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.

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 $^1$C NMR spectroscopic data of 307 naturally occurring diarylheptanoids, which were mainly isolated from *Alpinia* species. In 2011, the pharmacological and phytochemical studies of *Alpinia 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 constituents 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. 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, 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-dehydrokavaain, 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

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, enterobezoa 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.

†Electronic supplementary information (ESI) available: The name, source, plant part, and reference for each compound. A comparison of *Alpinia* species names from the references and the accepted name in The Plant List. See DOI: 10.1039/c6ra27830b
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), isourbraine (2), and sumadain C (3) were three new monoterpenone–chalcone conjugates obtained from *A. katsumadai*. 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. *A. katsumadai* Hayata yielded a new monoterpenone–kavalactone conjugate, katsumadain (4) and a new (E)-1-(1-terpinen-4-olyl)-3-methoxystilbene (5). While *A. densibracteata* T. L. Wu and Senjen yielded two diastereoisomers of cinnamate diol (6) and 2β-cinnamoyl cinnole (7). From rhizomes of *A. tonkinensis* Gagnep., 2x-(p-hydroxycinnamyl) cinnole (8) was isolated. Two endoperoxides, (1S,4R,6R)-1,4-epidioxyp-menth-2-ene (9) and (1R,4S,6R)-1,4-epidioxyp-menth-2-ene (10), were isolated from aerial parts of *A. densibracteata* T. L. Wu and Senjen. Whilst (3R,4R,6S)-3,6-dihydroxy-1-methene (11) and 1-terpinen-4-ol (12) were obtained from *A. sichuanensis* Z. Y. Zhu [a synonym of *A. jiangangeng* T. L. Wu] and *A. katsumadai* Hayata, respectively. Fruit of *A. oxyphylla* Miq. was the source of (1R,2R)-p-menth-3-ene-1,2-diol (13). And aerial parts of *A. densibracteata* T. L. Wu and Senjen yielded 3,4-dihydroxy-p-menth-1-ene (14). Compounds 15–17 were three hydroxy-1,8-cineole glucopyranosides, which were mainly isolated from rhizomes of *A. galanga* (L.) Willd.

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 neuroaminidase inhibitory activity in vitro (IC_{50} = 81.4 μM). Nerolidol (19), another acyclic sesquiterpene, was obtained from rethizoms of *A. japonica*. 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. While 9β-hydroxyoootkatone (31), (11S)-12-chlorooootkotan-11-ol (32), and (11R)-12-chlorooootkotan-11-ol (33) displayed anti-acetylcholinesterase (AChE) activities by TLC-bioautographic assays. 12-Norootkotan-6-ene-11-one (35) was a novel nor-eremophilane. It showed potent anti-AChE bioactivity at 10 nM using the same TLC-bioautographic assay. The rest of five eremophilanes (36–40) were isolated from three different species. Eremophil-10β-ol (36) and eremophil-11-ol (37) were obtained from *A. intermedia* Gagnep. and *A. japonica* (Thunb.) Miq., respectively, whilst nootkatone (38), valencene (39), and dehydro-nootkatone (40) were all identified from *A. oxyphylla* Miq. Among 44 eudesmane sesquiterpenoids, oxyphylloenes 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. Oxyphylone A displayed moderate anti-AChE activity. Also obtained from *A. oxyphylla* Miq. were compounds 43–63. *A. intermedia* Gagnep. was the source of intermedeol (64) and β-selinene (65). Investigations of *A. japonica* (Thunb.) Miq. led to the identification of 66–75, 77,78 Two novel trinor-eudesmanes, oxyphylloenes A (76) and B (77) were obtained from *A. oxyphylla*, together with four known ones (78–81). Investigation on *A. oxyphylla* Miq. provided three nor-eudesman sesquiterpenoids, oxyphylloene C (82), (5R,7S,10S)-3-hydroxy-13-noreudesma-3-en-2,11-dione (83), and 4-methoxy-oxyphylloene A (84).

A new 1,10-seco-15-norcadinane sesquiterpene nominated oxyphenol A (85) was isolated from *A. oxyphylla*. Fruits of *A. oxyphylla* Miq. also provided one tricyclic sesquiterpene, mustakone (86), nine nor-cadinanes, 87–94 and 2β-hydroxy-3-cadinol (95). *A. oxtinirita* K. Schum. was the source of (−)-(1R,4S)-8-hydroxy-13-calamenenoic acid (96). Alpinapterene A (97) was provided by *A. officinarum* Hance, whilst 4(15)-cadinene-6,10-diol (98) by *A. tonkinensis* Gagnep. 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.

