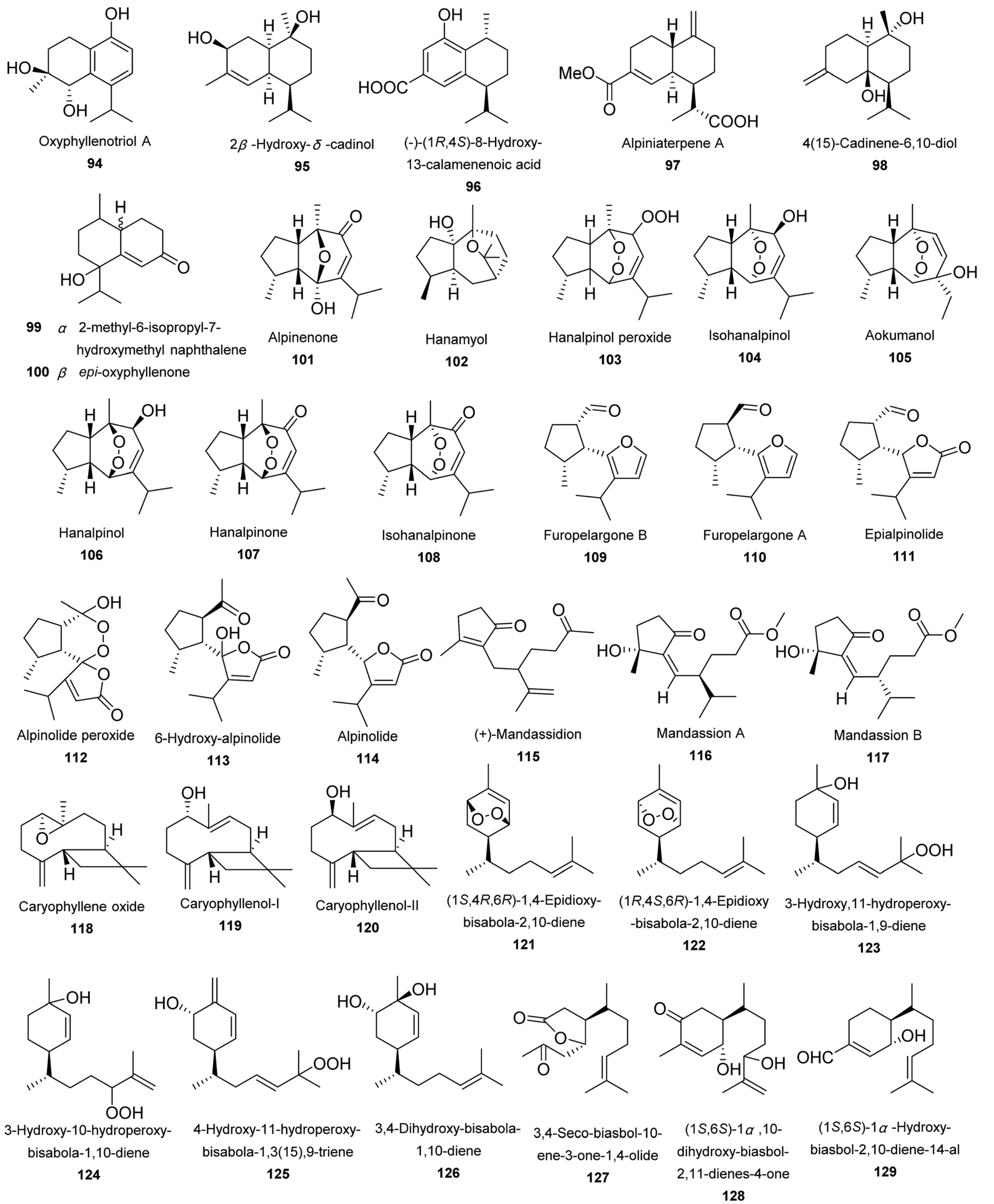


Fig. 2 Sesquiterpenoids from *Alpinia* species (continued).

indicating **151** might be a potential candidate as a future anti-diabetic drug.[70] *A. formosana*, *A. calcarata* Rosc., and *A. pahangensis* Ridley provided (*E*)-labda-8(17),12-diene-15-ol-16-al (**152**),[81,85,96] while (*E*)-labda-8(17),13-dien-15-al (**153**) was only obtained from *A. pahangensis* Ridley.[96] Flowers of *A. chinensis* Rosc. provided compounds **154–161**.[81,85,97] *A. tonkinensis*

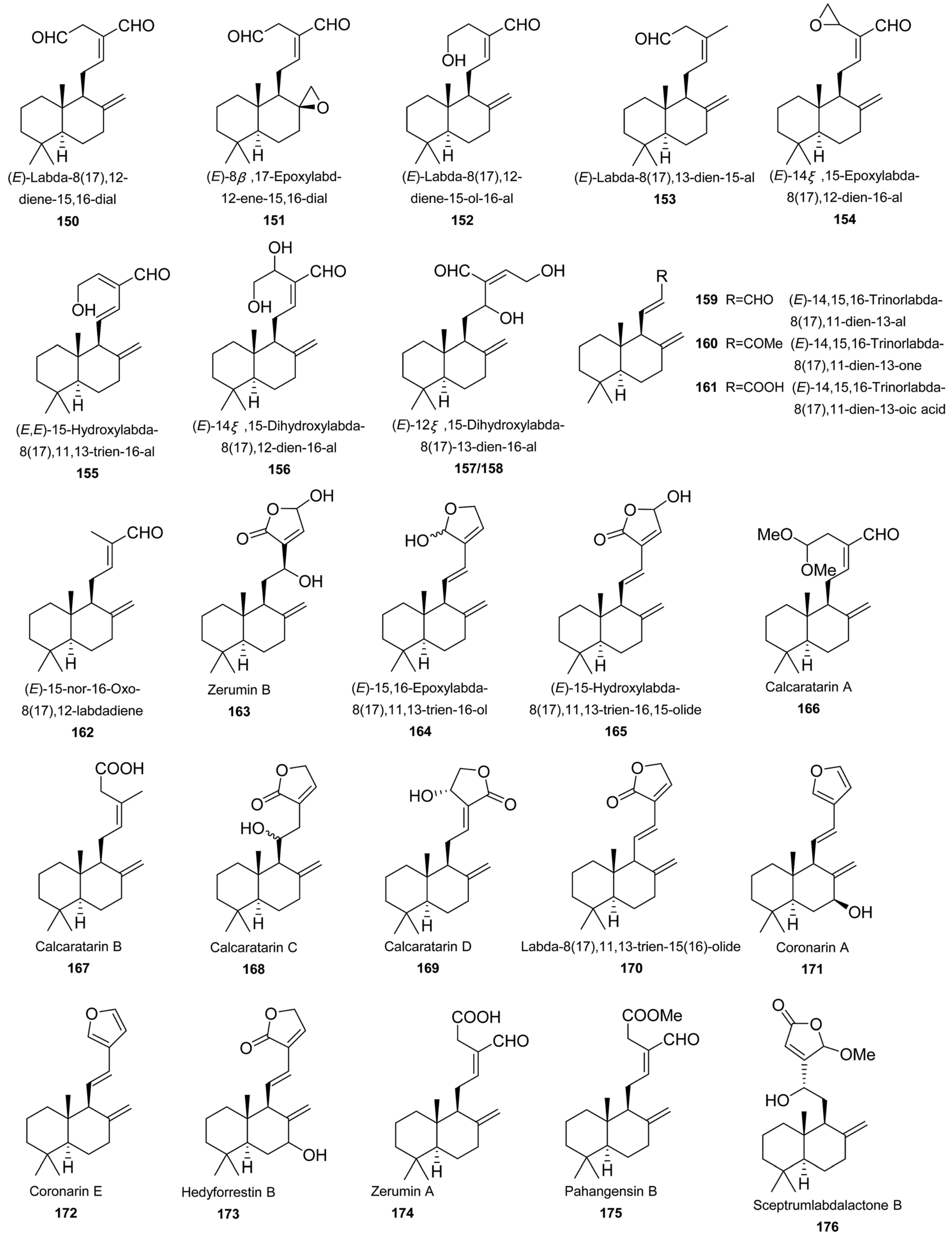


Fig. 3 Diterpenoids from *Alpinia* species.

Gagnep. and *A. speciosa* K. Schum. (the accepted name is *A. zerumbet* (Pers.) B. L. Burtt & R. M. Sm.) were the sources of (*E*)-15-nor-16-oxo-8(17),12-labdadiene (**162**).[51,98] Both *A. zerumbet* (Pers.) Burtt and P. M. Smith and *A. pahangensis* Ridley gave birth to zerumin B (**163**).[96,99] (11*E*)-15,16-Epoxylabda-8(17),11,13-trien-16-ol (**164**) and (*E*)-15-hydroxylabda-8(17),11,13-trien-16,15-olide

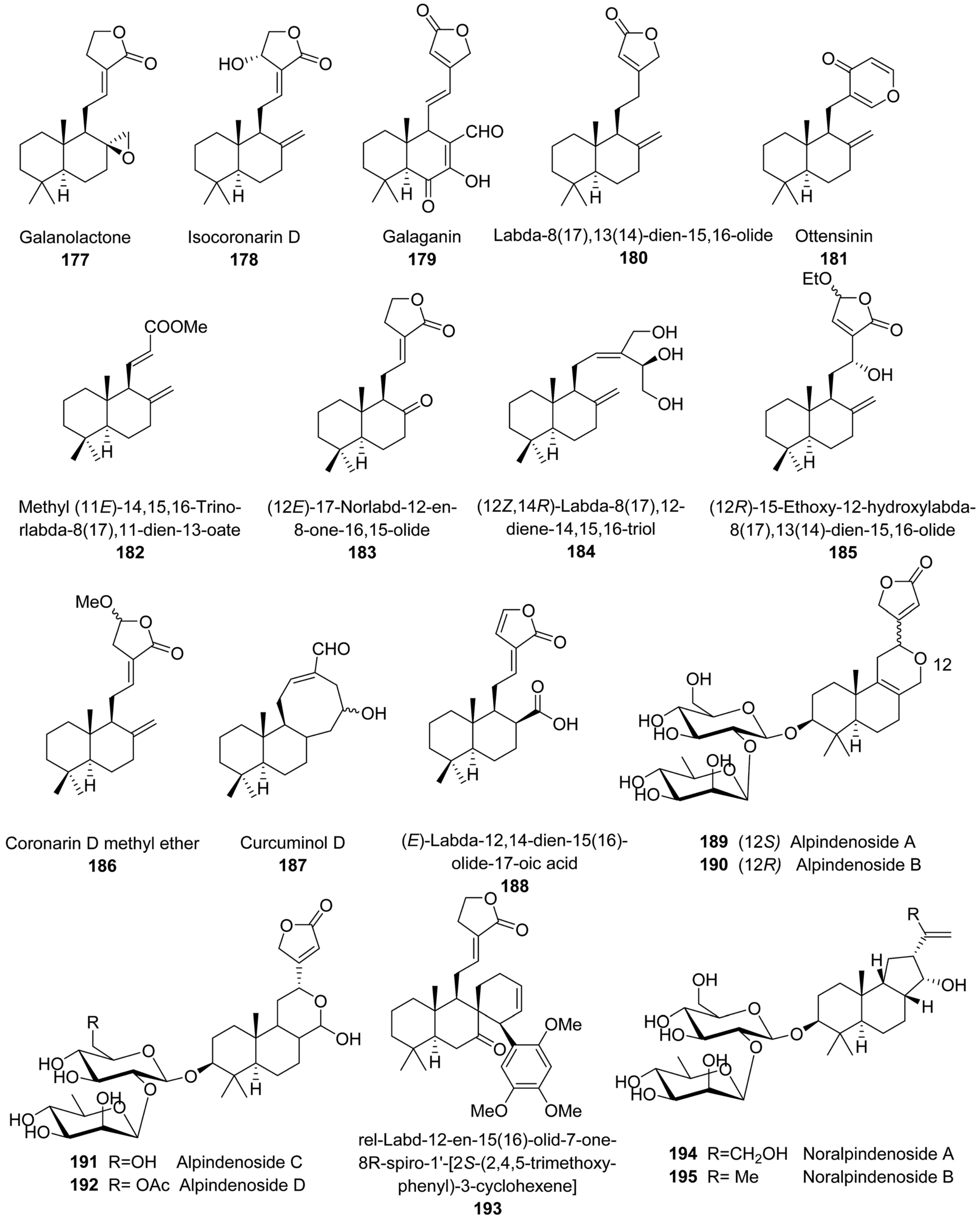


Fig. 3 Diterpenoids from *Alpinia* species (continued).

