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

Xiao-Ni Ma, Chun-Lan Xie, Zi Miao, Quan Yang and Xian-Wen Yang

*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-aminergic, anticancer, etc.

1. Introduction

The genus *Alpinia* is an important member of the Zingiberaceae family. It includes ca. 230 species. 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. 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; *A. blepharocalyx* K. Schum. is a natural dye; *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 and in the preparation of beverages in Europe; and *A. officinarum* Hance, listed as medicinal and edible food by the Chinese Ministry of Health, are used in medicinal diets, wines, sauces, and flavorings. Moreover, *A. galanga* (L.) Willd is also applied to preserve food and fruits. 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, enterocolitis etc. Thus, a growing investigation on the chemical constituents and bioactivities of this genus has been carried out since 1955. Consequently, *Alpinia* species were proved to have various biological activities including antiulcer, antiemetic, antibacterial, antitumor, hypoglycemic, cardioprotective, antifungi, neuroprotection, and antianxiety activities.

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 C NMR spectroscopic data of 307 naturally occurring diarylheptanoids, which were mainly isolated from *Alpinia* species. 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. galanga*, it actually collected all reported compounds including volatile oil. In 2012, structural characterization and biological effects of compounds from the seeds of *A. katsumadai* was described. Sixty compounds were reported together with their structures and bioactivities with 18 references. In 2013, chemical constituents in fruits of *A. oxyphylle* 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, antianxiety, anti-aging, anti-inflammatory, and anti-anaphylaxis. 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. 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*. In addition, the isolation, synthesis, and characterization of dihydro-5,6-dehydrokavain, the major constituent of *A. zerumbet* were also reviewed. However, so far there has been no comprehensive review for chemical constituents of this species. Herein, we describe all isolated compounds and their
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 monoterpenene–chalcone conjugates obtained from *A. katsumadai*.36 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 IC50 value of around 40.0 μM.44 *A. katsumadai* Hayata yielded a new monoterpene–kavalactone conjugate, katsumadain (4) and a new (E)-1-(1-terpinen-4-olyl)-3-methoxytellinene (5).49 While *A. densibracteata* T. L. Wu and Senjen yielded two diastereoisomers of cinnamate esters, 217 were three hydroxyl-1,8-cineole glucopyranosides, which were isolated.25

Two endoperoxides, (1S,4R,6R)-1,4-epidioxy-p-menth-2-ene (9) and (1R,4S,6R)-1,4-epidioxy-p-menth-2-ene (10), were isolated from aerial parts of *A. densibracteata* T. L. Wu and Senjen.49 Whilst (3R,4R,6S)-3,6-dihydroxy-1-methene (11) and 1-terpinen-4-ol (12) were obtained from *A. szechuanae* Z. Y. Zhu (a synonym of *A. jiangangfeng* T. L. Wu) and *A. katsumadai* Hayata, respectively.49,52 Fruit of *A. oxyphylla* Miq. was the source of (1R,2R)-p-menth-3-en-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).49 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), carabane (143), oplopane (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 (IC50 = 81.4 μM).56 Nerolidol (19), another acyclic sesquiterpene, was obtained from rhizomes of *A. japonica*.57

Investigations on fruits of *A. oxyphylla* Miq. afforded 16 eremophilanes (20–35). Epinoottkatol (29) and nootkatone (30) displayed insecticidal activities against larvae and adults of *Drosophila melanogaster* with IC50 values of 11.5 μM and 96 μg per adult, respectively.28 While 9β-hydroxynootkatone (31), (11S)-12-chloronootkaton-11-ol (32), and (11R)-12-chloronootkaton-11-ol (33) displayed anti-acetylcholinesterase (AChE) activities by TLC-bioautographic assays.29,30 12-Nornerootkaton-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.31 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,58,59 whilst nootkatene (38), valencene (39), and dehydro-nootkatone (40) were all identified from *A. oxyphylla* Miq.56,57

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.60 Oxyphyllone A displayed moderate anti-AChE activity.59 Also obtained from *A. oxyphylla* Miq. were compounds 43–63.60,61 *A. intermedia* Gagnep. was the source of intermedeol (64) and β-selinene (65).62 Investigations of *A. japonica* (Thunb.) Miq. led to the identification of 66–75,77,78 Two novel trinor-eudesmanes, oxyphyllanenes A (76) and B (77) were obtained from *A. oxyphylla*, together with four known ones (78–81).77,78 Investigation on *A. oxyphylla* Miq. provided three nor-eudesmane sesquiterpenoids, oxyphyllane C (82), (5R,7S,10S)-3-hydroxy-13-nor-eudesma-3-en-2,11-dione (83), and 4-methoxy-oxypollone A (84).63,73,74