Rhizomes of *A. japonica* (Thunb.) Miq. provided alpinenone (101), an inhibitor of AChE. [99,100] Hanamylone (102), containing a cyclic ether linkage, was also isolated from *A. japonica* (Thunb.) Miq. [102] Rhizomes of *A. intermedia* Gagnep. provided hanalpinol peroxide (103), isohanalpinol (104), and aokumanol (105). While *A. intermedia* Gagnep. and *A. japonica* (Thunb.) Miq. produced hanalpinol (106), hanalpinone (107), and isoahanalpinone (108). [61,79] From *A. japonica* (Thunb.) Miq. and *A. intermedia* Gagnep., furopelargones A (109) and B (110) were obtained. [62,80,88] Later on, 110 was also found from *A. formossana*. [61] 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). [62,79,80] A 1,10-seco-guaianes 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.

Caryophyllene oxide (118), caryophyllenol-I (119), and caryophyllenol-II (120) were caryophyllanes from *A. galanga*. In addition, caryophyllene oxide was also distributed in rhizomes of *A. conchigera* Griff. [118,119] 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). [118] Compounds 127–137 were reported from rhizomes of *A. japonica* (Thunb.) Miq. *A. oxyphylla* Miq. was the source of 3(12),7(13),9(E)-humulatriene-2,6-diol (138). While *A. formossana* and *A. japonica* produced humulene epoxide II (139) and (E)-humulene-2,3,6-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.\textsuperscript{59,84} Interestingly, the structure and molecular formula for \textsuperscript{140} (CAS Registry Number: 21956-93-4) provided by SciFinder were not correct. It should be C\textsubscript{15}H\textsubscript{24}O\textsubscript{2} instead of C\textsubscript{14}H\textsubscript{21}O\textsubscript{2}.

Rhizomes of \textit{A. calcarata} Rosc. afforded a drimane-type sesquiterpene (γ-bicyclomofarnesal, \textsuperscript{141}), and an elemene one (shyobunone, \textsuperscript{142}).\textsuperscript{83} Pubescone (\textsuperscript{143}) was isolated from \textit{A. oxyphylla} Miq. and showed weak anti-AChE activity at the concentration of 100 μM.\textsuperscript{59} (−)-Oplopanone (\textsuperscript{144}) and oxiphylione F (\textsuperscript{145}) were obtained from fruits of \textit{A. oxyphylla} Miq.\textsuperscript{84} Seeds of \textit{A. galanga} (L.) Willd. produced caryolane-1,9β-diol (\textsuperscript{147}), which suppressed the proliferation of four cancer cell lines of HeLa, A549, HepG2, and SMMC-7721 with IC\textsubscript{50} values ranging from 252 to 378 μM.\textsuperscript{86} \textit{A. japonica} (Thunb.) Miq. yielded alpiniol (\textsuperscript{148}).\textsuperscript{87} Compound 2-ethyl-6-isopropyl-7-hydroxymethyl naphthalene (\textsuperscript{149}) was a novel naphthalene from \textit{A. oxyphylla}.\textsuperscript{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.\textsuperscript{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.\textsuperscript{58–60,62,67,71,73,88–90} While (10R)-13-noreudesma-4,6-dien-3,11-dione (\textsuperscript{46}), (5S,8R,10R)-2-oxoedicsma-3,7(11)-dien-12,8-olide (\textsuperscript{47}), (5R,7S,10S)-5-hydroxy-13-noreudesma-3-en-2,11-dione (\textsuperscript{83}), and (4S)-10-nor-calamenen-10-one (\textsuperscript{90}) showed potent auxo-action of NO production at 10 μM induced by lipopolysaccharide (LPS) in microglia.\textsuperscript{71}