(**165**) were found in the flowers of *A. chinensis* Rosc.[97] It is noteworthy that **164** was actually a mixture of two epimers. Rhizomes of *A. calcarata* Rosc. produced calcaratarins A–D (**166–169**) and labda-8(17),11,13-trien-15(16)-olide (**170**).[85] Rhizomes of *A. malaccensis* yielded coronarin A (**171**), coronarin E (**172**), and hedyforrestin B (**173**).[100] Coronarin E (**172**) was also isolated from *A.*

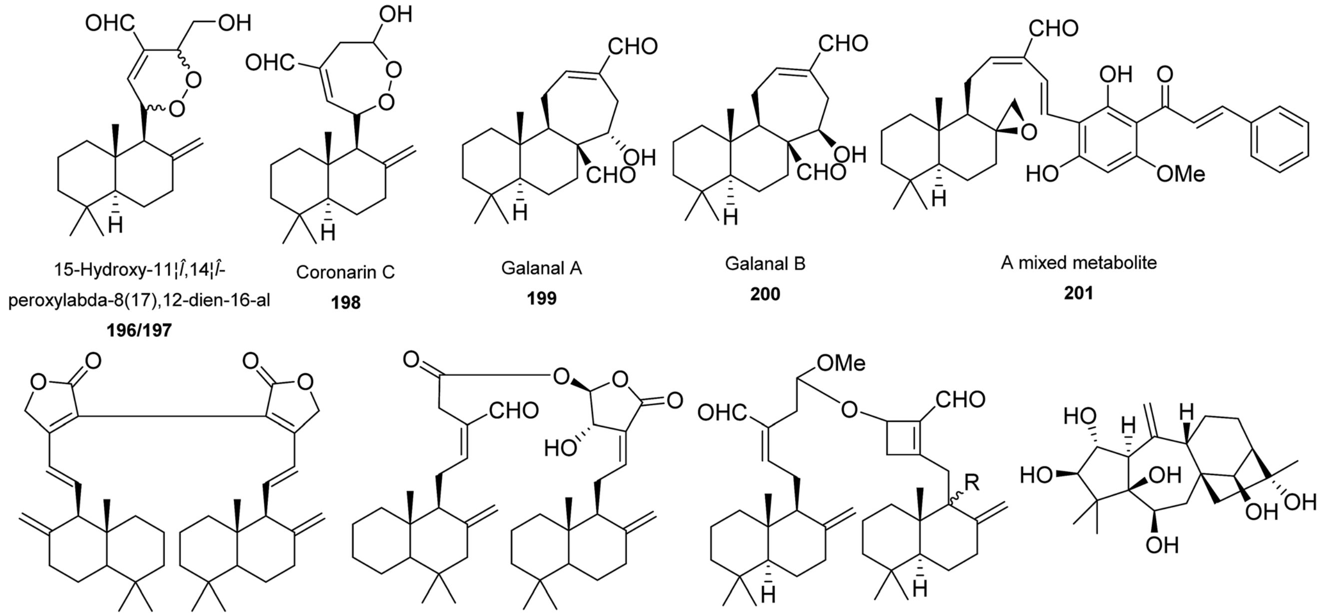


Fig. 3 Diterpenoids from *Alpinia* species (continued).

zerumbet (Pers.) Burtt and P. M. Smith, and *A. chinensis* Rosc.[97,99,100] Three antibacterial constituents, zerumin A (**174**), pahangensin B (**175**), and sceptrumlabdalactone B (**176**), were isolated from *A. pahangensis* Ridley.[96] Interestingly, zerumin A (**174**) was also obtained from *A. calcarata* Rosc. and *A. zerumbet* (Pers.) Burtt and P. M. Smith.[85,99] Compound **175** was also found in *A. japonica* (Thunb.) Miq., with NO production inhibition (IC_{50} = 34.3 μM) in LPS-induced RAW264.7 macrophages.[101] Galanolactone (**177**) was isolated from *A. katsumadai* Hayata and *A. galanga*. It was reported to have moderate antifungal activity to *Candida guilliermondii* PW44 and *Candida tropicalis* PW30 with both MIC values of 25 μg mL^{-1}.[93] Isocoronarin D (**178**) was found in *A. galanga* (L.) Willd and *A. calcarata* Rosc., which weakly suppressed the proliferation of four cancer cells lines of HeLa, A549, HepG2, and SMMC-7721 in a concentration-dependent way with IC_{50} values ranging from 69.1 to 87.0 μg mL^{-1}.[64,67] Seeds of *A. galanga* yielded galaganin (**179**), which showed moderate cytotoxicity towards DU145, MCF-7, H522, and k562 cells with IC_{50} values of 8.2, 13.8, 17.8, and 16.1 μM, respectively.[102] Rhizomes of *A. pinnanensis* T. L. Wu et Senjen produced labda-8(17),13(14)-di-en-15,16-olide (**180**) and ottensinin (**181**).[96] *A. japonica* provided compounds **182–187**, of which **182** and **183** were norlabdanes.[101] Compounds **182**, **185**, and **186** exhibited

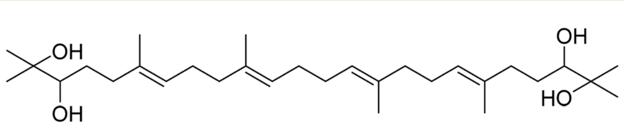


Fig. 4 Triterpenoids from *Alpinia* species.

significant NO production inhibitory effects in LPS-induced RAW264.7 macrophages, with respective IC_{50} values of 25.9, 14.6, and 25.6 μM, compare to 39.6 μM of the positive control, *N*-monomethyl-L-arginine (L-NMMA).[101] Ethanol extract of *A. oxyphylla* Miq. provided **188**, which showed moderate hypoglycemic effect with inhibitory rates of 10.0% at 60 μM.[77] Ottensinin showed moderate antibacterial activity on the Gram-positive bacteria of *Bacillus cereus* with MIC value of 0.25 μg μL^{-1}.[96] Alpindenosides A–D (**189–192**) were four labdane glycosides from *A. densespicata* Hayata. They didn't show cytotoxic activities against four human tumor cell lines of Hela, KB, Doay, and WiDr at 20 μM. Instead, they all exhibited moderate NO inhibitory activities with IC_{50} ranging from 30 to 49 μM.[103] Leaves of *A. flabellate* provided *rel*-labda-12-en-15(16)-olid-7-one-8*R*-spiro-1′-[2*S*-(2,4,5-trimethoxyphenyl)-3-cyclohexene] (**193**), a unique labdane diterpene coupled with a phenylbutenoid.[104] Noralpindenosides A (**194**) and B (**195**) were two norditerpene glycosides from *A. densespicata* Hayata, both of which showed moderate inhibitory effects on NO production with IC_{50} values of 34.2 and 49.3 μM, respectively.[103] (*E*,*E*)-15-Hydroxylabda-8(17),11,13-trien-16-al (**196**) and its diastereoisomer (**197**) from *A. chinensis* Rosc. may arise by direct oxygenation of (*E*,*E*)-15-hydroxylabda-8(17),11,13-trien-16-al.[97] From flowers of *A. chinensis* Rosc., coronarin B (**198**) containing a seven-membered endoperoxide hemiacetal was isolated.[97] It should be noted that although the structure and its NMR and MS spectroscopic data referred to coronarin B (CAS number: 119188-38-4) in the reference, the author gave a wrong name for this compound as coronarin C (CAS number: 119188-35-1) which was previously isolated from *Hedychium coronarium*.[105] Galanals A (**199**) and B (**200**) were obtained from *A. galanga* (L.) Willd. Both compounds showed significant antifungal activities against

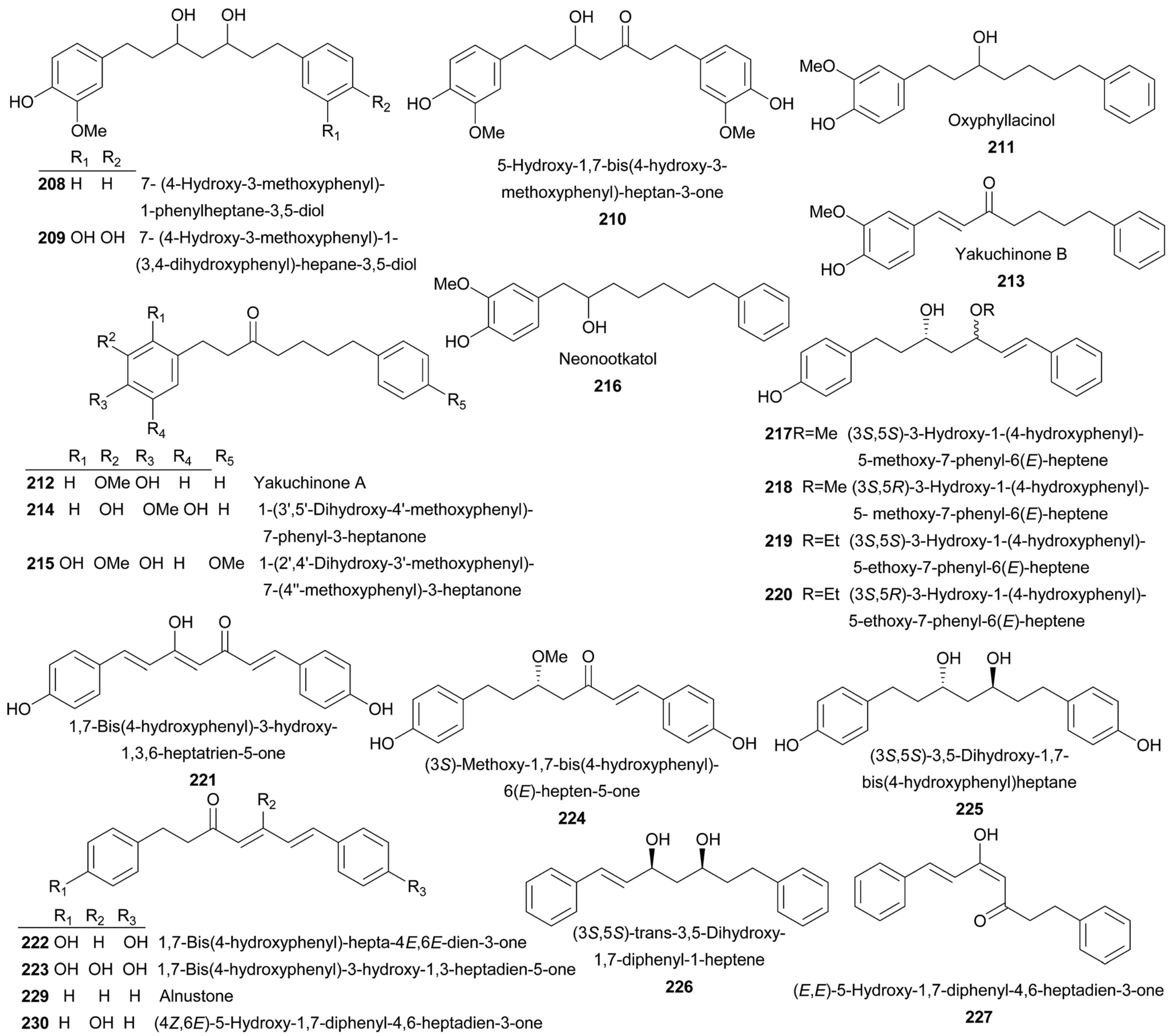


Fig. 5 Diarylheptanoids from *Alpinia* species.

Candida guilliermondii PW44 with MIC values of 12.5 μg mL^{-1}. Furthermore, galanal A exhibited potent cytotoxic activity against KB cells (IC_{50} = 3.25 μg mL^{-1}).[7,93] Compound **201** was a novel metabolite conjugated of labdane diterpene with chalcone from aerial parts of *A. katsumadai* Hayata.[49] *A. pahangensis* Ridley provided pahangensins A (**202**) and C (**203**) as antibacterial constituents.[96,106] *A. pahangensis* Ridley produced calcaratarins D (**204**) and E (**205**), both of which were cytotoxic against human KB cells *in vitro* with IC_{50} value of 0.21 and 0.15 μg mL^{-1}, respectively.[107] From seeds of *A. katsumadai* Hayata, a grayanane diterpenoid was isolated and characterized as rhodomollein I (**206**).[108]

2.4. Triterpenoids

Up to now, only one triterpene was found from this genus (Fig. 4). It was named as 2,3,22,23-tetrahydroxyl-2,6,10,15,19,23-hexamethyl-6,10,14,18-tetracosatetraene (**207**), an acyclic triterpenoid, isolated from the seeds of *A. katsumadai* L.[109] It showed weak cholesterol acyltransferase inhibitory activity with IC_{50} value of 47.9 μM.[109]

3. Diarylheptanoids

A total of 143 diarylheptanoids (**208–350**, Fig. 5) were isolated from *Alpinia* species, including 66 acyclic diarylheptanoids (**208–273**), 11 cyclic diarylheptanoids (**274–284**), 50 diarylheptanoid and flavonoid conjugates (**285–334**), 10 dimeric diarylheptanoids (**335–344**), and six others (**345–350**).

Compounds **208–210** were isolated from rhizomes of *A. officinarum* Hance. They were moderate or weak NO production inhibitors.[110] From fruits of *A. oxyphylla*, oxyphyllacinol (**211**) and yakuchinones A–B (**212–213**) were isolated, of which **211** was a NO production inhibitor, while **212** and **213** exhibited anti-tumor activities to human promyelocytic leukemia (HL-60) cells in a concentration-related manner.[32,67] In addition, **212**