A new 1,10-seco-15-nor-cadinane sesquiterpene nominated oxyphenol A (85) was isolated from *A. oxyphylla*.64 Fruits of *A. oxyphylla* Miq. also provided one tricyclic sesquiterpene, mustakone (86), nine nor-cadinanes, 87–94 and 2β-hydroxy-8-cadinol (95).53,59,68,74 *A. oxyntira* K. Schum. was the source of (−)-(1R,4S)-8-hydroxy-13-calamenenoic acid (96).75 Alpinpipteronene A (97) was isolated from *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 alpinopine (101), an inhibitor of AChE.79,80 Hanamoly (102), containing a cyclic ether linkage, was also isolated from *A. japonica* (Thunb.) Miq.78 Rhizomes of *A. intermedia* Gagnep. provided hanapinol peroxide (103), isohanapinol (104), and aokumanol (105).64 While *A. intermedia* Gagnep. and *A. japonica* (Thunb.) Miq. produced hanapinol (106), hanapinone (107), and isohanapinone (108).65,79 From *A. japonica* (Thunb.) Miq. and *A. intermedia* Gagnep., furopelargones A (109) and B (110) were obtained.67,68,80 Later on, 110 was also found from *A. formosanensii*.69 Compounds 111–114 were four secoguaiane-type sesquiterpenes with an α,β-unsaturated butenolide. *A. intermedia* Gagnep. produced epilpinolide (111), whilst *A. japonica* (Thunb.) Miq. yielded alpinolide peroxide (112), 6-hydroxy-alpinolide (113), and alpinolid (114).63,78,79 A 1,10-secoaquianese sesquiterpene, (+)-mandassin (115), and two 1,10-seco-15-nor-guaiane 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. galingal*. In addition, caryophyllene oxide was also distributed in rhizomes of *A. conchigera* Griff.24,62

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-bisabol-1,10-diene (126).66 Compounds 127–137 were reported from rhizomes of *A. japonica* (Thunb.) Miq.81 *A. oxyphylla* Miq. was the source of 3(12),7(13),9(E)-humulatriene-2,6-diol (138).138 While *A. formosanensia* and *A. japonica* produced humulene epoxide II (139), (9E)-Humulene-2,3,6,7-diepoxide (140) was reported from the fruits of *A. oxyphylla* Miq. However, its relative configuration remained undetermined. It
exhibited moderate anti-AChE activity in bioautographic assay at 10 nM. Interestingly, the structure and molecular formula for \( \text{CAS Registry Number: 21956-93-4} \) 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 \( A. \text{calcicrata} \) Rosc. afforded a drimane-type sesquiterpene (\( \gamma \)-bicyclohomofarnesal, \( 141 \)) and an elemene one (shyobunone, \( 142 \)). Pubescone (\( 143 \)) was isolated from \( A. \text{oxyphylla} \) Miq. and showed weak anti-AChE activity at the concentration of 100 \( \mu \text{M} \). \( - \)-Oplopanone (\( 144 \)) and oxyphyllone \( F \) (\( 145 \)) were obtained from fruits of \( A. \text{oxyphylla} \) Miq. (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 \( A. \text{oxyphylla} \) Miq.

Seeds of \( A. \text{galanga} \) (L.) Willd. produced caryolane-1,9\( \beta \)-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 \( \mu \text{M} \). \( A. \text{japonica} \) (Thunb.) Miq. yielded alpiniol (\( 148 \)). Compound 2-ethyl-6-isopropyl-7-hydroxymethyl naphthalene (\( 149 \)) was a novel naphthalene from \( A. \text{oxyphylla} \). It showed bioactive activity with the inhibitory rates of 10.3%, compare to 41.9% of the positive control acarbose at 0.9 mM.

Noteworthy, compounds 22–31, 34, 48–56, 58–63, 79–82, 87–89, 117, and 129–136 exerted NO production inhibitory activities at different levels. While (10R)-13-norudesma-4,6-dien-3,11-dione (\( 46 \)), (5S,8R,10R)-2-oxoedesma-3,7(11)-dien-12,8-olide (\( 47 \)), (5R,7S,10S)-5-hydroxy-13-norudesma-3-en-2,11-dione (\( 83 \)), and (4S)-10-nor-calamenen-10-one (90) showed potent auxo-action of NO production at 10 \( \mu \text{M} \) induced by lipopolysaccharide (LPS) in microglia.

2.3. Diterpenoids

Labdane diterpenes is undoubtedly predominant in Zingiberaceae family, notably in \( Alpinia \) genus. Almost all diterpenes are...
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, α-glucosidase inhibition, NO production inhibition, antifungal, antiglycation, HIV-1 integrase, and neuraminidase inhibitory activities. A. katsumadai Hayata, A. galanga (L.) Willd, and A. nigra yielded (E)-8β,17-epoxylabd-12-
ene-15,16-dial (151). It exhibited extensive antibacterial activities, especially against *Candida guilliermondii* and *Candida tropicalis*.