2.3. Diterpenoids

Labdane diterpenes is undoubtedly predominant in Zingiberaceae family, notably in \textit{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, \( \alpha \)-glucosidase inhibition, NO production inhibition, antifungal, \( \alpha \)-glycation, HIV-1 integrase, and neuraminidase inhibitory activities. *A. katsumadai* Hayata, *A. galanga* (L.) Willd, and *A. nigra* yielded (E)-8\( \beta \),17-epoxylabd-12-
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 \(\alpha\)-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 antidiabetic drug. 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.86 Flowers of A. chinensis Rosc. provided compounds 154–161,81,85,97 A. tonkinensis
Gagnep. and A. speciosa K. Schum. (the accepted name is A. zerumbet (Pers.) B. L. Burtt & R. M. Smith) were the sources of \((E)-15\text{-nor}-16\text{-oxo}-8(17),12\text{-labdadiene}\) (162).\(^{53,98}\) Both A. zerumbet (Pers.) Burtt and P. M. Smith and A. pahangensis Ridley gave birth to zerumin B (163),\(^{59,99}\) \((11E)-15,16\text{-Epoxylabda}-8(17),11,13\text{-trien}-16\text{-ol}\) (164) and \((E)-15\text{-hydroxylabda}-8(17),11,13\text{-trien}-16,15\text{-olide}\) (170).
(165) were found in the flowers of *A. chinensis* Rosc. 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). Rhizomes of *A. malaccensis* yielded coronarin A (171), coronarin E (172), and hedyforrestin B (173). Coronarin E (172) was also isolated from *A.
A. pahangensis isolated from *A. japonica*.  

*Candida guilliermondii galanga* way with IC50 values ranging from 69.1 to 87.0 suppressed the proliferation of four cancer cells lines of HeLa, labda-8(17),13(14)-di-en-15,16-olide (*A. japonica* in *Rosc.*).  

Three antibacterial constituents, zerumin A (174), pahangensin B (175), and scepumlabdalactone B (176), were isolated from *A. pahangensis*. Interestingly, zerumin A (174) was also obtained from *A. calcarea Rosc.* and *A. zerumbet* (Pers.) Burtt and P. M. Smith. Compound 175 was also found in *A. japonica* (Thunb.) Miq., with NO production inhibition (IC50 = 34.3 μM) in LPS-induced RAW264.7 macrophages. 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. Isocoronarin D (178) was found in *A. galanga* (L.) Willd and *A. calcarea Rosc.*, which weakly suppressed the proliferation of four cancer cells lines of HeLa, A549, HepG2, and SMMC-7721 in a concentration-dependent way with IC50 values ranging from 69.1 to 87.0 μg mL⁻¹. Seeds of *A. galanga* yielded galaganin (179), which showed moderate cytotoxicity towards DU145, MCF-7, H522, and K562 cells with IC50 values of 8.2, 13.8, 17.8, and 16.1 μM, respectively. Rhizomes of *A. pinnanensis* T. L. Wu et Senjen produced labda-8(17),13(14)-di-en-15,16-olide (180) and ottensinin (181). *A. japonica* provided compounds 182–187, of which 182 and 183 were norlabdanes. Compounds 182, 185, and 186 exhibited significant NO production inhibitory effects in LPS-induced RAW264.7 macrophages, with respective IC50 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). Ethanol extract of *A. oxyphylla* Miq. provided 188, which showed moderate hypoglycemic effect with inhibitory rates of 10.0% at 60 μM. Ottensinin showed moderate antibacterial activity on the Gram-positive bacteria of *Bacillus cereus* with MIC value of 0.25 μg mL⁻¹. Alpinendosides 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, Doxa, and WiDr at 20 μM. Instead, they all exhibited moderate NO inhibitory activities with IC50 ranging from 30 to 49 μM. Leaves of *A. flabellate* provided rel-labda-12-en-15(16)-olid-7-one-8R-spiro-1-[2S-(2,4,5-trimethoxyphenyl)]-3-cyclohexene] (193), a unique labdane diterpene coupled with a phenylbutenoid. 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 IC50 values of 34.2 and 49.3 μM, respectively. (E,E)-15-Hydroxylabda-8(17),11,13-trien-16-ol (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-ol. From flowers of *A. chinensis*, coronarin B (198) containing a seven-membered endoperoxide hemiacetal was isolated. 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*. 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). Compound 201 was a novel metabolite conjugated of labdane diterpene with chalcone from aerial parts of A. katsumadai Hayata. A. pahangensis Ridley provided pahangensins A (202) and C (203) as antibacterial constituents. 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. From seeds of A. katsumadai Hayata, a grayanane diterpenoid was isolated and characterized as rhodomollein I (206).

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. It showed weak cholesterol acyltransferase inhibitory activity with IC₅₀ value of 47.9 μM.