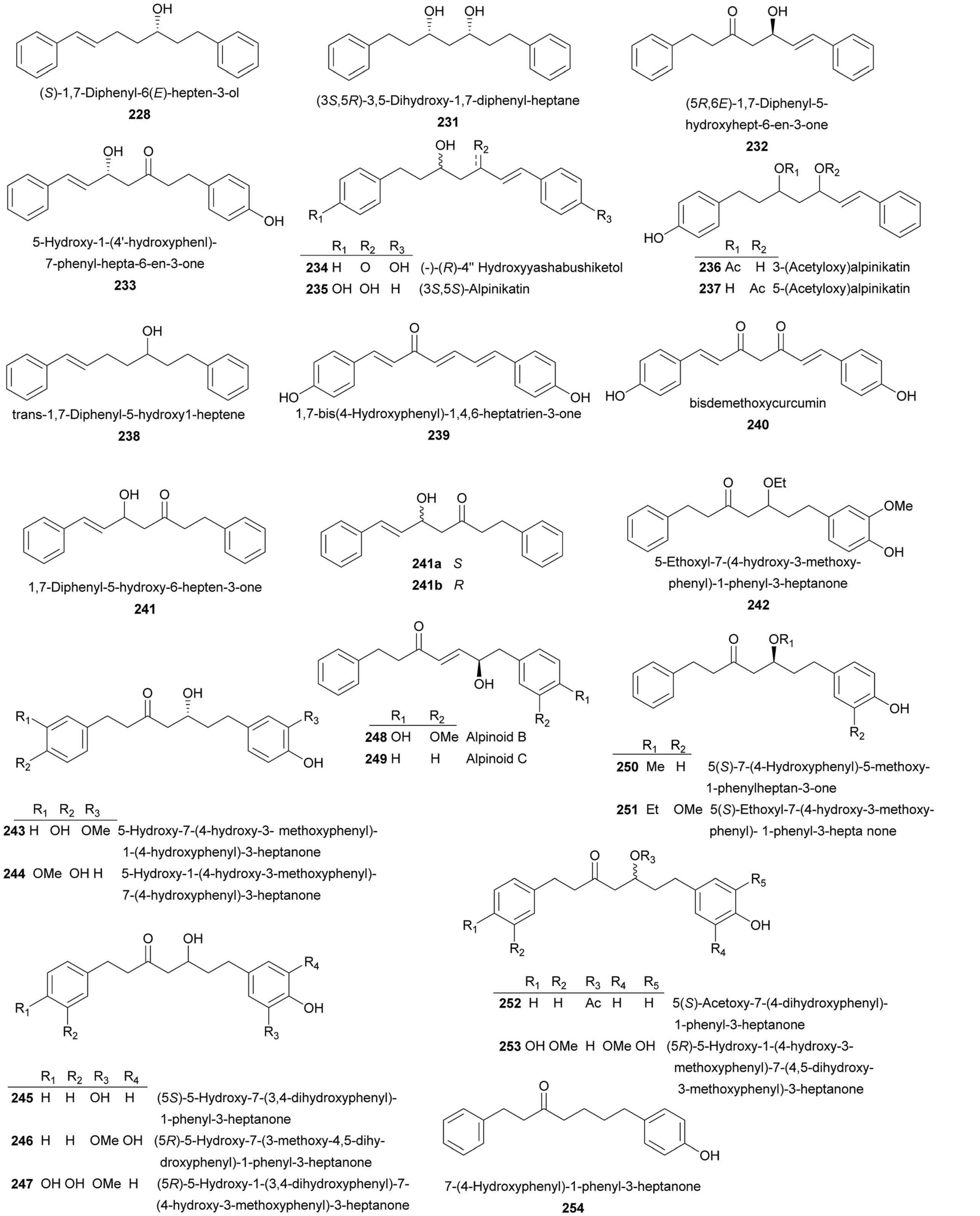


Fig. 5 Diarylheptanoids from *Alpinia* species (continued).

also possessed insecticidal,[36] anti-adipocyte differentiation,[111] NO production inhibitory,[46] and cardiotonic activities.[112] Compounds **213–216** were also yielded by fruits of *A. oxyphylla*.[113,114] Seeds of *A. blepharocalyx* K. Schum. gave birth to **217–225**.[115–117] Among these compounds, 1,7-bis(4-hydroxyphenyl)-3-hydroxy-1,3-heptadien-5-one (**223**) significantly inhibited platelet aggregation induced by

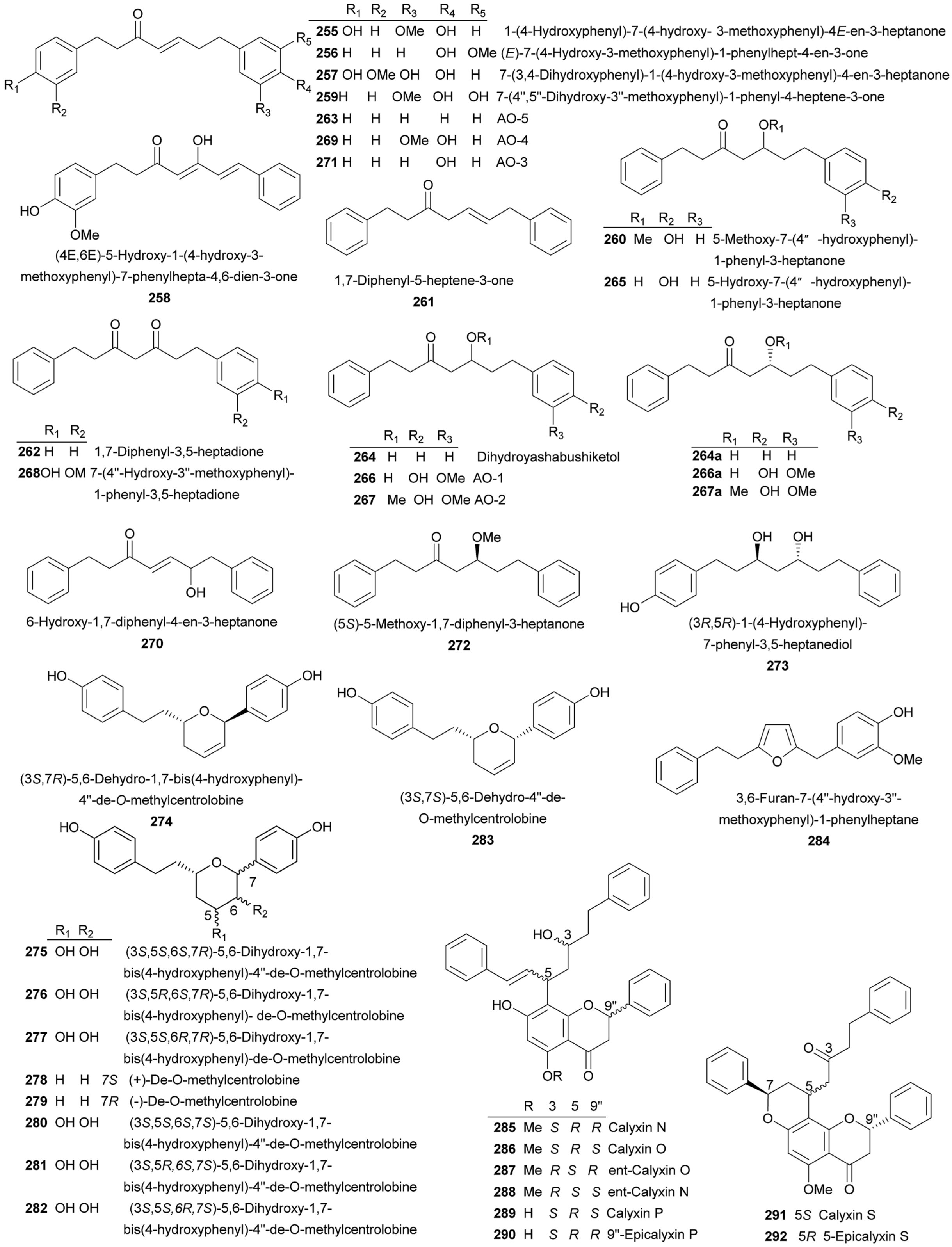


Fig. 5 Diarylheptanoids from *Alpinia* species (continued).

collagen with IC_{50} value of 14.7 μg mL^{-1}.[117] (3*S*,6*E*)-Methoxy-1,7-bis(4-hydroxyphenyl)-6-hepten-5-one (**224**) and (3*S*,5*S*)-3,5-dihydroxy-1,7-bis(4-hydroxyphenyl)heptane (**225**) showed significant antiproliferative activities against murine colon 26-L5 carcinoma and human HT-1080 fibrosarcoma with IC_{50} values of 5.2 and 12.8 μM, respectively.[115,116] Both *A. pinnanensis*

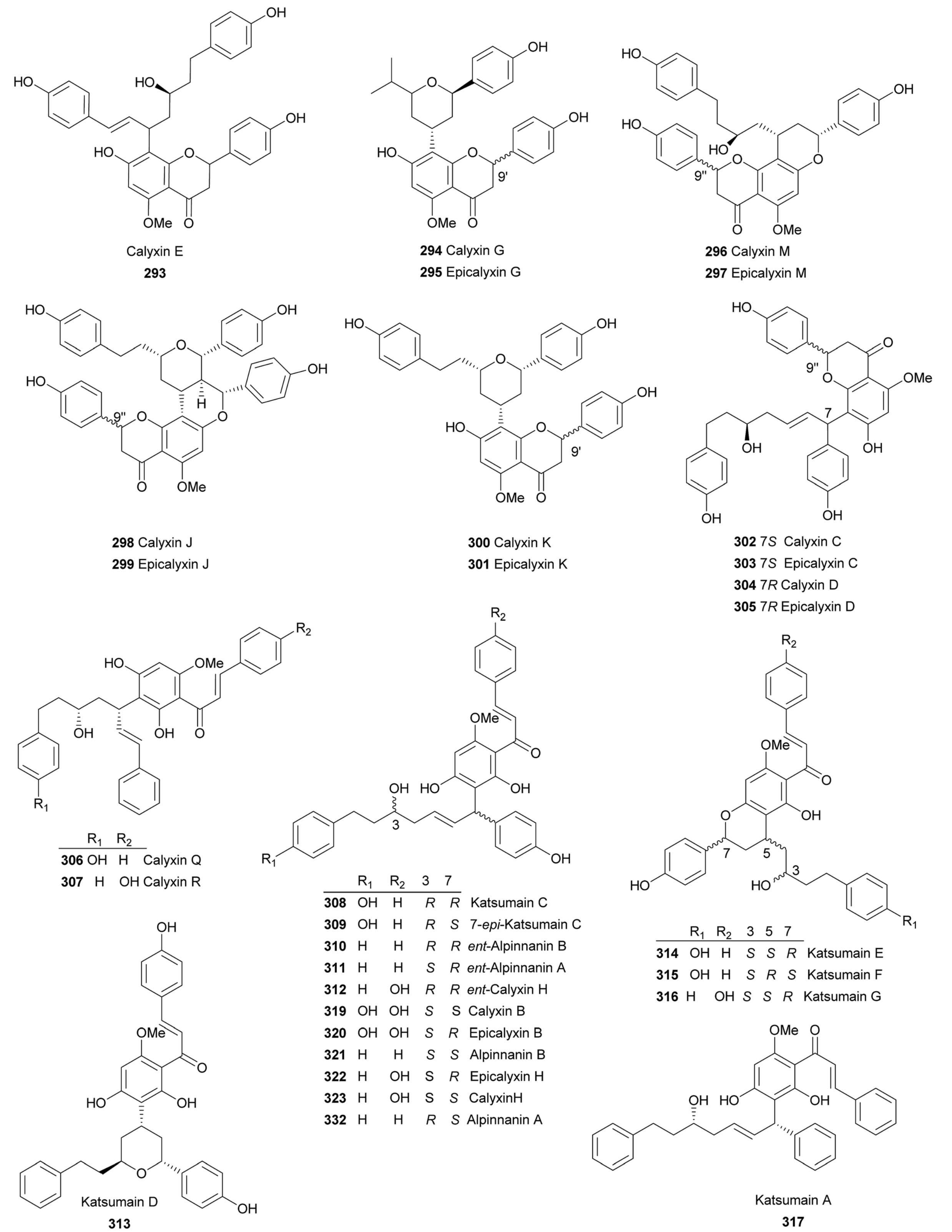


Fig. 5 Diarylheptanoids from *Alpinia* species (continued).

T. L. Wu et Senjen and *A. katsumadai* Hayata provided (3*S*,5*S*)-*trans*-3,5-dihydroxy-1,7-diphenyl-1-heptene (**226**).[118,119] It did not showed antimycobacterial activity (MIC ≥ 64 mg L^{-1}). Instead, it exhibited weak neuraminidase inhibitory activity (IC_{50} = 29.75 ± 8.15 μM) *in vitro*.[56,120] (*E*,*E*)-5-Hydroxy-1,7-diphenyl-4,6-heptadien-3-one (**227**), (*S*)-1,7-diphenyl-6(*E*)-hepten-3-ol (**228**),

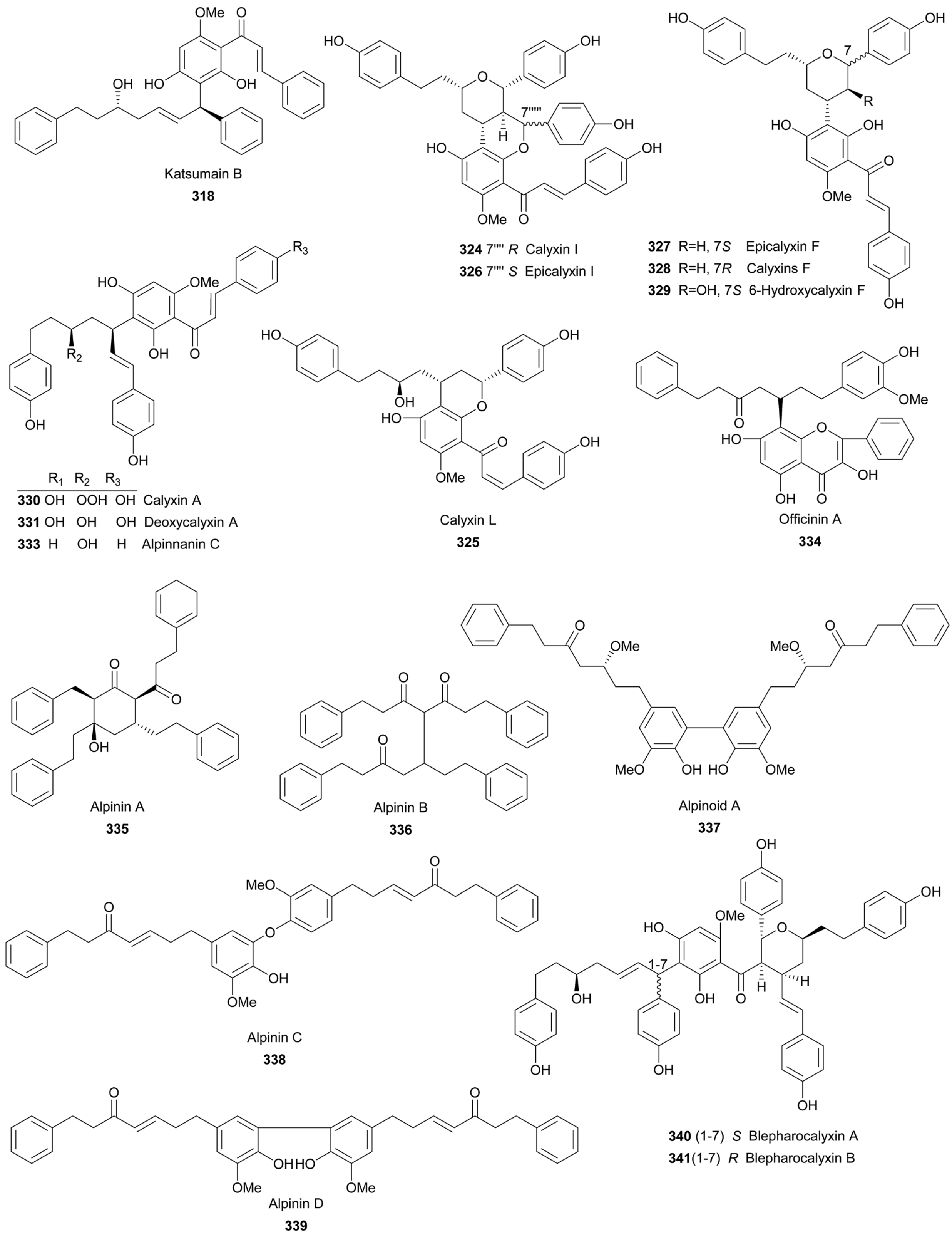


Fig. 5 Diarylheptanoids from *Alpinia* species (continued).