Moreover, 151 also showed $\alpha$-glucosidase inhibitory activity with IC$_{50}$ value between 5 \(\mu\)M and 10 \(\mu\)M.\(^{74}\) The $\alpha$-glucosidase inhibitory activity of 151 was even much higher than the positive control, acarbose (IC$_{50} = 400 \mu\)M),
indicating 151 might be a potential candidate as a future anti-diabetic drug.\textsuperscript{79} A. formosana, A. calcarata Rosc., and A. pahangensis Ridley provided \textsuperscript{(E)}-labda-8(17),12-diene-15-ol-16-al (152),\textsuperscript{81,85,96} while \textsuperscript{(E)}-labda-8(17),13-dien-15-al (153) was only obtained from A. pahangensis Ridley.\textsuperscript{79} Flowers of A. chinensis Rosc. provided compounds 154–161.\textsuperscript{81,85,97} A. tonkinensis
Gagnep. and *A. speciosa* K. Schum. (the accepted name is *A. zerumbet* (Pers.) B. L. Burtt & R. M. Sm.) were the sources of \((E)-15\text{-}\text{nor}-16\text{-}\text{oxo}-8(17),12\text{-}\text{labdadiene}\) \((162)\).\(^{51,98}\) Both *A. zerumbet* (Pers.) Burtt and P. M. Smith and *A. pahangensis* Ridley gave birth to zerumin B \((163)\),\(^{96,99}\) \((11E)-15,16\text{-}\text{Epoxylabda}-8(17),11,13\text{-}\text{trien}-16\text{-}\text{ol}\) \((164)\) and \((E)-15\text{-hydroxy}-8(17),11,13\text{-}\text{trien}-16\text{-}15\text{-}\text{olide}\) \((165)\).
were found in the flowers of *A. chinensis* Rosc.\(^7\) It is noteworthy that 164 was actually a mixture of two epimers. Rhizomes of *A. calcarata* Rosc. produced calcaratins A–D (166–169) and labda-8(17),11,13-trien-15(16)-olide (170).\(^8\) Rhizomes of *A. malaccensis* yielded coronarin A (171), coronarin E (172), and hedyforrestin B (173).\(^9\) Coronarin E (172) was also isolated from *A.
zerumbet (Pers.) Burtt and P. M. Smith, and A. chinensis Rosc.\textsuperscript{37,99,100} Three antibacterial constituents, zerumin A (174), pahangensis B (175), and sceptrumlabadacolate B (176), were isolated from A. pahangensis.\textsuperscript{96} Interestingly, zerumin A (174) was also obtained from A. calcarata Rosc. and A. zerumbet (Pers.) Burtt and P. M. Smith.\textsuperscript{85,99} Compound 175 was also found in A. japonica (Thunb.) Miq., with NO production inhibition (IC\textsubscript{50} = 34.3 \textmu M) in LPS-induced RAW264.7 macrophages.\textsuperscript{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 \textmu g mL\textsuperscript{-1}.\textsuperscript{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 SMCC-7721 in a concentration-dependent way with IC\textsubscript{50} values ranging from 69.1 to 87.0 \textmu g mL\textsuperscript{-1}.\textsuperscript{64,67} Seeds of A. galanga yielded galaganin (179), which showed moderate cytotoxicity towards DU145, MCF-7, H522, and K562 cells with IC\textsubscript{50} values of 8.2, 13.8, 17.8, and 16.1 \textmu M, respectively.\textsuperscript{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).\textsuperscript{96} A. japonica provided compounds 182–187, of which 182 and 183 were norlabdanes.\textsuperscript{104} Compounds 182, 185, and 186 exhibited significant NO production inhibitory effects in LPS-induced RAW264.7 macrophages, with respective IC\textsubscript{50} values of 25.9, 14.6, and 25.6 \textmu M, compare to 39.6 \textmu M of the positive control, N-nomomethyl-L-arginine (L-NMMA).\textsuperscript{105} Ethanol extract of A. oxyphylla Miq. provided 188, which showed moderate hypoglycemic effect with inhibitory rates of 10.0% at 60 \textmu M.\textsuperscript{77} Ottensinin showed moderate antibacterial activity on the Gram-positive bacteria of Bacillus cereus with MIC value of 0.25 \textmu g mL\textsuperscript{-1}.\textsuperscript{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, Doya, and WiDr at 20 \textmu M. Instead, they all exhibited moderate NO inhibitory activities with IC\textsubscript{50} ranging from 30 to 49 \textmu M.\textsuperscript{106} Leaves of A. flabellate provided rel-labda-12-en-15(16)-ol-7-one-8R-spiro-1\textsuperscript{25S}(2,4,5-trimethoxyphenyl)-3-cyclohexene \textsuperscript{193}, a unique labdane diterpene coupled with a phenylbutenoid.\textsuperscript{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\textsubscript{50} values of 34.2 and 49.3 \textmu M, respectively.\textsuperscript{106} (E,E)-15-Hydroxylabda-8(17),11,13-trien-16-al (196) and its diastereoisomer (197) from flowers of A. chinensis Rosc., coronarin B (198) containing a seven-membered endoperoxide hemiacetal was isolated.\textsuperscript{77} 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.\textsuperscript{105} Galanals A (199) and B (200) were obtained from A. galanga (L.) Willd. Both compounds showed significant antifungal activities against...
Candida guilliermondii PW44 with MIC values of 12.5 μg mL⁻¹. Furthermore, galanal A exhibited potent cytotoxic activity against KB cells (IC₅₀ = 3.25 μg mL⁻¹).⁷,³⁹ 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.⁶,¹⁰⁶ A. pahangensis Ridley produced calcaratarins D (204) and E (205), both of which were cytotoxic against human KB cells in vitro with IC₅₀ 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).¹⁰⁹