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. 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.
also possessed insecticidal, anti-adipocyte differentiation, NO production inhibitory, and cardiotonic activities. Compounds 213–216 were also yielded by fruits of *A. oxyphylla*. Seeds of *A. blepharocalyx* K. Schum. gave birth to 217–225. Among these compounds, 1,7-bis(4-hydroxyphenyl)-3-hydroxy-1,3-heptadien-5-one (223) significantly inhibited platelet aggregation induced by...
collagen with IC₅₀ value of 14.7 μg mL⁻¹.¹¹⁷ (3S,6E)-Methoxy-1,7-bis(4-hydroxyphenyl)hexa-2,5-diene-3-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 IC₅₀ values of 5.2 and 12.8 μM, respectively.¹¹⁵,¹¹⁶ Both A. pinnanensis
T. L. Wu et Senjen and A. katsumadai Hayata provided (3S,5S)-trans-3,5-dihydroxy-1,7-diphenyl-1-heptene (226). It did not showed antimycobacterial activity (MIC $\leq$ 64 mg L$^{-1}$). Instead, it exhibited weak neuraminidase inhibitory activity (IC$_{50}$ = 29.75 ± 8.15 µM) 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 IC₅₀ values between 1.0 and 6.1 μM. In addition, 229 also possessed antiemetic, antimycobacterial activities, and significantly inhibited proliferation of Bel 7402 and LO-2 cells. Investigation of *A. katsumadai* Hayata also led the isolation of...
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, S5 (241a) and 5R (241b) counterparts, were identified from A. mutica Roxb.130 and A. katsumadai Hayata,131 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 (4E,6E)-5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-7-phenyletha-4,6-dien-3-one (258) showed weak cytotoxicity against two cancer cell lines of MCF-7 and T98G with IC50 values of 22.68 and 4.44 μM, respectively.135 Meanwhile, 258–267 were proved to be inhibitors of Helicobacter 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 (IC50 = 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 IC50 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.
production inhibitory activity.\textsuperscript{136,140,144} AO-2 (267) was identified as an inhibitor of prostaglandin (PG) biosynthesis and exerted antioxidant activity.\textsuperscript{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.\textsuperscript{136,144}

7-(4"-Hydroxy-3"-methoxyphenyl)-1-phenyl-3,5-heptadiene (268) also exhibited prostaglandin biosynthesis inhibitory effect.
with IC₅₀ values of 50 μM. 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 CuSO\textsubscript{4} with 37.7% inhibition at a dose of 50 mg kg\textsuperscript{-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\textsuperscript{O}′-methoxyphenyl)-1-phenylheptane (284).\textsuperscript{131} From the seeds of A. katsumadai, 285–292 were obtained,\textsuperscript{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\textsubscript{50} values of 15.39–42.24 mM.\textsuperscript{155,159} A. blepharocalyx K. Schum. was the source of 293–305.\textsuperscript{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.115,116 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−1.117 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.118 Calyxin B (319) and epicalyxin B (320) were obtained from A. blepharocalyx K. Schum. and A. pinnanensis as NO production inhibitors.115,116 In addition, 319 showed potent anti-proliferative activity against human HT-1080 fibrosarcoma cells with an ED50 value of 0.69 μM.118 Both A. pinnanensis T. L. Wu et Senjen and A. katsumadai Hayata yielded alpinannin B (321).118,119 From A. katsumadai Hayata and A. blepharocalyx K. Schum., epicalyxin H (322) and calyxin H (323) were isolated.118,119,120 Epicalyxin H was identified as NO production inhibitor.115,116,117 Seeds of A. blepharocalyx yielded 324–330.111,112,113 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.110,111 Meanwhile, 326 and 327 were cytotoxic against human fibrosarcoma cells with IC50 values ranging from 0.9 to 12.1 μM.112 6-Hydroxycalyxin F (329) and calyxin A (330) demonstrated NO production inhibitory activities with IC50 values of 49 and 62 μM, respectively.115,116 Rhizomes of A. pinnanensis T. L. Wu et Senjen provided deoxycalynin A (331), alpinannins A (332), and C (333).118 In addition, 331 was also found in A. blepharocalyx K. Schum.117 While officinain A (334) was obtained from rhizomes of A. officinarum Hance.115