and alnustone (**229**) were isolated from *A. katsumadai* Hayata with significantly neuraminidase inhibitory *in vitro* with IC_{50} values between 1.0 and 6.1 μM.[56] In addition, **229** also possessed antiemetic,[121] antimycobacterial activities,[120] and significantly inhibited proliferation of Bel 7402 and L0-2 cells.[122] Investigation of *A. katsumadai* Hayata also led the isolation of

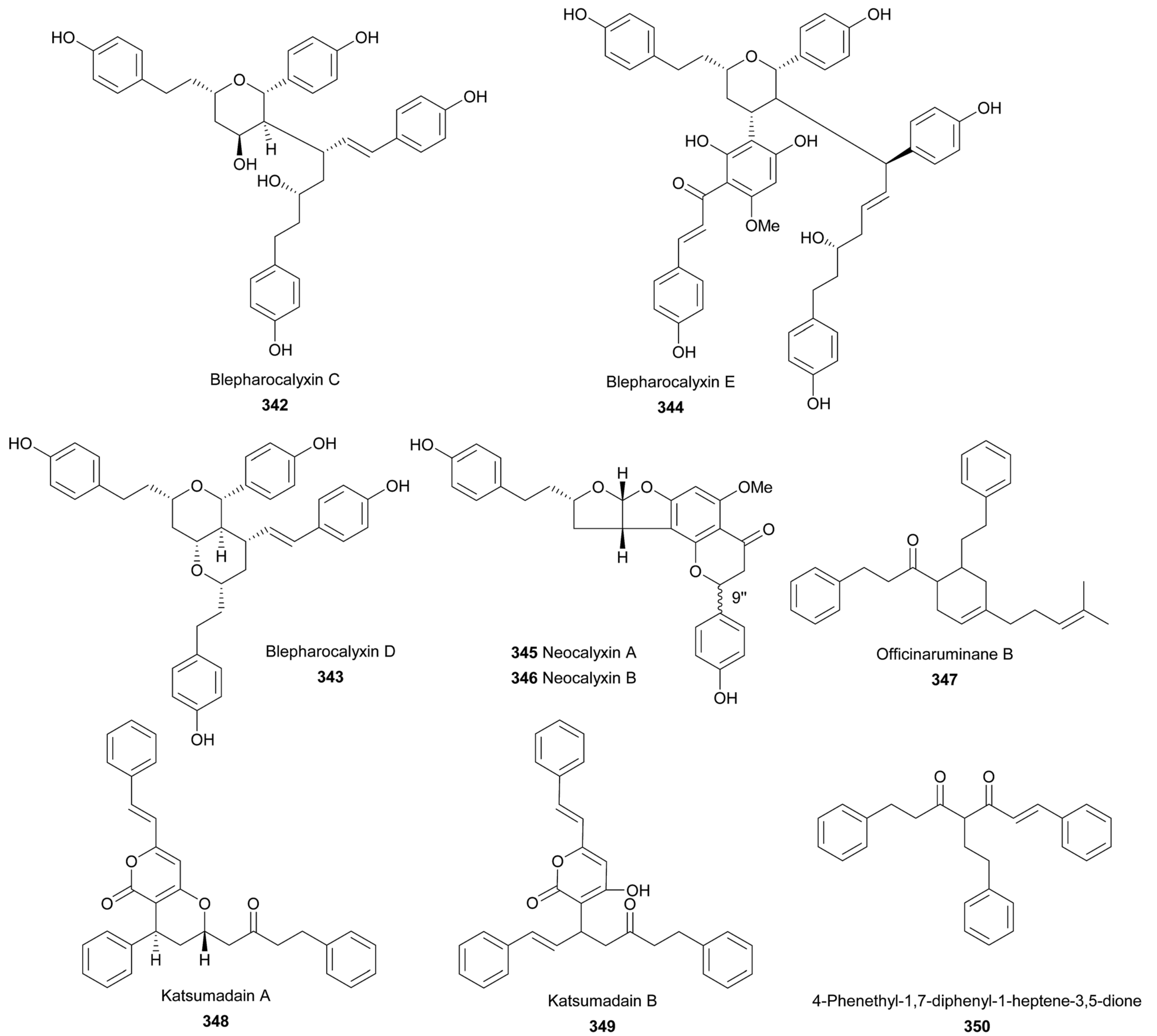


Fig. 5 Diarylheptanoids from *Alpinia* species (continued).

compounds **230–238**.[49,119,121,123–125] 1,7-Bis(4-hydroxyphenyl)-1,4,6-heptatrien-3-one (**239**) and bisdemethoxycurcumin (**240**) were obtained from rhizomes of *A. galanga* (L.) Willd, both of which significantly inhibited the proliferation of melanoma cells and indistinctively inhibited cellular tyrosinase.[126] A planar structure of 1,7-diphenyl-5-hydroxy-6-hepten-3-one (**241**) was reported from *A. nutans* Rosc.,[127] *A. rafflesiana* Wall.ex.Bak.,[128] and *A. officinarum* Hance.[129] While its enantiomers, 5*S* (**241a**) and 5*R* (**241b**) counterparts, were identified from *A. mutica* Roxb.[130] and *A. katsumadai* Hayata,[119] respectively. It was shown that a large amount of diarylheptanoids (**242–276**) were obtained from the rhizomes of *A. officinarum* Hance.[27,131–136] 7-(3,4-Dihydroxyphenyl)-1-(4-hydroxy-3-methoxyphenyl)-4-en-3-heptanone (**257**) displayed moderate cytotoxicity against human tumor cell lines of HepG2, MCF-7, and SF-268. While (4*E*,6*E*)-5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-7-phenylhepta-4,6-dien-3-one (**258**) showed weak cytotoxicity against two cancer cell lines of MCF-7 and T98G with IC_{50} values of 22.68 and 4.44 μM, respectively.[135] Meanwhile, **258–267** were proved to be inhibitors of *Helicobactor pylori* (Hp-Sydney and Hp-F44).[129] AO-5 (**263**) showed anti-inflammatory activity induced by 12-*O*-tetradecanoylphorbol-13-acetate (TPA), platelet-activating factor (PAF), and NO.[110,136,137] Moreover, it exhibited very weak cytotoxic activity against human glioblastoma T98G cells (IC_{50} = 27 μM).[138] The acetone extract of the rhizomes of *A. officinarum* Hance showed 5α-reductase inhibitory effect, which was superior to the drug used in the treatment of androgen-dependent disorders. Therefore, a bioactivity-guided isolation was performed and resulted in the isolation of **263–266** which exerted 5α-reductase inhibitory effect with IC_{50} values ranging from 220 to 390 μM, indicating potent usage in treating androgen-dependent diseases.[139] Besides, AO-1 (**266**) also showed anti-helicobacter pylori, hypolipidemic activities, and NO

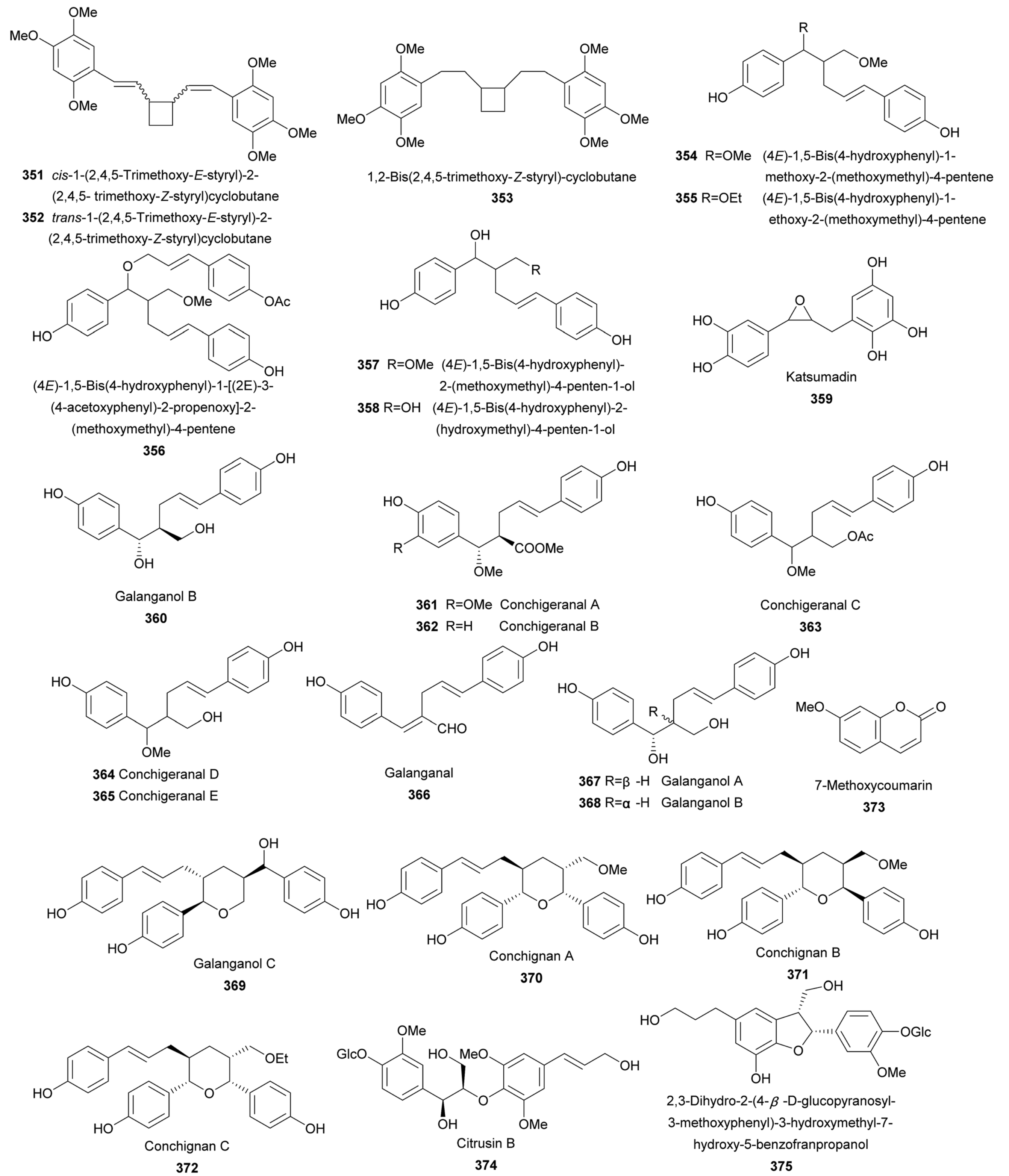


Fig. 6 Lignans from *Alpinia* species.

production inhibitory activity.[110,140,141] AO-2 (**267**) was identified as an inhibitor of prostaglandin (PG) biosynthesis and exerted anti-oxidant activity.[142,143] It is interesting to note that dihydroyashabushiketol (**264**), AO-1 (**266**), and AO-2 (**267**) were firstly reported as planar structures, and later, their absolute configurations were established as **264a**, **266a**, and **267a**, respectively.[136,144]

7-(4″-Hydroxy-3″-methoxyphenyl)-1-phenyl-3,5-heptadione (**268**) also exhibited prostaglandin biosynthesis inhibitory effect