### 2.4. Triterpenoids

Up to now, only one triterpene was found from this genus (Fig. 4). It was named as 2,3,22,23-tetrahydroxy-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 IC₅₀ 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.¹³⁹ 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

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**Fig. 5** Diarylheptanoids from Alpinia species.
also possessed insecticidal,\textsuperscript{36} anti-adipocyte differentiation,\textsuperscript{111} NO production inhibitory,\textsuperscript{46} and cardiotonic activities.\textsuperscript{112} Compounds 213–216 were also yielded by fruits of \textit{A. oxyphylla}.\textsuperscript{113,114} Seeds of \textit{A. blepharocalyx} K. Schum. gave birth to 217–225.\textsuperscript{115–117} Among these compounds, 1,7-bis(4-hydroxyphenyl)-3-hydroxy-1,3-heptadien-5-one (223) significantly inhibited platelet aggregation induced by
collagen with IC\textsubscript{50} value of 14.7 μg mL\textsuperscript{-1}.\textsuperscript{117} (3S,6E)-Methoxy-1,7-bis(4-hydroxyphenyl)-6-hepten-5-one (224) and (3S,5S)-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\textsubscript{50} values of 5.2 and 12.8 μM, respectively.\textsuperscript{115,116} Both A. pinnanensis

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<tr>
<td>268CH OMe</td>
<td>H</td>
<td>7-(4'-Hydroxy-3'-methoxyphenyl)-1-phenyl-3,5-heptadione</td>
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<tr>
<td>269 H</td>
<td>H</td>
<td>1,7-Diphenyle-4-en-3-one</td>
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<tr>
<td>270 OMe</td>
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<td>6-Hydroxy-1,7-diphenyl-4-en-3-one</td>
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<td>S</td>
<td>R</td>
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<td>9'-Epicylixin P</td>
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<td>292 5R</td>
<td>5'-Epicylixin S</td>
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Fig. 5 Diarylheptanoids from Alpinia species (continued).
T. L. Wu et Senjen and A. katsumadai Hayata provided (3S,5S)-trans-3,5-dihydroxy-1,7-diphenyl-1-heptene (226).<sup>118,119</sup> It did not showed antimycobacterial activity (MIC $\geq$ 64 mg L$^{-1}$). Instead, it exhibited weak neuraminidase inhibitory activity (IC$_{50} = 29.75 \pm 8.15$ μM) <sup>56,120</sup> in vitro. (E,E)-5-Hydroxy-1,7-diphenyl-4,6-heptadien-3-one (227), (S)-1,7-diphenyl-6(E)-hepten-3-ol (228), it exhibited weak neuraminidase inhibitory activity (IC$_{50} = 29.75 \pm 8.15$ μM) <sup>56,120</sup> in vitro. (E,E)-5-Hydroxy-1,7-diphenyl-4,6-heptadien-3-one (227), (S)-1,7-diphenyl-6(E)-hepten-3-ol (228),...
and alnustone (229) were isolated from A. katsumadai Hayata with significantly neuraminidase inhibitory in vitro with IC\textsubscript{50} values between 1.0 and 6.1 \textmu M.\textsuperscript{26} In addition, 229 also possessed antiemetic\textsuperscript{,121} antimycobacterial activities,\textsuperscript{120} and significantly inhibited proliferation of Bel 7402 and LO-2 cells.\textsuperscript{122} Investigation of A. katsumadai Hayata also led the isolation of
compounds 230–238, 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. A planar structure of 1,7-diphenyl-5-hydroxy-6-hepten-3-one (241) was reported from A. nutans Rosc., A. rafflesiana Wall.ex.Bak., and A. officinarum Hance. While its enantiomers, 5S (241a) and 5R (241b) counterparts, were identified from A. mutica Roxb. and A. katsumadai Hayata, respectively. It was shown that a large amount of diarylheptanoids (242–276) were obtained from the rhizomes of A. officinarum Hance. 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 (AE,SE)-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\textsubscript{50} values of 22.68 and 4.44 µM, respectively. Meanwhile, 258–267 were proved to be inhibitors of Helicobacter pylori (Hp-Sydney and Hp-F44). AO-5 (263) showed anti-inflammatory activity induced by 12-O-tetradecanoylphorbol-13-acetate (TPA), platelet-activating factor (PAF), and NO. Moreover, it exhibited very weak cytotoxic activity against human glioblastoma T98G cells (IC\textsubscript{50} = 27 µM). 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\textsubscript{50} values ranging from 220 to 390 µM, indicating potent usage in treating androgen-dependent diseases. Besides, AO-1 (266) also showed anti-helicobacter pylori, hypolipidemic activities, and NO.
AO-2 was identified as an inhibitor of prostaglandin (PG) biosynthesis and exerted antioxidant activity. It is interesting to note that dihydroya-shabushiketol, AO-1, and AO-2 were firstly reported as planar structures, and later, their absolute configurations were established as 264a, 266a, and 267a, respectively. 7-(4′"-Hydroxy-3"-methoxyphenyl)-1-phenyl-3,5-heptadiene (268) also exhibited prostaglandin biosynthesis inhibitory effect.
AO-4 (269) was found to have marked inhibitory effect on TPA-induced inflammation and antioxidant activity. 6-Hydroxy-1,7-diphenyl-4-en-3-heptanone (270) was a PAF inhibitor. AO-3 (271) and (5S)-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 with IC50 values of 50 \mu M. AO-4 (269) was found to have marked inhibitory effect on TPA-induced inflammation and antioxidant activity. 6-Hydroxy-1,7-diphenyl-4-en-3-heptanone (270) was a PAF inhibitor. AO-3 (271) and (5S)-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.
of 0.8–2.7 μmol per ear.\textsuperscript{144} \((3R,5R)-1-(4-Hydroxyphenyl)-7-phenyl-3,5-
heptanediol (273)\) showed significantly antiemetic effect induced by
\(\text{CuSO}_4\) with 37.7\% inhibition at a dose of 50 mg kg\(^{-1}\).\textsuperscript{27,145}