Five dimeric diarylheptanoids (335–339) were obtained from rhizomes of A. officinarum Hance.115,116,117,118,119 Only alpinin C (338) displayed selective cytotoxic against MCF-7 (IC50 = 62.3 μM) and T98G cells (IC50 = 57.3 μM).135 Seeds of A. blepharocalyx K. Schum. provided 340–344 possessing two diarylheptanoid units and a chalcone moiety.115,116,117 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 J774.1.118 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 (ED50 = 3.6 μM), whereas blepharocalyxin E (344) showed the strongest activity against human HT-1080 fibrosarcoma cells (ED50 = 9.02 μM).115,117,118 It is worth mentioning that the stereochemistry at C-1-5 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-1-6 and C-1-5 by Scifinder. Instead, it should be joined through C-1-6 and C-1-7. 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.115,116

Rhizomes of A. officinarum Hance produced officinaruminane B (347), a diarylheptanoid coupled with a monoterpenic unit.131 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 (IC50 = 1.05 μM).\textsuperscript{28} 4-Phenethyl-1,7-diphenyl-1-heptene-3,5-dione (350) was isolated from rhizomes of \textit{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.\textsuperscript{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 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.\(^{144}\) Investigation on the whole plant of *A. conchigera* afforded eight rare 8–9' linked neo lignans 361–368.\(^ {165}\) Although conchigenans 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\(^{-1}\).\(^{167}\) Interestingly, 366 and 368 also inhibited NO production in mouse peritoneal macrophages.\(^{168}\) Galanganol C (369) was obtained from rhizomes of *A. galanga* (L.) Willd as a NO production inhibitor.\(^{169}\) The whole plant of *A. conchigera* yielded three unusual sesquioleignans, conchignans A–C (370–372) bearing a tetrahydropyran ring.\(^{167}\) 7-Methoxycoumarin (373) is a coumarin known from *A. calcara-ata* Rose.\(^{85}\)

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 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 (EC\(_{50}\) = 90 ± 1 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).\(^{160,171}\) Kaempferol-3',4',7-trimethoxy flavanone (383) was afforded by *A. sichuanensis* Z. Y. Zhu.\(^{20}\) 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.\(^{172}\) 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).\(^ {32}\) 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 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-Tri-methoxy-E-styrlyl}-2-{2,4,5-trimethoxy-Z-styrlyl}cyclobutane (351) and *trans*-1-{2,4,5-trimethoxy-E-styrlyl}-2-{2,4,5-trimethoxy-Z-styrlyl}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.\(^{163}\)