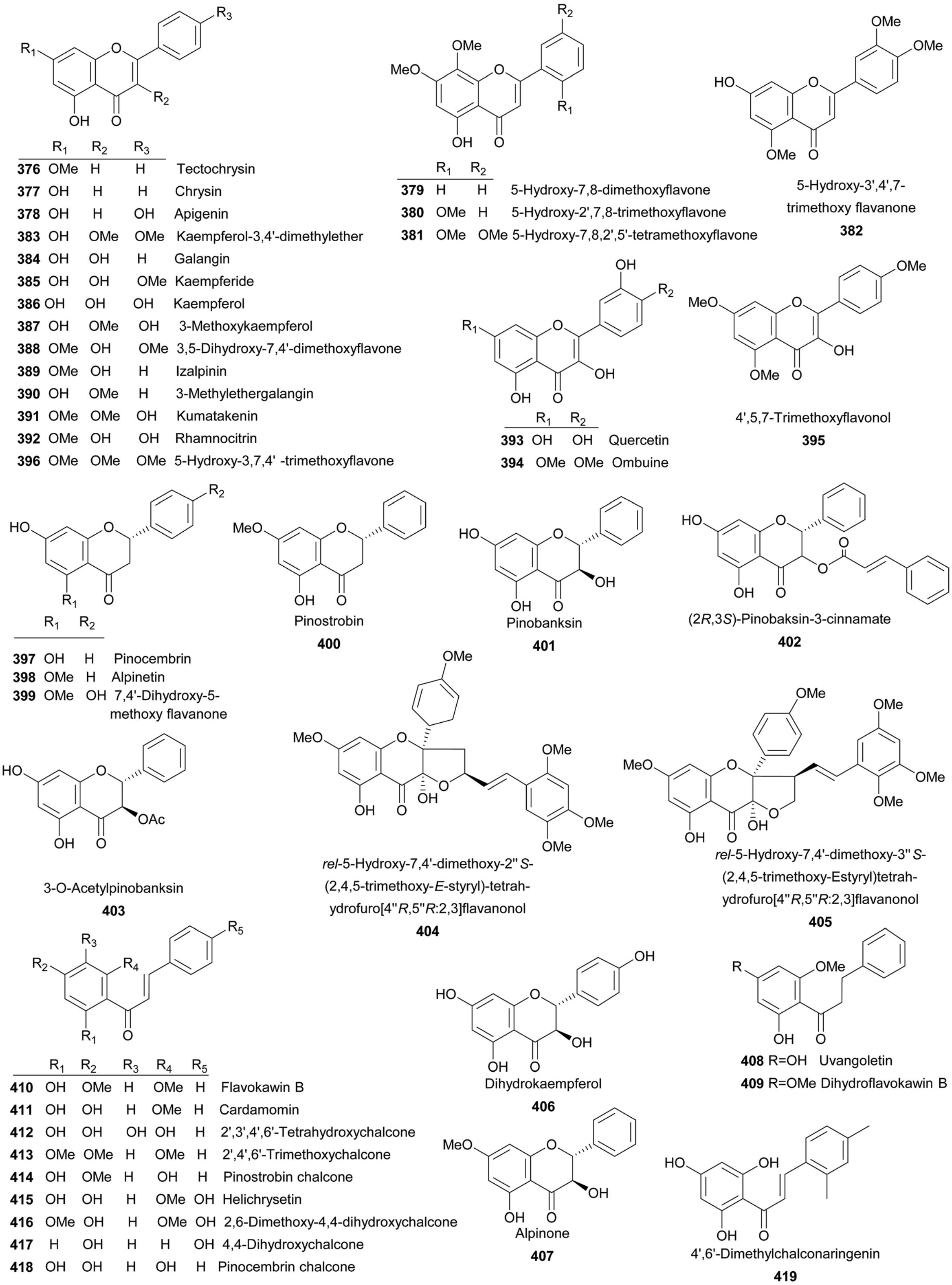


Fig. 7 Flavonoids from *Alpinia* species.

with IC_{50} values of 50 μM.[143] AO-4 (**269**) was found to have marked inhibitory effect on TPA-induced inflammation and antioxidant activity.[142,144] 6-Hydroxy-1,7-diphenyl-4-en-3-heptanone (**270**) was a PAF inhibitor.[137] AO-3 (**271**) and (5*S*)-5-methoxy-1,7-diphenyl-3-heptanone (**272**) displayed potent inhibitory effects on TPA-induced inflammation in mice with 50% of inhibition at a dose

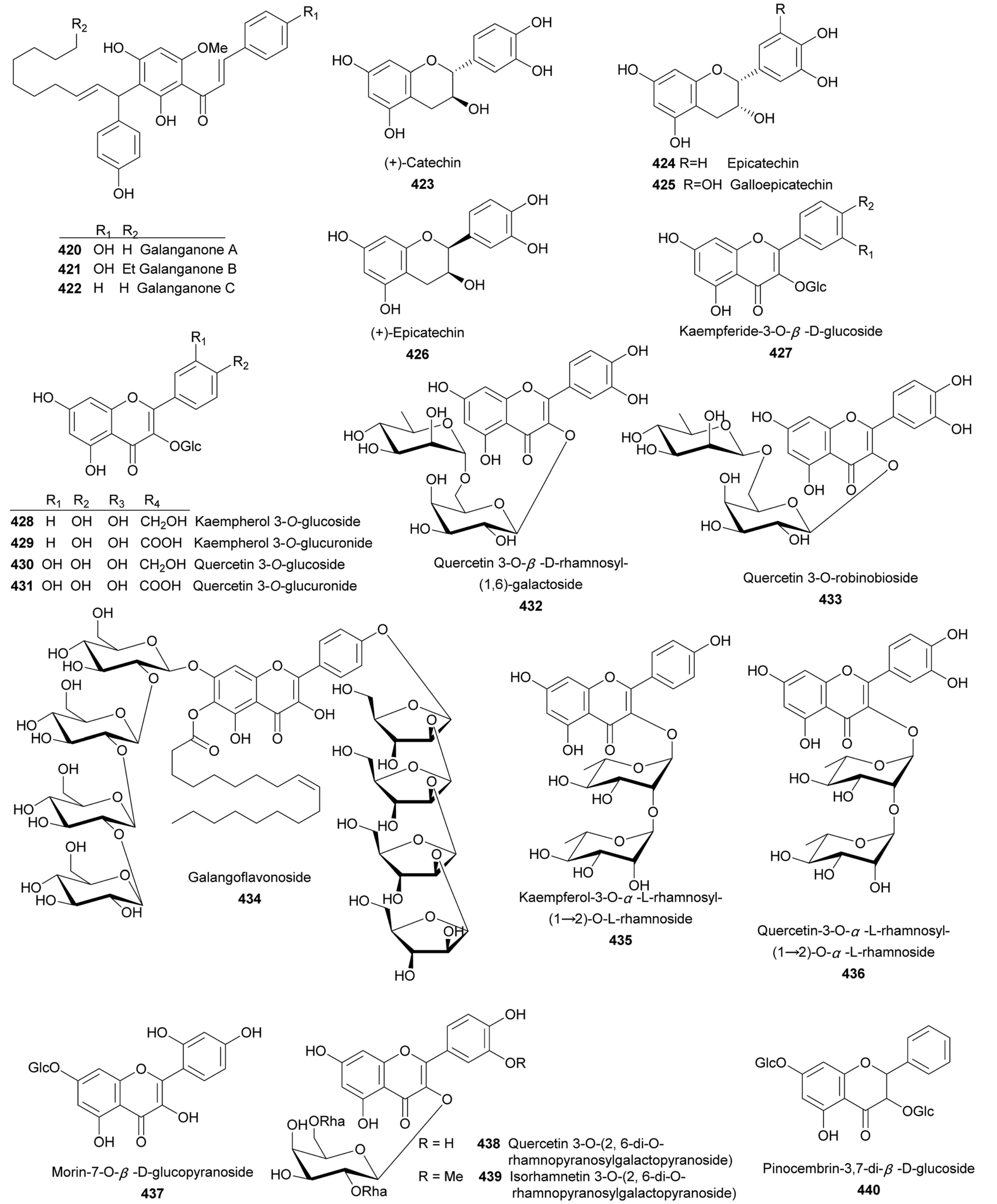
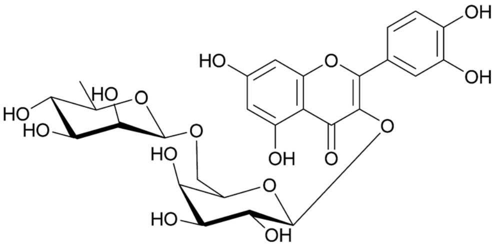


Fig. 7 Flavonoids from *Alpinia* species (continued).

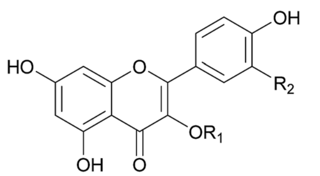
of 0.8–2.7 μmol per ear.[144] (3*R*,5*R*)-1-(4-Hydroxyphenyl)-7-phenyl-3,5-heptanediol (**273**) showed significantly antiemetic effect induced by $CuSO_4$ with 37.7% inhibition at a dose of 50 mg kg^{-1}.[27,145]

Investigation on seeds of *A. blepharocalyx* K. Schum. led to the isolation of ten cyclic diarylheptanoids (**274–283**).[115,146–148] Rhizomes of *A. officinarum* Hance provided 3,6-furan-7-(4″-

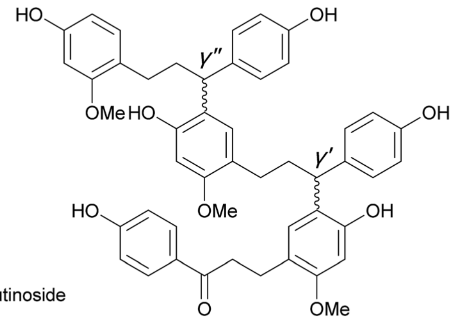


Isorhamnetin-3-O-β-D-galactosyl-(6→1)-α-L-rhamnoside

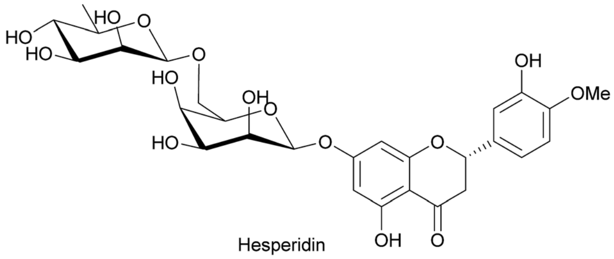
441



	R_1	R_2	
442	Rutinoside	OH	Rutin
443	Rutinoside	H	Kaempferol-3-O-rutinoside

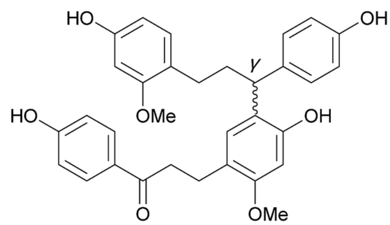


445a γ′-*S* γ″-*S*
445b γ′-*R* γ″-*R*



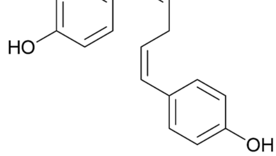
Hesperidin

444



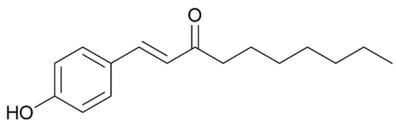
446a γ-*R*
446b γ-*S*

Fig. 7 Flavonoids from *Alpinia* species (continued).



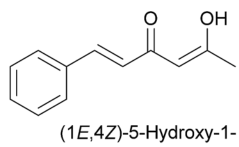
[Di-(*p*-hydroxy-cis-styryl)] methane

447



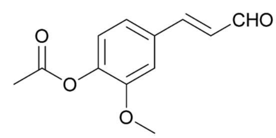
Alpininone

448



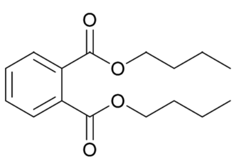
(1*E*,4*Z*)-5-Hydroxy-1-phenylhexa-1,4-dien-3-one

449



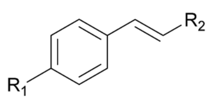
2-Propenal,3-[4-(acetyloxy)-3-methoxyphenyl]

450

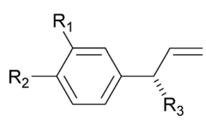


Dibutyl phthalate

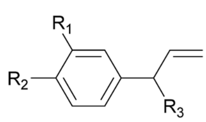
451



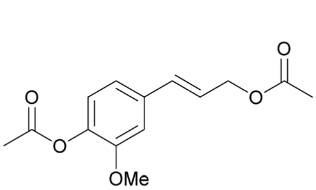
	R_1	R_2	
452	OH	CH_2OH	(*E*)-*p*-Coumary*l* alcohol
453	OH	CH_2OMe	(*E*)-*p*-Coumary*l* alcohol γ-O-methy*l* ether
454	OH	CHO	*trans-p-Hydroxy*cinnamaldehyde
455	OH	CH_2OAc	*trans-p*-Hydroxycinnamyl acetate
456	OH	CH_2OH	*trans-p-Coumaryl* alcohol
457	OAc	CH_2OAc	*trans-p-Coumaryl* diacetate
458	OAc	CH_2OH	*trans-p-Acetoxy*cinnamyl alcohol
459	OAc	CHO	*trans-p-Hydroxyl*cinnamaldehyde acetate
460	OH	COOH	*p*-Coumaric acid
461	H	COOMe	Methyl *trans*-cinnamate
462	OH	COOMe	Methyl *p*-hydroxy*c*innamate
463	OH	COMe	Methyl *p*-hydroxy*c*innamyl ketone



	R_1	R_2	R_3	
464	H	OAc	OAc	1′*S*-1′-Acetoxychavicol acetate
465	OMe	OAc	OAc	1′-Acetoxyeugenol acetate

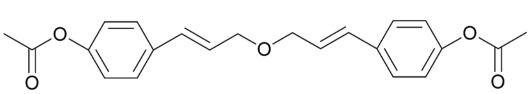


	R_1	R_2	R_3	
466	OMe	OMe	H	Methyleugenol
467	H	OAc	OH	Hydroxychavicol acetate



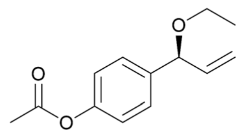
trans-Coniferyl diacetate

468



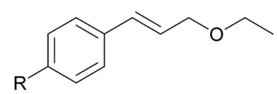
4,4′[(2*E*,2′*E*)-Bis(prop-2-ene)-1,1′-oxy]-diphenyl-7,7′-diacetata

469



(*S*)-1′-Ethoxy chavicol acetate

470



471 R=OCOMe (*E*)-4-Acetoxy cinnamyl ethyl ether
472 R=OH (*E*)-*p*-Coumaryl alcohol ethyl ether

Fig. 8 Phenolics from *Alpinia* species.