Investigation on seeds of \textit{A. blepharocalyx} K. Schum. led to
the isolation of ten cyclic diarylheptanoids (274–283).\textsuperscript{115,146–148}
Rhizomes of \textit{A. officinarum} Hance provided 3,6-furan-7-(4′-
Fig. 7 Flavonoids from *Alpinia* species (continued).

Fig. 8 Phenolics from *Alpinia* species.
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 IC50 values of 15.39–42.24 mM.115,149 A. blepharocalyx K. Schum. was the source of 293–305.115,148,150,151 However,
the stereochemistry at C-9 of six stereoisomers (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 ED50 values from 0.3–8.2 μM.\cite{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\(^{-1}\).\cite{115} 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 IC50 values of 15.3–42.2 μM.\cite{149} Calyxin B (319) and epicalyxin B (320) were obtained from A. blepharocalyx K. Schum. and A. pinnanensis as NO production inhibitors.\cite{115,151} In addition, 319 showed potent antiproliferative activity against human HT-1080 fibrosarcoma cells with an ED50 value of 0.69 μM.\cite{148} Both A. pinnanensis T. L. Wu et Senjen and A. katsumadai Hayata yielded alpinnanin B (321).\cite{118,124} From A. katsumadai Hayata and A. blepharocalyx K. Schum., epicalyxin H (322) and calyxin H (323) were isolated.\cite{118,124,153} Epicalyxin H was identified as NO production inhibitor.\cite{115,152} Seeds of A. blepharocalyx yielded 324–330.\cite{117,125,127} 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 antiproliferative activities toward colon 26-L5 carcinoma and HT-1080 fibrosarcoma with IC50 values ranging from 0.5 to 10.1 μM.\cite{115,153} Meanwhile, 326 and 327 were cytotoxic against human fibrosarcoma cells with IC50 values ranging from 0.9 to 12.1 μM.\cite{152} 6-Hydroxycalyxin F (329) and calyxin A (330) demonstrated NO production inhibitory activities with IC50 values of 49 and 62 μM, respectively.\cite{115,153}\n\nRhzomes of A. pinnanensis T. L. Wu et Senjen provided deoxycalyxin A (331), alpinnanins A (332), and C (333).\cite{118} In addition, 331 was also found in A. blepharocalyx K. Schum.\cite{117} While officinin A (334) was obtained from rhizomes of A. officinarum Hance.\cite{155}\n\nFive dimeric diarylheptanoids (335–339) were obtained from rhizomes of A. officinarum Hance.\cite{115,116,118,136,137} Only alpinin C (338) displayed selective cytotoxic against MCF-7 (IC50 = 62.3 μM) and T98G cells (IC50 = 57.3 μM).\cite{135} Seeds of A. blepharocalyx K. Schum. provided 340–344 possessing two diarylheptanoid units and a chalcone moiety.\cite{115,116,153} Both blepharocalxins 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.\cite{158} Blepharocalxins C–E (342–344) were tested for antiproliferative activities against two tested cancer cells, blepharocalxyn D (343) exhibited the strongest effect against highly liver-metastatic murine colon 26-L5 carcinoma cells (ED50 = 3.6 μM), whereas blepharocalxyn E (344) showed the strongest activity against human HT-1080 fibrosarcoma cells (ED50 = 9.02 μM).\cite{115,116,159} 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-5. 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 unidentified.\cite{115,153}\n\nRhzomes of A. officinarum Hance produced officinaruminane B (347), a diarylheptanoid coupled with a monoterpene unit.\cite{111} Investigation on seeds of A. katsumadai Hayata identified two novel anti-emetic diarylheptanoids, katsumadains A (348) and B...
Besides, 348 also exerted promising neuraminidase inhibitory effect against human influenza virus A/PR/8/34 (IC$_{50}$ = 1.05 µM). 349 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
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 linolate in bulk phase.163 Extracts of seeds of *A. katsumadai* Hayata afforded antiemetic catumadin (359) with antiemetic activity on CuSO4-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 conchigerans D (364) and E (365) shared the same planar structure, their relative conformations were not determined. Galanganol (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 IC50 values ranging from 1.5 to 5.29 µg mL−1.167 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 sesquileonignans, conchignans A–C (370–372) bearing a tetrahydropyran ring.167 7-Methoxycoumarin (373) is a coumarin known from *A. calcatta* Rosc.168