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

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

Fig. 10 The number of publications on *Alpinia* since 1955.
tonkinensis Gagnep. yielded 3,5-dihydroxy-7,4′-dimethoxyflavone (388),113,161,171 Izalpin (389) from different parts of A. oxyphilla Miq. was a NO production inhibitor and exhibited potent antioxidant activity.113,176 From rhizomes of A. officinarum, 3-methylethylalangalin (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.173 5-Hydroxy-3,7,4′-trimethoxyflavone (396) was yielded by leaves of A. flabellata Ridley.188 Pinocembrin (397) and alpinetin (398) were distributed in several Alpinia species and both showed antimiematic activities.121,181 In addition, 397 also demonstrated several bioactivities, such as cytotoxicity (on human T4 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 flavone (399), pinostrobin (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 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. oxyphilla.189 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.188 A. speciosa K. Schum. and A. formosana afforded another dihydrochalcone, dihydroflavokawin B (409).181,188 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 species106,118,123,148,150 and exhibited extensive bioactivities including death receptor 5 etc against PC12 cells.176,187 Compound 1 from A. angustifolia (L.) Willd was an inhibitor of alpinone (412) was obtained from A. rafflesiana Wall. ex Bak., was potentely active to DPPH free radical scavenging (IC_{50} = 55 μM).128 Rhizomes of A. pricei Hayata yielded 2′,4′,6′-trimethoxycalcone (413) and pinostrobin chalcone (414).189 Compounds 415–417 were isolated from the seeds of A. blepharocalyx K. Schum.,116,117 while helichrysent (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.121,126 Compound 418 was also isolated from A. platychilus.193 Galanganes A-C (420–422) were three novel chalcones bearing a long-chain alkyphenol from A. galanga.194 While 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.197 (+)-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 428–432.199 Quercetin 3-O-robinoiside (433) and galangoflavorosodic (434) were obtained from A. katsumadai Hayata and A. galanga (L.) Swartz., respectively.196,199 Compounds 433–437 from A. densespicata Hayata exhibited moderate NO inhibitory activities.181 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).12 Two pairs of enantiomers of flavonoidilignomes (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(β-hydroxy-cis-styryl)methane (447) was obtained from A. galanga (L.) Willd.200 Whilpinalone (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 (1E,4Z)-5-Hydroxy-1-phenyhexa-1,4-dien-3-one (449) and 2-propenal, 3-[4-(acetoxy)-3-methoxyphenyl] (450) were provided by A. katsumadai Hayata and A. galanga (L.) Willd, respectively.196,198 From A. sichuanensis and A. oxyphilla, dibutyl phthalate (451) was isolated.21,220 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 antioxidation of methyl linoleate in bulk phase.196 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-hydroxyxycinnamyl acetate (455).170,203 Compound 454 displayed weak anti allergic effect,184 and NO production inhibitory activities (IC_{50} = 20 μM).185 and 455 exerted inhibitory activity towards Staphylococcus aureus strain VISA (MIC = 203 μM).21 trans-p-Coumaryl alcohol (456) was a weak NO production inhibitor from A. galanga (L.) Willd (IC_{50} = 72 μM).186 trans-p-Coumaryl diacetate (457) from A. galanga showed a number of bioactivities, including anti-allergy,204 efflux pump inhibition,205 NO production inhibition,165 xanthine oxidase inhibition,206 antileishmania,164 cytotoxicity,165 and antibacteria.25 trans-p-Acetoxyxycinnamyl alcohol (458), trans-p-hydroxycinnamaldehyde acetate (459), and p-coumaric acid (460) were obtained from rhizomes of A. galanga (L.) Willd.184,205 In addition, compound 460 was also distributed in A. galanga (L.) Willd.184, A. sichuanensis Z. Y. Zhu,22 A. speciosa,198 A. blepharocalyx K. Schum.,146 and A. oxyphilla.200 Both A. formosana and A. speciosa K. Schum. were sources of methyl trans-cinnaminate (461).181,188 Seeds of A. blepharocalyx yielded methyl p-hydroxycinnamate (462) and methyl p-hydroxycinnamyl ketone (463).199 From rhizomes of A. galanga (L.) Willd, 12 compounds (464–475) were obtained.13,81,203,207 Among them, 15-1′-acetoxycavhalic 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,\textsuperscript{24} antileishmanial,\textsuperscript{24,48} and antitumor bioactivities,\textsuperscript{25,32,30,28,208} Furthermore, \textit{464} also showed antiallergic,\textsuperscript{204} efflux pump inhibitor,\textsuperscript{205} NO production inhibitor,\textsuperscript{166} xanthine oxidase inhibitor,\textsuperscript{206} gastroprotective,\textsuperscript{209} anti-HIV,\textsuperscript{210} anti-cancer,\textsuperscript{96} antibacterial,\textsuperscript{10,211} plant growth-inhibitory and fungal growth-inhibitory activities.\textsuperscript{212} Two compounds, methyleugenol (466) and hydroxychavicol acetate (467), were isolated from \textit{A. galanga} (L.) Wild.\textsuperscript{531,166,106,204,211} It was demonstrated that 467, a chavicol acetate analogue, suppressed T-bet expression in Th cells.\textsuperscript{211} Besides, 467 also showed weak antibacterial activity against \textit{Staphylococcus aureus} strain VISA (MIC = 0.8 mM).\textsuperscript{32} trans-Confieril dialacetate (468) was proved to be a xanthine oxidase inhibitor.\textsuperscript{206} Three new phenolics \textit{469, 470}, and 471, along with four known ones \textit{472--475} were also yielded by \textit{A. galang}.\textsuperscript{33,101,307} Chavicol acetate (476) and 1’S-acetoxyeugenol acetate (477) were two known phenolics found from \textit{A. conchigera} Griff.\textsuperscript{48} Compound 477 possessed antibacterial,\textsuperscript{206} xanthine oxidase inhibitory,\textsuperscript{206} gastro-protective,\textsuperscript{209} and anti-cancer activities.\textsuperscript{86} Investigation on leaves of \textit{A. flabellata} Ridley provided \textit{478--480}, with strong antibacterial activities against \textit{Staphylococcus aureus}.\textsuperscript{161,162,180} Compounds 481--489 were nine phenolic acids isolated from several \textit{Alpinia} species.\textsuperscript{2,12,128,120,126,211,212} Protocatechuic acid (489) showed potent neuroprotective effect on MPP⁺-induced neurotoxicity and H₂O₂-induced oxidative damage in PC12 cells.\textsuperscript{125,219} In addition, it also exerted anti-aging effect on spleen and liver antioxidative system of senescent mice.\textsuperscript{24} 4-Hydroxybenzaldehyde (490), isolated from \textit{A. sichuanensis} Z. Y. Zhu, \textit{A. blepharocalyx} K. Schum., \textit{A. bracteata}, and \textit{A. galanga} (L.) Wild.\textsuperscript{52,116,157,170} didn’t show any DPPH radical-scavenging activity. Instead, it exhibited inhibitory activity on xanthine oxidase (IC₅₀ = 19.6 μM).\textsuperscript{170,206} Compounds 491--496 were provided by several \textit{Alpinia} plants.\textsuperscript{52,181,157,167,230} 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 \textit{A. speciosa}, both of which showed antioxidant activities.\textsuperscript{197} Investigation on rhizomes of \textit{A. officinarum} Hance yielded \textit{499--506}.\textsuperscript{33} While from rhizomes of \textit{A. bracteata}, a new phenolic glycoside (507) was isolated and showed moderate antioxidant activity on scavenging DPPH free radicals (EC₅₀ = 169 ± 4.8 μM).\textsuperscript{170} Leaves of \textit{A. speciosa} K. Schum. provided coniferin (508) and syringin (509).\textsuperscript{168} Dihydro-5,6-dehydrokawain (510) and 5,6-dehydrokawain (511) were major chemical constituents in several \textit{Alpinia} species.\textsuperscript{51,100,128,177,188,221} They showed antieleucogenic, antithrombotic,\textsuperscript{195} antifungal,\textsuperscript{191} anti-obesity,\textsuperscript{222} and plant growth inhibitory activities.\textsuperscript{223} Recently, it was reported that they could strongly inhibit HIV-1 integrase with respective IC₅₀ values of 4.4 and 3.6 μM L⁻¹. In addition, they exhibited mixed type of inhibition against neuraminidase with both IC₅₀ values of 25 μM.\textsuperscript{224} 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 activity.\textsuperscript{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 \textit{A. speciosa}\textsuperscript{K. Schum. leaves.}\textsuperscript{223} 4-Hydroxy-5,6-dehydrokawain (512) was an α-pryone isolated from \textit{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.\textsuperscript{116,117} It also showed inhibitory effect on platelet aggregation induced by collagen, arachidonic acid (AA), adenosine diphosphate, and ristocetin.\textsuperscript{96} 