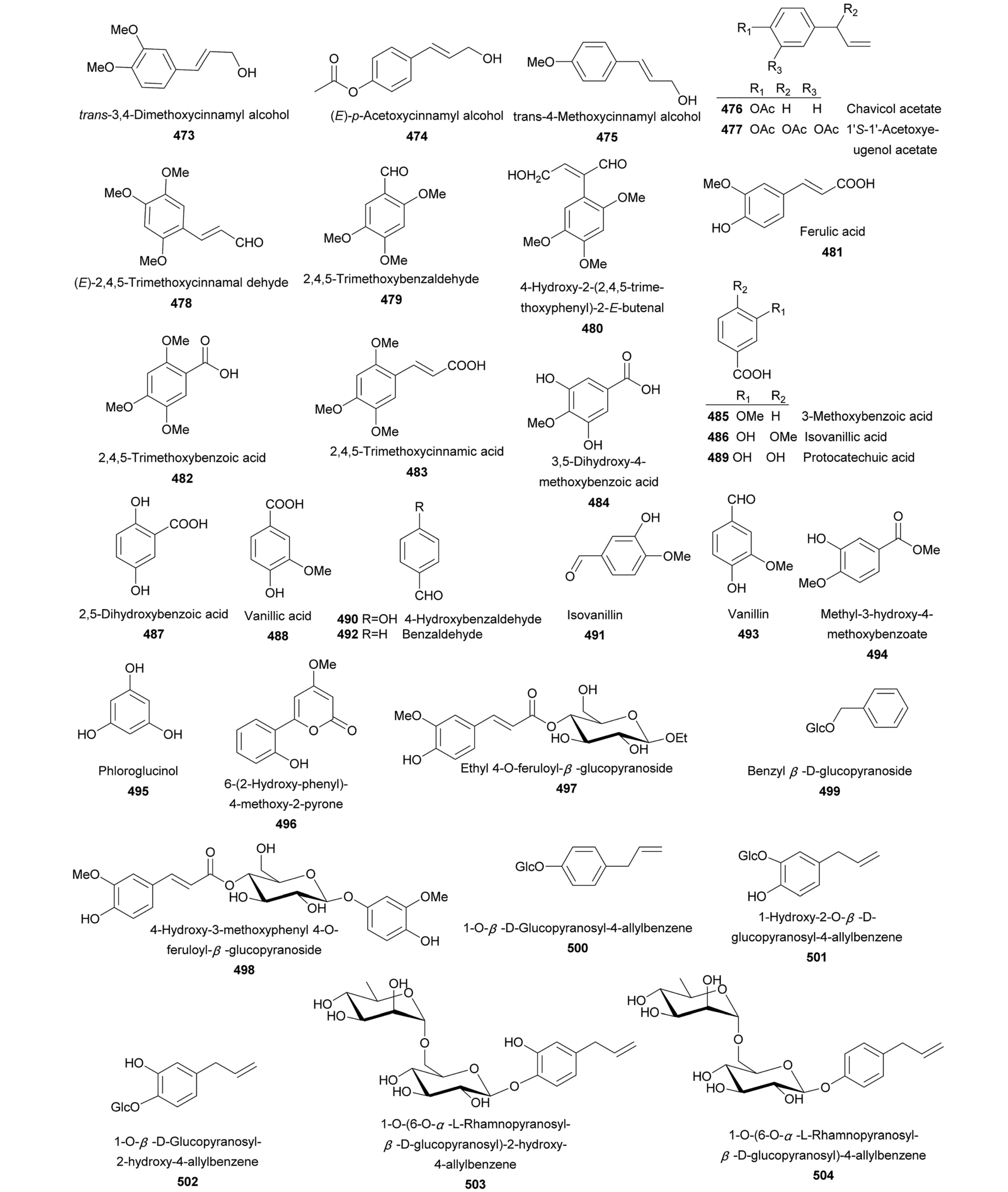


Fig. 8 Phenolics from *Alpinia* species (continued).

hydroxy-3″-methoxyphenyl)-1-phenylheptane (**284**).[131] From the seeds of *A. katsumadai*, **285–292** were obtained,[149] three of which (**285–287**) displayed weak antiproliferative activities against four cancer cell lines of NCI-H460, HeLa, SMMC-7721, and HCT-116 with IC_{50} values of 15.39–42.24 mM.[115,149] *A. blepharocalyx* K. Schum. was the source of **293–305**.[115,148,150,151] However,

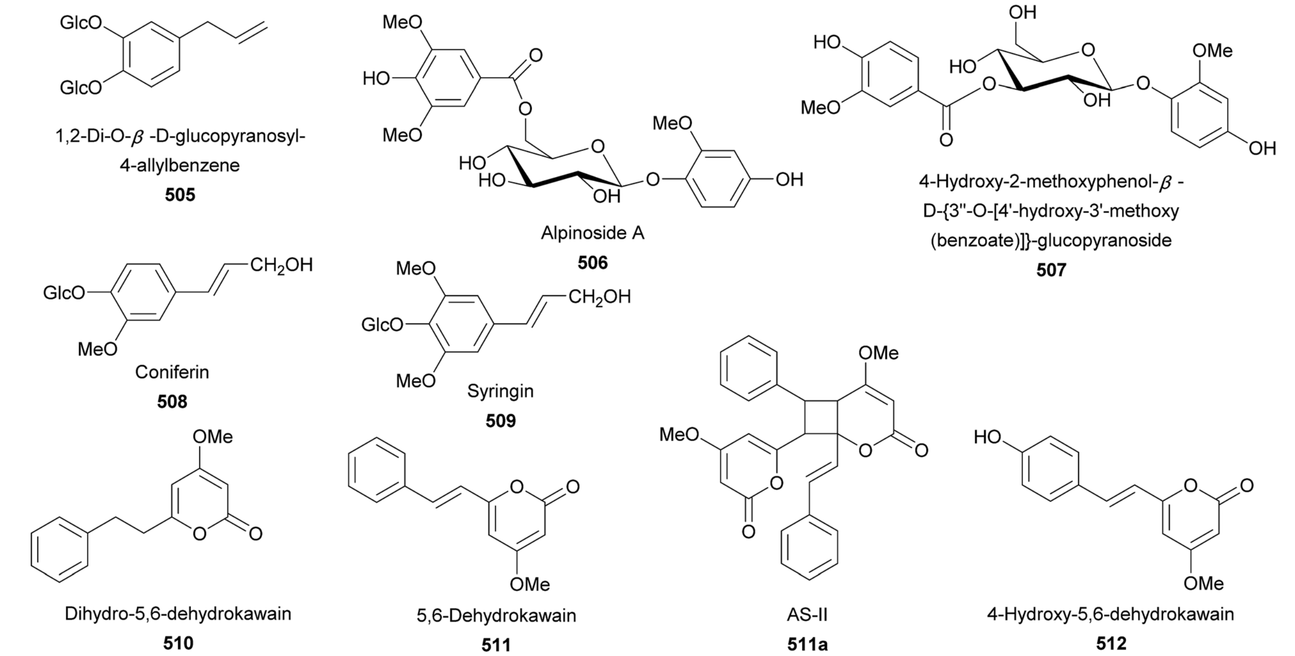


Fig. 8 Phenolics from *Alpinia* species (continued).

the stereochemistry at C-9″ of six stereoisomerics (**294**/**295**, **296**/**297**, **298**/**299**, **300**/**301**, **302**/**303**, **304**/**305**) remained unsolved. Calyxin J (**298**), epicalyxin J (**299**), calyxin K (**300**), and epicalyxin K (**301**) showed marked anti-proliferative activity against human HT-1080 fibrosarcoma cells with ED_{50} values from 0.3–8.2 μM.[115,152] Compounds **302–305** were proved to inhibit NO production in endotoxin activated murine macrophage J774.1 with 90–94% inhibitory rate at a concentration of 100 μg mL^{-1}.[151] Seeds of *A. katsumadai* Hayata provided **306–318**. Calyxins Q (**306**) and R (**307**) exerted potent antiproliferative activities against four cancer cell lines of NCI-H460, HeLa, SMMC-7721, and HCT-116 at the level of IC_{50} values of 15.3–42.2 μM.[149] Calyxin B (**319**) and epicalyxin B (**320**) were obtained from *A. blepharocalyx* K. Schum. and *A. pinnanensis* as NO production inhibitiors.[115,151] In addition, **319** showed potent anti-proliferative activity against human HT-1080 fibrosarcoma cells with an ED_{50} value of 0.69 μM.[148] Both *A. pinnanensis* T. L. Wu et Senjen and *A. katsumadai* Hayata yielded alpinnanin B (**321**).[118,124] From *A. katsumadai* Hayata and *A. blepharocalyx* K. Schum., epicalyxin H (**322**) and calyxin H (**323**) were isolated.[118,124,153] Epicalyxin H was identified as NO production inhibitor.[115,153] Seeds of *A. blepharocalyx* yielded **324–330**.[115,152,154] It's worth mentioning that all three structures of calyxin L (**325**), epicalyxin F (**327**), and calyxins F (**328**) in the Scifinder were wrong. Out of a serious of diarylheptanoids bearing a chalcone or a flavanone moiety, epicalyxins I (**326**), F (**327**), and calyxin F (**328**) were shown to possess strong anti-proliferative activities toward colon 26-L5 carcinoma and HT-1080 fibrosarcoma with IC_{50} values ranging from 0.5 to 10.1 μM.[115,150] Meanwhile, **326** and **327** were cytotoxic against human fibrosarcoma cells with IC_{50} values ranging from 0.9 to 12.1 μM.[152] 6-Hydroxycalyxin F (**329**) and calyxin A (**330**) demonstrated NO production inhibitory activities with IC_{50} values of 49 and 62 μM, respectively.[115,150] Rhizomes of *A. pinnanensis* T. L. Wu et Senjen provided deoxycalyxin A (**331**), alpinnanins A (**332**), and C (**333**).[118] In addition, **331** was also found in *A. blepharocalyx* K. Schum.[115] While officinin A (**334**) was obtained from rhizomes of *A. officinarum* Hance.[155]

Five dimeric diarylheptanoids (**335–339**) were obtained from rhizomes of *A. officinarum* Hance.[135,136,138,156,157] Only alpinin C (**338**) displayed selective cytotoxic against MCF-7 ($IC_{50} = 62.3$ μM) and T98G cells ($IC_{50} = 57.3$ μM).[135] Seeds of *A. blepharocalyx* K. Schum. provided **340–344** possessing two diarylheptanoid units and a chalcone moiety.[115,146,153] Both blepharocalyxins A (**340**) and B (**341**) showed concentration-dependent inhibition in the range of 1–100 μg mL^{-1} against NO production in endotoxin-activated murine macrophages J774.1.[158] Blepharocalyxins C–E (**342–344**) were tested for antiproliferative activities against two tested cancer cells, blepharocalyxin D (**343**) exhibited the strongest effect against highly liver-metastatic murine colon 26-L5 carcinoma cells ($ED_{50} = 3.6$ μM), whereas blepharocalyxin E (**344**) showed the strongest activity against human HT-1080 fibrosarcoma cells ($ED_{50} = 9.02$ μM).[115,146,159] It is worth mentioning that the stereochemistry at C-I-5 position for **343** in Scifinder was *S*, which was not correct and should be revised as *R*. Moreover, the two diarylheptanoid moieties in **344** were wrongly connected through C-I-6 and C-II-5 by Scifinder. Instead, it should be joined through C-I-6 and C-II-7. Two unusual diarylheptanoid derivatives, neocalyxin A (**345**) and its epimer neocalyxin B (**346**), were found from the seeds of *A. blepharocalyx* K. Schum., with the stereochemistry at C-9″ undetermined.[115,152]

Rhizomes of *A. officinarum* Hance produced officinaruminane B (**347**), a diarylheptanoid coupled with a monoterpene unit.[131] Investigation on seeds of *A. katsumadai* Hayata identified two novel anti-emetic diaryllheptanoids, katsumadains A (**348**) and B

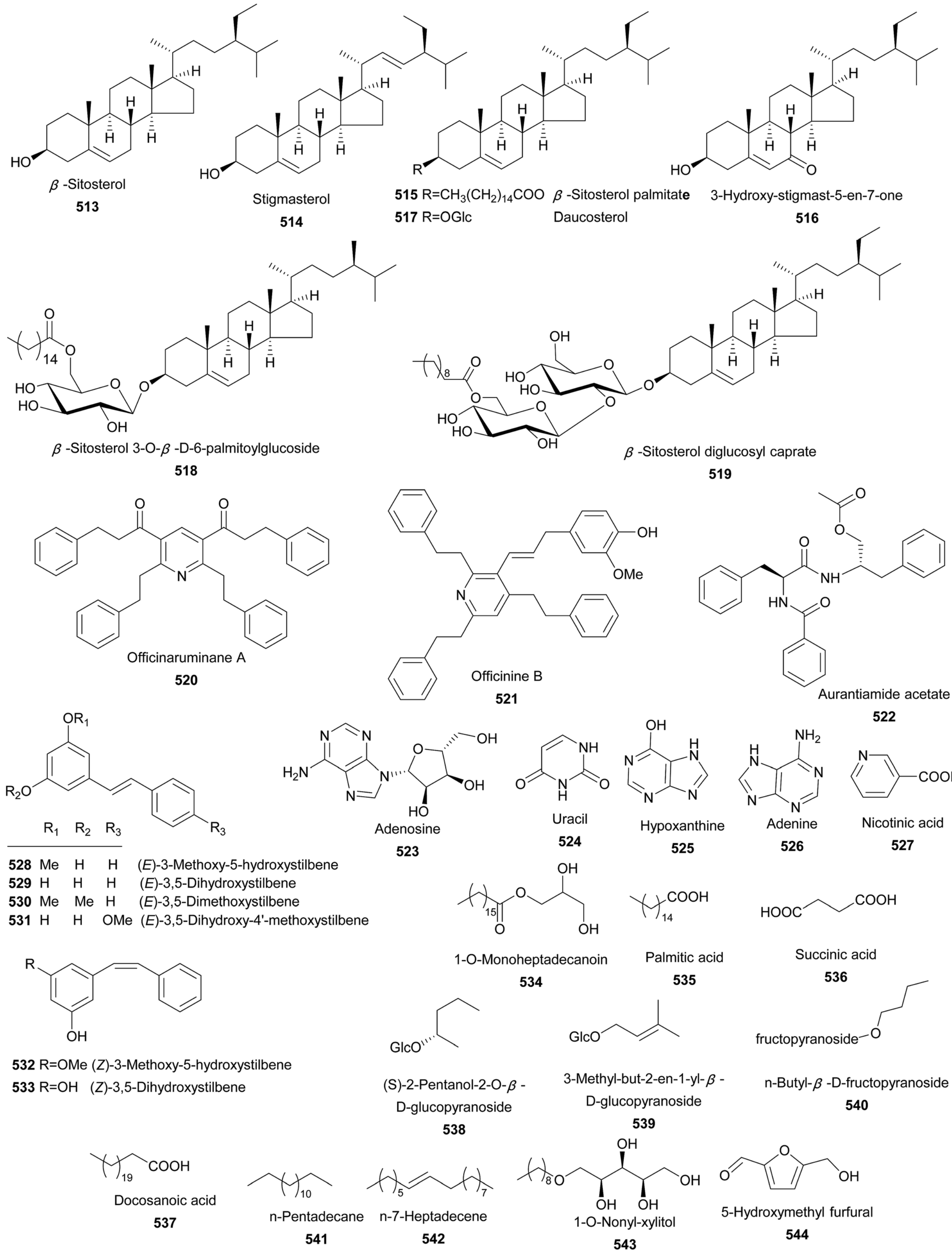


Fig. 9 Steroids, alkaloids, stilbenes, and other miscellaneous compounds from *Alpinia* species