Citrusin B (374) and 2,3-dihydro-2-(4-β-o-glucopyranosyl-3-methoxyphenyl)-3-hydroxymethyl-7-hydroxy-5-benzofuranopropane (375) were the only two lignan glycosides isolated from leaves of *A. speciosa*.164

5. Flavonoids

To date, 71 flavonoids (Fig. 7) were isolated from the *Alpinia* species, including seven flavones (376–382), 14 flavonols (383–396), four flavanones (397–400), seven flavanones (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 (EC50 = 90 ± 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).180,171 Kaempferol-3′,4′-dimethylether (383) was afforded by *A. sichuanensis* Z. Y. Zhu.172 Galangin (384) and kaempferide (385) were the major flavonoids distributed in several plants of *Alpinia*, both of which exhibited inhibitory against penicillinase and potent antioxidant activities.113,132 In addition, galangin effectively inhibited the TPA-induced invasion and migration of HepG2 cells at concentrations of 2.5–5 µM.172 In 2001, a review summarized anti-genotoxic activity of galangin and demonstrated that galangin was a promising candidate for cancer chemoprevention.173 Investigation on the whole plant of *A. sichuanensis* Z. Y. Zhu provided kaempferol (386).172 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.

4. Lignans

Twenty-four lignans (351–374) were reported from the genus *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.163,164 cis-1-(2,4,5-Trimethoxy-E-aryl)-2-(2,4,5-trimethoxy-Z-aryl)cyclobutane (351) and trans-1-(2,4,5-trimethoxy-E-aryl)-2-(2,4,5-trimethoxy-Z-aryl)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