(**349**).[160] Besides, **348** also exerted promising neuraminidase inhibitory effect against human influenza virus A/PR/8/34 (IC_{50} = 1.05 μM).[56] 4-Phenethyl-1,7-diphenyl-1-heptene-3,5-dione (**350**) was isolated from rhizomes of *A. officinarum* Hance. It exhibited weak antibacterial activity against Hp-Sydney and Hp-F44 with the MIC values of 23.6–31.4 and 78.5 μM, respectively.[129]

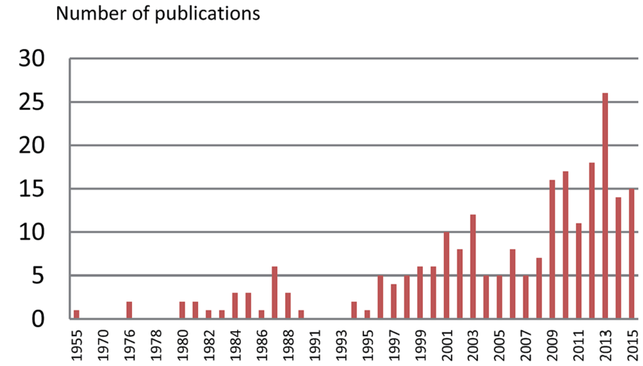


Fig. 10 The number of publications on *Alpinia* since 1955.

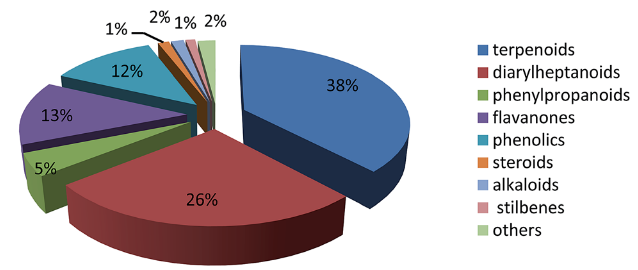


Fig. 11 The percentage of each type of compounds from *Alpinia* species.

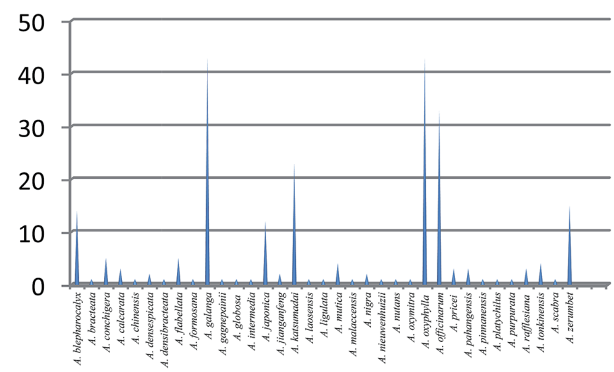


Fig. 12 The number of published papers for each investigated *Alpinia* species on chemical constituents and their bioactivities over last six decades since 1955.

4. Lignans

Twenty-four lignans (**351–374**) were reported from the genus of *Alpinia* (Fig. 6). Separation for leaves of *A. flabellata* Ridley resulted in the isolation of **351–353**, three phenylbutanoid dimers bearing a novel tetracyclic moiety.[161,162] cis-1-(2,4,5-Trimethoxy-*E*-styryl)-2-(2,4,5-trimethoxy-*Z*-styryl)cyclobutane (**351**) and *trans*-1-(2,4,5-trimethoxy-*E*-styryl)-2-(2,4,5-trimethoxy-*Z*-styryl)cyclobutane (**352**) showed weak antibacterial against *Staphylococcus aureus* with MIC values of 5.0 and 2.5 mM, respectively.[161] Furthermore, **351** significantly decreased the ovalbumin permeability in intestinal cells.[161]

Rhizomes of *A. officinarum* Hance yielded **354–358** containing a rare β–γ linkage. All five compounds exhibited weak antioxidant activities against the autoxidation of methyl linoleate in bulk phase.[163] Extracts of seeds of *A. katsumadai* Hayata afforded antiemetic katsumadin (**359**) with antiemetic activity on $CuSO_4$-induced emesis in young quail.[121] Galanganol B (**360**) was isolated from rhizomes of *A. galanga* (L.) Willd.[164] Investigation on the whole plant of *A. conchigera* afforded eight rare 8–9′ linked neolignans **361–368**.[165] Although conchigeranals D (**364**) and E (**365**) shared the same planar structure, their relative configurations were not be determined. Galanganal (**366**), galanganols A (**367**), and B (**368**) were also found from rhizomes of *A. galanga* (L.) Willd.[166] Compounds **361–367** exhibited significant cytotoxic activity against cancer Hela cells with IC_{50} values ranging from 1.5 to 5.29 μg mL^{-1}.[165] Interestingly, **366** and **368** also inhibited NO production in mouse peritoneal macrophages.[166] Galanganol C (**369**) was obtained from rhizomes of *A. galanga* (L.) Willd as a NO production inhibitor.[166] The whole plant of *A. conchigera* yielded three unusual sesquineolignans, conchignans A–C (**370–372**) bearing a tetrahydropyrane ring.[167] 7-Methoxycoumarin (**373**) is a coumarin known from *A. calcarata* Rosc.[85]

Citrusin B (**374**) and 2,3-dihydro-2-(4-β-D-glucopyranosyl-3-methoxyphenyl)-3-hydroxymethyl-7-hydroxy-5-benzofranpropanol (**375**) were the only two lignan glycosides isolated from leaves of *A. speciosa*.[168]

5. Flavonoids

To date, 71 flavanoides (Fig. 7) were isolated from the *Alpinia* species, including seven flavones (**376–382**), 14 flavonols (**383–396**), four flavanones (**397–400**), seven flavanonols (**401–407**), two dihydrochalcones (**408** and **409**), 13 chalcones (**410–422**), four flavanols (**423–426**), and 18 flavonoid glycosides (**427–444**), two flavonoid oligomers (**445** and **446**).

Tectochrysin (**376**) and chrysin (**377**) were isolated from *A. oxyphylla* Miq. and exhibited moderate anti-inflammatory activities against LPS-induced NO production in RAW264.7 macrophage cells.[169] Both *A. bracteata* and *A. officinarum* Hance produced apigenin (**378**), which displayed moderate activity on scavenging DPPH free radicals ($EC_{50} = 90 \pm 1.5$ μM).[170] *A. galanga* (L.) Willd was the source of **379–381** and *A. tonkinensis* Gagnep. produced 5-hydroxy-3′,4′,7-trimethoxy flavanone (**382**).[102,171] Kaempferol-3,4′-dimethylether (**383**) was afforded by *A. sichuanensis* Z. Y. Zhu.[52] Galangin (**384**) and kaempferide (**385**) were the major flavonols distributed in several plants of *Alpinia*, both of which exhibited inhibitory against penicillinase and potent antioxidant activities.[113,172] In addition, galangin effectively inhibited the TPA-induced invasion and migration of HepG2 cells at concentrations of 2.5–5 μM.[173] In 2001, a review summarized anti-genotoxic activity of galangin and demonstrated that galangin was a promising candidate for cancer chemoprevention.[174] Investigation on the whole plant of *A. sichuanensis* Z. Y. Zhu provided kaempferol (**386**).[52] From *A. speciosa*, *A. galanga* (L.) Willd, *A. katsumadai* Hayata, and *A. tonkinensis* Gagnep., 3-methoxykaempferol (**387**) was isolated.[175–178] While *A. flabellata* Ridley, *A. oxyphylla*, and *A.*

tonkinensis Gagnep. yielded 3,5-dihydroxy-7,4′-dimethoxyflavone (**388**).[113,161,171] Izalpinin (**389**) from different parts of *A. oxyphylla* Miq. was a NO production inhibitor and exhibited potent antioxidant activity.[113,176] From rhizomes of *A. officinarum*, 3-methylethergalangin (**390**) was identified as an inhibitor of pancreatic lipase with an IC_{50} value of 1.3 mg mL^{-1}.[179] Compounds **391–395** were mainly obtained from *A. tonkinensis* Gagnep.[171] 5-Hydroxy-3,7,4′-trimethoxyflavone (**396**) was yielded by leaves of *A. flabellata* Ridley.[180] Pinocembrin (**397**) and alpinetin (**398**) were distributed in several *Alpinia* species and both showed antiemetic activities.[121,181] In addition, **397** also demonstrated several bioactivities, such as cytotoxicity (on human T4 lymphoblastoid cancer cells),[182] anti-inflammation,[169] and antiplatelet aggregation *etc.*[183] While, **398** was a PAF receptor binding inhibitor.[184] 7,4′-Dihydroxy-5-methoxy flavanone (**399**), pinostrobin (**400**) were reported from several species.[116,118,128,182] Pinobanksin (**401**), (2*R*,3*S*)-pinobaksin-3-cinnamate (**402**), and 3-*O*-acetylpinobanksin (**403**) were mainly obtained from *A. galanga* (L.) Willd and *A. katsumadai* Hayata.[176,177,185] Compound **402** showed potent neuroprotective effect against PC12 cells.[177,186] Leaves of *A. flabellata* Ridley provided **404** and **405**.[180] Dihydrokaempferol (**406**) were isolated from *A. oxyphylla*.[169] Both *A. japonica* (Thunb.) Miq. and *A. galanga* (L.) Willd were sources for alpinone (**407**).[176,187] From seeds of *A. katsumadai* Hayata, a dihydrochalcone uvangoletin (**408**) was isolated.[108] *A. speciosa* K. Schum. and *A. formosana* afforded another dihydrochalcone, dihydroflavokawin B (**409**).[81,188] Flavokawin B (**410**) was isolated from several plants and showed strong cytotoxicity against human T4 lymphoblastoid cancer cells (IC_{50} = 6.5 μM) and anti-inflammatory activity.[182,189] Cardamomin (**411**) distributed in many *Alpinia* species[100,118,123,188,190] and exhibited extensive bioactivities including death receptor 5 (DR5) promotor,[175] antimicrobial,[191] antiemetic,[121] anticoagulation,[183] and anti-inflammation.[128] Interestingly, it also protected septic mice from acute lung injury by preventing endothelial barrier dysfunction.[192] 2′,3′,4′,6′-Tetrahydroxychalcone (**412**), which was obtained from *A. rafflesiana* Wall.ex.Bak., was potently active to DPPH free radical scavenging (IC_{50} = 55 μM).[128] Rhizomes of *A. pricei* Hayata yielded 2′,4′,6′-trimethoxychalcone (**413**) and pinostrobin chalcone (**414**).[189] Compounds **415–417** were isolated from the seeds of *A. blepharocalyx* K. Schum.,[116,117] while helichrysetin (**415**) was also found in *A. katsumadai* Hayata.[108] Pinocembrin chalcone (**418**) and 4′,6′-dimethylchalconaringenin (**419**) were provided by *A. katsumadai* Hayata and *A. pinnanensis* T. L. Wu et Senjen, respectively.[118,181] Compound **418** was also isolated from *A. platychilus*.[193] Galanganones A–C (**420–422**) were three novel chalcones bearing a long-chain alkylphenol from *A. galanga*.[194] Whilst *A. katsumadai* Hayata and *A. zerumbet* (Pers.) B. L. Burttet Smith. provided (+)-catechin (**423**).[195,196] Epicatechin (**424**) and galloepicatechin (**425**) were yielded by *A. oxymitra* K. Schum.[75] (+)-Epicatechin (**426**) was isolated from *A. speciosa* K. Schum. and displayed antioxidant activity.[197] Kaempferide-3-*O*-β-D-glucoside (**427**) from *A. officinarum* Hance had an weak inhibitory activity against penicillinase.[172] Study on *A. speciosa* K. Schum. lead to the isolation of **428–432**.[198] Quercetin 3-*O*-robinobioside (**433**) and galangoflavonoside (**434**) were obtained from *A. katsumadai* Hayata and *A. galanga* (L.) Swartz., respectively.[196,199] Compounds **435–437** from *A. densespicata* Hayata exhibited moderate NO inhibitory activities.[103] Compounds **438–440** were obtained from the seeds of *A. katsumadai* Hayata and isorhamnetin-3-*O*-β-D-galactosyl-(6 → 1)-α-L-rhamnoside (**441**) was isolated from rhizomes of *A. tonkinensis* Gagnep.[51,196] Leaves of *A. zerumbet* (Pers.) B. L. Burttet Smith. contained rutin (**442**) and kaempferol-3-*O*-rutinoside (**443**).[195] The whole plant of *A. sichuanensis* Z. Y. Zhu yielded hesperidin (**444**).[52] Two pairs of enantiomers of flavonoidoligomers (**445a** and **445b**, **446a** and **446b**) were found from rhizomes of *A. platychilus*. The compounds mixture of **446a** and **446b** showed anticoagulant activity on the prolongation of both prothrombin times (PT) and the thrombin times (TT) with a dose-effect relationship at 6.25–100 mM.[193]