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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.
tonkinensis \textit{Gagnep.} yielded 3,5-dihydroxy-7,4′-dimethoxyflavone (388),115,161,171 Izalpinin (389) from different parts of \textit{A. oxyphylla} Miq. was a NO production inhibitor and exhibited potent antioxidant activity.113,176 From rhizomes of \textit{A. officinarum}, 3-methylthylgalangin (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 \textit{A. tonkinensis} Gagnep.171 5-Hydroxy-3,7,4′-trimethoxyflavone (396) was yielded by leaves of \textit{A. flabellata} Ridley.188 Pinocembrin (397) and alpinetin (398) were distributed in several \textit{Alpinia} species and both showed antiemic activities.121,181 In addition, 397 also demonstrated several bioactivities, including cytotoxicity (on human T lymphoblastoid cancer cells),182 anti-inflammation,189 and antiplatelet aggregation etc.183 While, 398 was a PAF receptor binding inhibitor.184 7,4′-Dihydroxy-5-methoxy flavanone (399), pinosintron (400) were reported from several species.116,118,128,182 Pinobanksin (401), (2R,3S)-pinobanksin-3-cinnamate (402), and 3-O-acetylpinobanksin (403) were mainly obtained from \textit{A. galanga} (L.) Willd and \textit{A. katsumadai} Hayata.176,177,183 Compound 402 showed potent neuroprotective effect against PC12 cells.177,186 Leaves of \textit{A. flabellata} Ridley provided 404 and 405.180 Dihydrokaempferol (406) were isolated from \textit{A. oxyphylla}.189 Both \textit{A. japonica} (Thum.) Miq. and \textit{A. galanga} (L.) Willd were sources for alpinone (407).176,187 From seeds of \textit{A. katsumadai} Hayata, a dihydrochalcone uvaogonitin (408) was isolated.188 \textit{A. speciosa} K. Schum. and \textit{A. formasana} afforded another dihydrochalcone, dihydroflavokawin B (409).81,188 Flavokawin B (410) was isolated from several plants and showed strong cytotoxicity against human T lymphoblastoid cancer cells (IC_{50} = 6.5 \mu M) and anti-inflammatory activity.182,189 Cardamomin (411) distributed in many \textit{Alpinia} species90,118,123,148,150 and exhibited extensive bioactivities including death receptor 5 (DR5) promoter,175 antimicrobial,191 anti-angiogenic,192 anti-coagulation,183 and anti-inflammation.122 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 \textit{A. rafflesiana} Wall.\textit{ex} Bak., was potently active to DPPH free radical scavenging (IC_{50} = 55 \mu M).128 Rhizomes of \textit{A. pricei} Hayata yielded 2′,4′,6′- trimethoxychalcone (413) and pinostrobin chalcone (414).199 Compounds 415–417 were isolated from the seeds of \textit{A. blepharocalyx} K. Schum.116,117 while helichrysin (415) was also found in \textit{A. katsumadai} Hayata.188 Pinocembrin chalcone (418) and 4′,6′-dimethylchalconaringenin (419) were provided by \textit{A. katsumadai} Hayata and \textit{A. pinnanensis} T. L. Wu et Senjen, respectively.118,122 Compound 418 was also isolated from \textit{A. platychilus}.195 Galangonanes A–C (420–422) were three novel chalcones bearing a long-chain alkyphenol from \textit{A. galanga}.194 whilst \textit{A. katsumadai} Hayata and \textit{A. zerumbet} (Pers.) B. L. Burttet Smith. provided (+)-catechin (423),195,196 Epicatechin (424) and galloepicatechin (425) were yielded by \textit{A. oxymitra} K. Schum.75 (+)-Epicatechin (426) was isolated from \textit{A. speciosa} K. Schum. and displayed antioxidant activity.197 Kaempferide-3-O-beta-glucoside (427) from \textit{A. officinarum} Hance had an weak inhibitory activity against penicillinase.172 Study on \textit{A. speciosa} K. Schum. lead to the isolation of 428–432.198 Quercetin 3-O-robinobioside (433) and galangoflavonoside (434) were obtained from \textit{A. katsumadai} Hayata and \textit{A. galanga} (L.) Swartz., respectively.196,199 Compounds 433–437 from \textit{A. densespicata} Hayata exhibited moderate NO inhibitory activities.181 Compounds 438–440 were obtained from the seeds of \textit{A. katsumadai} Hayata and isorhamnetin-3-O-beta-galactosyl (6 → 1)-a-L-rhamnosoide (441) was isolated from rhizomes of \textit{A. tonkinensis} Gagnep.51,196 Leaves of \textit{A. zerumbet} (Pers.) B. L. Burttet Smith. contained rutin (442) and kaempferol-3-O-rutinoside (443).195 The whole plant of \textit{A. sichuanensis} Z. Y. Zhu yielded hesperidin (444).12 Two pairs of enantiomers of flavonoidoligomers (445a and 445b, 446a and 446b) were found from rhizomes of \textit{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 \textit{Alpinia} species (Fig. 8). [Di-(p-hydroxy-cis-styryl)methanes (447) was obtained from \textit{A. galanga} (L.) Willd.200 Whilst alpinone (448) was isolated from \textit{A. gagnepainii} K. Schum. with antibacterial effect against \textit{E. coli}, \textit{B. subtilis}, and \textit{S. aureus} with the same MIC value of 12.5 \mu g mL^{-1}.191 (1E,4Z)-5-Hydroxy-1-phenylenoxa,1,4-dien-3-one (449) and 2-propanol, 3-[4-[(acetoxy)-3-methoxophenyl] (450) were provided by \textit{A. katsumadai} Hayata and \textit{A. galanga} (L.) Willd, respectively.86,108 From \textit{A. sichuanensis} and \textit{A. oxyphylla}, dibutyl phthalate (451) was isolated.182,201 Two compounds named as (E)-p-coumaryl alcohol (452) and (E)-p-coumaryl alcohol 3-O-methyl ether (453) exhibited potent inhibitory activities against the autoxidation of methyl linoleate in bulk phase.165 In addition, compound 453 exerted potent cytotoxic activity against the SNU638 cells with IC_{50} value of 1.62 \mu g mL^{-1}.202 \textit{A. galanga} (L.) Willd and \textit{A. conchigera} Griff. produced trans-p-hydroxycinnamaldehyde (454) and trans-p-hydroxycinnamyl acetate (455).170,205 Compound 454 displayed weak antiallergic effect,164 and NO production inhibitory activities (IC_{50} = 20 \mu M).185 and 455 exerted no inhibitory activity towards \textit{Staphylococcus aureus} strain VISA (MIC = 203 \mu M).12 trans-p-Coumaryl alcohol (456) was a weak NO production inhibitor from \textit{A. galanga} (L.) Willd (IC_{50} = 72 \mu M).166 trans-p-Coumaryl diacetate (457) from \textit{A. galanga} showed a number of bioactivities, including anti-allergy,204 efflux pump inhibition,205 NO production inhibition,166 xanthine oxidase inhibition,206 antileishmaniasis,164 cytotoxicity,12 and antibacteria.165 trans-p-Acetoxycinnamyl alcohol (458), trans-p-hydroxycinnamaldehyde acetate (459), and p-coumaric acid (460) were obtained from rhizomes of \textit{A. galanga} (L.) Willd.164,205 In addition, compound 460 was also distributed in \textit{A. galanga} (L.) Willd.141 \textit{A. sichuanensis} Z. Y. Zhu,142 \textit{A. speciosa},190 \textit{A. blepharocalyx} K. Schum.,119 and \textit{A. oxyphylla}.199 Both \textit{A. formasana} and \textit{A. speciosa} K. Schum. were sources of methyl trans-cinnamate (461).81,188 Seeds of \textit{A. blepharocalyx} yielded methyl p-hydroxycinnamyl (462) and methyl p-hydroxycinnamyl ketone (463).195 From rhizomes of \textit{A. galanga} (L.) Willd, 12 compounds (464–475) were obtained.116,203,207 Among them, 15′-1′-acetoxycinnamic acid (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.31,202,208 Furthermore, 464 also showed antiallergic,204 efflux pump inhibitor,205 NO production inhibitor,160 xanthine oxidase inhibitor,206 gastroprotective,209 anti-HIV,216 anti-cancer,96 anti-bacterial,10,211 plant growth-inhibitory and fungal growth-inhibitory activities.212 Two compounds, methyleugenol (466) and hydroxychavicol acetate (467), were isolated from *A. galanga* (L.) Willd.15,164,166,204,211 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. galanga*.31,101,307 Chavicol acetate (467) and 1′-S-acetoxyeugenol acetate (477) were two known phenolics found from *A. conchigera* Griff.83 Compound 477 possessed antibacterial,83 xanthine oxidase inhibitory,206 gastro-protective,209 and anti-cancer activities.83 Investigation on leaves of *A. fiabellata* Ridley provided 478–480, with strong antibacterial activities against *Staphylococcus aureus*.163,164,168 Compounds 481–489 were nine phenolic acids isolated from several *Alpinia* species.52,80,112,180,308,313,215 Protocatechuic acid (489) showed potent neuroprotective effect on MPP−-induced neurotoxicity and H2O2-induced oxidative damage in PC12 cells.125,219 In addition, it also exerted anti-aging effect on spleen and liver antioxidative system of senescent mice.84 4-Hydroxybenzaldehyde (490), isolated from *A. sichuanensis* Z. Y. Zhu, *A. blepharocalyx* K. Schum., *A. bracteata*, and *A. galanga* (L.) Willd.32,117,166,170 didn’t show any DPPH radical-scavenging activity. Instead, it exhibited inhibitory activity on xanthine oxidase (IC50 = 19.6 μM).317,306 Compounds 491–496 were provided by several *Alpinia* plants.32,84,137,307,220