6. Phenolics

A total number of 66 phenolics (**447–512**) were obtained from *Alpinia* species (Fig. 8). [Di-(*p*-hydroxy-cis-styryl)]methane (**447**) was obtained from *A. galanga* (L.) Willd.[200] Whist alpininone (**448**) was isolated from *A. gagnepainii* K. Schum. with antibacterial effect against *E. coli*, *B. subtilis*, and *S. aureus* with the same MIC value of 12.5 μg mL^{-1}.[191] (1*E*,4*Z*)-5-Hydroxy-1-phenylhexa-1,4-dien-3-one (**449**) and 2-propenal, 3-[4-(acetyloxy)-3-methoxyphenyl] (**450**) were provided by *A. katsumadai* Hayata and *A. galanga* (L.) Willd, respectively.[86,108] From *A. sichuanensi* and *A. oxyphylla*, dibutyl phthalate (**451**) was isolated.[52,201] Two compounds named as (*E*)-*p*-coumaryl alcohol (**452**) and (*E*)-*p*-coumaryl alcohol γ-*O*-methyl ether (**453**) exhibited potent inhibitory activities against the autoxidation of methyl linoleate in bulk phase.[163] In addition, compound **453** exerted potent cytotoxic activity against the SNU638 cells with IC_{50} value of 1.62 μg mL^{-1}.[202]

A. galanga (L.) Willd and *A. conchigera* Griff. produced *trans*-*p*-hydroxycinnamaldehyde (**454**) and *trans*-*p*-hydroxycinnamyl acetate (**455**).[170,203] Compound **454** displayed weak antiallergic effect,[204] and NO production inhibitory activities (IC_{50} = 20 μM),[166] and **455** exerted no inhibitory activity towards *Staphylococcus aureus* strain VISA (MIC = 203 mM).[82] *trans*-*p*-Coumaryl alcohol (**456**) was a weak NO production inhibitor from *A. galanga* (L.) Willd (IC_{50} = 72 μM).[166] *trans*-*p*-Coumaryl diacetate (**457**) from *A. galanga* showed a number of bioactivities, including anti-allergy,[204] efflux pump inhibition,[205] NO production inhibition,[166] xanthine oxidase inhibition,[206] antileishmania,[164] cytotoxicity,[203] and antibacteria.[82] *trans*-*p*-Acetoxycinnamyl alcohol (**458**), *trans*-*p*-hydroxylcinnamaldehyde acetate (**459**), and *p*-coumaric acid (**460**) were obtained from rhizomes of *A. galanga* (L.) Willd.[164,205] In addition, compound **460** was also distributed in *A. galanga* (L.) Willd,[164] *A. sichuanensis* Z. Y. Zhu,[52] *A. speciosa*,[198] *A. blepharocalyx* K. Schum.,[116] and *A. oxyphylla*.[169] Both *A. formosana* and *A. speciosa* K. Schum. were sources of methyl *trans*-cinnamate (**461**).[81,188] Seeds of *A. blepharocaly* yielded methyl *p*-hydroxycinnamate (**462**) and methyl *p*-hydroxycinnamyl ketone (**463**).[116] From rhizomes of *A. galanga* (L.) Willd, 12 compounds (**464–475**) were obtained.[33,82,203,207] Among them, 1*S*-1′-acetoxychavicol acetate (**464**) and 1-acetoxyeugenol acetate (**465**) were the most abundant phenylpropanoids presented in *A. galanga* (L.) Swartz., *A. officinarum* Hance, and *A. conchigera* Griff. They were reported to have anti-ulcer,[24] antileishmanial,[164] and antitumor bioactivities,[33,202,208] Furthermore, **464** also showed antiallergic,[204] efflux pump inhibitory,[205] NO production inhibitory,[166] xanthine oxidase inhibitory,[206] gastroprotective,[209] anti-HIV,[210] anti-cancer,[86] antibacterial,[30,211] plant growth-inhibitory and fungal growth-inhibitory activities.[212] Two compounds, methyleugenol (**466**) and hydroxychavicol acetate (**467**), were isolated from *A. galanga* (L.) Willd.[82,164,166,204,211] It was demonstrated that **467**, a chavicol acetate analogue, suppressed T-bet expression in Th cells.[211] Besides, **467** also showed weak antibacterial activity against *Staphylococcus aureus* strain VISA (MIC = 0.8 mM).[82] *trans*-Coniferyl diacetate (**468**) was proved to be a xanthine oxidase inhibitor.[206] Three new phenolics **469**, **470**, and **471**, along with four known ones **472–475** were also yielded by *A. galang*.[33,203,207] Chavicol acetate (**476**) and 1′*S*-acetoxyeugenol acetate (**477**) were two known phenolics found from *A. conchigera* Griff.[82] Compound **477** possessed antibacterial,[82] xanthine oxidase inhibitory,[206] gastroprotective,[209] and anti-cancer activities.[86] Investigation on leaves of *A. flabellata* Ridley provided **478–480**, with strong antibacterial activities against *Staphylococcus aureus*.[161,162,180] Compounds **481–489** were nine phenolic acids isolated from several *Alpinia* species.[52,89,122,180,198,213,214] Protocatechuic acid (**489**) showed potent neuroprotective effect on MPP$^+$-induced neurotoxicity and H_2O_2-induced oxidative damage in PC12 cells.[215–219] In addition, it also exerted anti-aging effect on spleen and liver antioxidative system of senescent mice.[31] 4-Hydroxybenzaldehyde (**490**), isolated from *A. sichuanensis* Z. Y. Zhu, *A. blepharocalyx* K. Schum., *A. bracteata*, and *A. galanga* (L.) Willd,[52,116,117,166,170] didn't show any DPPH radical-scavenging activity. Instead, it exhibited inhibitory activity on xanthine oxidase (IC_{50} = 19.6 μM).[170,206] Compounds **491–496** were provided by several *Alpinia* plants.[52,84,137,167,220]

Ethyl 4-*O*-feruloyl-β-glucopyranoside (**497**) and 4-hydroxy-3-methoxyphenyl 4-*O*-feruloyl-β-glucopyranoside (**498**) were two new glucoside esters of ferulic acid from rhizomes of *A. speciosa*, both of which showed antioxidant activities.[197] Investigation on rhizomes of *A. officinarum* Hance yielded **499–506**.[55] While from rhizomes of *A. bracteata*, a new phenolic glycoside (**507**) was isolated and showed moderate antioxidant activity on scavenging DPPH free radicals (EC_{50} = 169 ± 4.8 μM).[170] Leaves of *A. speciosa* K. Schum. provided coniferin (**508**) and syringin (**509**).[168]

Dihydro-5,6-dehydrokawain (**510**) and 5,6-dehydrokawain (**511**) were major chemical constituents in several *Alpinia* species.[81,100,128,175,188,221] They showed antiulcerogenic, antithrombotic,[195] antifungal,[191] anti-obesity,[222] and plant growth inhibitory activities.[223] Recently, it was reported that they could strongly inhibit HIV-1 integrase with respective IC_{50} values of 4.4 and 3.6 μg mL^{-1}. In addition, they exhibited mixed type of inhibition against neuraminidase with both IC_{50} values of 25 μM.[95] Furthermore, **511** was also reported as a slow and time-dependent reversible inhibitor of neuraminidase, a moderated antioxidant, a strong inhibitor of skin diseases-related enzymes, and strong antiplatelet inhibitor.[95,127,224] Interestingly, a dimer of 5,6-dehydrokawain, AS-II (**511a**), was an artifact formed by photo-irradiation during the isolation procedure of *A. speciosa* K. Schum. leaves.[223] 4-Hydroxy-5,6-dehydrokawain (**512**) was an α-pyrone isolated from *A. blepharocalyx* K. Schum. It displayed antiproliferative activity against murine colon 26-L5 carcinoma and human HT-1080 fibrosarcoma with ED_{50} 20.7 and 20.1 μM, respectively.[116,117] It also showed inhibitory effect on platelet aggregation induced by collagen, arachidonic acid (AA), adenosine diphosphate, and ristocetin.[96]

7. Steroids

Seven steroids (Fig. 9) were isolated from *Alpinia* species including four cholestanes (**513–516**) and three sitosterol glycosides (**517–519**).[27,52,89,116,118,225] As it is the same in plants of the other genera, β-sitosterol (**513**) and stigmasterol (**514**) were also widely distributed in *Alpinia* species.[52,82,89,118,178,191,226–228] β-Sitosterol-3-*O*-β-D-6-palmitoylglucoside (**518**) showed potent antiemetic activity induced by $CuSO_4$.[27]

8. Alkaloids

Officinaruminane A (**520**) and officinine B (**521**), two alkaloids of bi-diarylheptanoid connecting by a pyridine ring were contributed by rhizomes of *A. officinarum* Hance.[131,157] A study on seeds of *A. katsumadai* Hayata afforded another six alkaloids (**522–527**) (Fig. 9).[108,196]

9. Stilbenes

Six stilbenes, **528–533** (Fig. 9), were all isolated from aerial parts of *A. katsumadai* Hayata.[29,121]

10. Others

One esters (**534**) and three fatty acids, **535–537**, were isolated from several *Alpinia* species.[64,227–229] (*S*)-2-Pentanol-2-*O*-β-D-glucopyranoside (**538**), which showed inhibitory effect on NO production from LPS-activated RAW264.7 macrophage cells, was obtained from fruits of *A. oxyphylla*.[89] Two glycosides known as 3-methyl-but-2-en-1-yl-β-D-glucopyranoside (**539**) and *n*-butyl-β-D-fructopyranoside (**540**) were isolated from *A. officinarum* Hance.[55,230] While **541–544** were found in different *Alpinia* species (Fig. 9).[24,51,108,196,201] Interestingly, 5-hydroxymethylfurfural (**544**) exerted memory improvement activity against Alzheimer's disease (AD) by mitigating the degree of neuronal damage.[231]

11. Conclusions

The number of publications on the chemical constituents and their bioactivities for *Alpinia* species from 1955 to 2015 are shown in Fig. 10. Before 1999, fewer investigations (less than five per year, except six in 1987) were performed on this genus. However, after 2009, there were more than 10 papers published for each year. In 2013, the number of published articles reached 26, indicating a growing interest in the genus of *Alpinia*.

Till 2015, investigations on chemical constitutes of the *Alpinia* species afforded a total of 544 compounds, including 207 terpenoids, 143 diarylheptanoids, 25 phenylpropanoids, 71

Table 1 The number of new compounds isolated from each *Alpinia* species since 1955

Sources of new compounds	Terpenoids	Diarylheptanoids	Lignans	Flavanoids	Phenolics	Sum
A. blepharocalyx	—	45	—	—	—	45
A. bracteata	—	—	—	—	1	1
A. conchigera	—	—	11	—	—	11
A. calcarata	6	—	1	—	—	7
A. chinensis	10	—	—	—	—	10
A. densibracteata	1	—	—	—	—	1
A. densespicata	6	—	—	—	—	6
A. flabellata	1	—	3	2	1	7
A. formosana	1	—	—	—	—	1
A. galanga	4	—	—	5	4	13
A. gagnepainii	—	—	—	—	1	1
A. intermedia	8	—	—	—	—	8
A. japonica	14	—	—	—	—	14
A. katsumadai	2	29	1	—	1	33
A. nigra	1	—	—	—	—	1
A. oxymitra	1	—	—	—	—	1
A. officinarum	1	18	5	—	6	30
A. oxyphylla	41	2	—	—	—	43
A. pahangensis	5	—	—	—	—	5
A. pinnanensis	—	2	—	—	—	2
A. rafflesiana	—	—	—	1	—	1
A. tonkinensis	2	—	—	—	—	2
A. zerumbet (*A. speciosa*)	2	—	—	—	2	4
Sum	106	96	21	8	16	247

flavanones, 66 phenolics, seven steroids, eight alkaloids, six stilbenes, and 11 others (Fig. 11). Among 207 terpenoids, 17 are monoterpenoids, 132 are sesquiterpenoids, 57 are diterpenoids, and the rest one is a triterpenoid. For sesquiterpenoids, eudesmanes and eremophilanes are undoubtedly predominant with 44 and 21 components, respectively. While for diterpenoids, almost all are labdanes.

Amongst 544 isolated compounds from the genus of *Alpinia*, 247 are new ones (Table 1), including 96 diarylheptanoids and 106 terpenoids. Obviously, diarylheptanoids, especially diarylheptane–flavonoids conjugates, are characteristic components for the genus of *Alpinia*.[149]

The crude extracts of *Alpinia* species and their chemical constituents were found to possess various biological activities. Mainly reported were antiemetic,[26,27] antibacterial,[29–31,37,82,232–236] antioxidant,[127,237–239] anticancer,[32–34,240–245] anti-inflammatory,[189,246,247] insecticidal,[36,164] and neuroprotective bioactivities.[38,39,231,248–250]

In addition, they also showed antiulcer,[25] antiplatelet,[117,183] hepatoprotective,[251] and hypolipidemic effects.[252] Meanwhile, evidences showed that ethanol extract of *A. galangal* can retard lipid oxidation for minced beef, indicating a great potential utility for food storage.[8] What should be aroused considerable interest was the promising anticancer and hepatoprotective properties, which could be a great potential to be developed as herbal medicines.

Although there are about 230 species for the *Alpinia* genus, only 35 were investigated for their chemical constituents and bioactivities (Fig. 12), because *A. jianganfeng* T. L. Wu includes *Alpinia sichuanensis* Z. Y. Zhu, and *A. zerumbet* (Pers.) B. L. Burtt & R. M. Sm. includes *A. speciosa* K. Schum. according to The Plant List. Among these species, *A. galanga*, *A. oxyphylla*, *A. officinarum*, and *A. katsumadai* are four most studied plants with referenced papers of 43, 40, 32, and 23, respectively. While for the rest of 31 species, only very fewer articles were published, most of which were less than five. As a matter of fact, there was even only one paper published for 18 species. Although this genus contributed a diverse array of bioactive compounds, the potential of *Alpinia* species remains virtually untapped. Thus, much attention should be paid to *Alpinia* species on further phytochemical and pharmacological studies, which would produce structurally interesting and biologically active compounds with potential use in agricultural and medicinal applications. In addition, although most of *Alpinia* species were also used as edible plants, the nutritious components and their effects were seldom investigated, which could be a hotspot in the near future.

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