Ethyl 4-O-feruloyl-β-glucopyranoside (497) and 4-hydroxy-3-methoxymethyl 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 499–504.116 While from rhizomes of *A. bracteata*, a new phenolic glycoside (500) was isolated and showed moderate antioxidant activity on scavenging DPPH free radicals (EC50 = 169 ± 4.8 μM).170 Leaves of *A. speciosa* K. Schum. provided coniferin (500) and syringin (509).168

Dihydro-5,6-dehydrokawain (510) and 5,6-dehydrokawain (511) were major chemical constituents in several *Alpinia* species.61,100,128,177,188,221 They showed antilucreogenic, antithrombotic,195 antifungal,191 anti-obesity,222 and plant growth inhibitory activities.222 Recently, it was reported that they could strongly inhibit HIV-1 integrase with respective IC50 values of 4.4 and 3.6 μg mL−1. In addition, they exhibited mixed type of inhibition against neuraminidase with both IC50 values of 25 μM.25 Furthermore, 511 was also reported as a slow and time-dependent reversible inhibitor of neuraminidase, a moderate antioxidant, a strong inhibitor of skin diseases-related enzymes, and strong antiplatelet inhibitor.95,227,224 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.221 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 ED50 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 stigmastanol (514) were also widely distributed in *Alpinia* species.52,82,89,118,178,191,226–228 β-Sitosterol-3-O-β-D-palmitoylglucoside (518) showed potent antiemic activity induced by CuSO4.27

8. Alkaloids

Officinarinumine A (520) and officinone B (521), two alkaloids of bi-diarylethapantoanoid connecting by a pyridine ring were produced by rhizomes of *A. officinarum* Hance.131,157 A study on seeds of *A. katusmadai* 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. katusmadai* Hayata.20,121

10. Others

One esters (534) and three fatty acids, 535–537, were isolated from several *Alpinia* species.54,227–229 (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*.48 Two glycosides known as 3-methylbut-2-en-1-yl-β-D-glucopyranoside (539) and n-buty1-β-D-fructopyranoside (540) were isolated from *A. officinarum* Hance.55,216 While 541–544 were found in different *Alpinia* species (Fig. 9).24,51,108,196,201 Interestingly, 5-hydroxymethylfurural (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*.10

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

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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,29–31,37,82,212–216 antioxidant,127,237–239 anticancer,32–34,240–247 anti-inflammatory,109,146,247 insecticidal,36,164 and neuroprotective bioactivities.36,39,231,248–250

In addition, they also showed antiulcer,25 antiplatelet,17,181 hepatoprotective,251 and hypolipidemic effects.252 Meanwhile, evidences showed that ethanol extract of *A. galanga* 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 unexplored. 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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Notes and references