7. Steroids

Seven steroids (Fig. 9) were isolated from \textit{Alpinia} species including four cholesterol (513--516) and three sitosterol glycosides (517--519).\textsuperscript{27,52,89,116,118,235} As it is the same in plants of the other genera, β-sitosterol (513) and stigmastanol (514) were also widely distributed in \textit{Alpinia} species.\textsuperscript{52,82,89,118,178,191,226--228} β-Sitosterol-3-O-β-D-glucopyranoside (518) showed potent antiemetic activity induced by CuSO₄.\textsuperscript{27}

8. Alkaloids

Officinaruminate A (520) and officininate B (521), two alkaloids of bi-diarylheptanoid connecting by a pyridine ring were characterized by reduced by chromizes of \textit{A. officinarum} Hance.\textsuperscript{131,157} A study on seeds of \textit{A. katsamadai} Hayata afforded another six alkaloids (522--527) (Fig. 9).\textsuperscript{108,196} 

9. Stilbenes

Six stilbenes, \textit{528--533} (Fig. 9), were all isolated from aerial parts of \textit{A. katsamadai} Hayata.\textsuperscript{20,121} 

10. Others

One esters (534) and three fatty acids, \textit{535--537}, were isolated from several \textit{Alpinia} species.\textsuperscript{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 \textit{A. oxyphylla}.\textsuperscript{29} Two glycosides known as 3-methyl-but-2-en-1-yl-β-D-glucopyranoside (539) and \textit{n-butyl-β-D-fructopyranoside} (540) were isolated from \textit{A. officinarum} Hance.\textsuperscript{55,219} While \textit{541--544} were found in different \textit{Alpinia} species (Fig. 9).\textsuperscript{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.\textsuperscript{231}

11. Conclusions

The number of publications on the chemical constituents and their bioactivities for \textit{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 \textit{Alpinia}. Till 2015, investigations on chemical constitutes of the \textit{Alpinia} species afforded a total of 544 compounds, including 207 terpenoids, 143 diarylheptanoids, 25 phenylpropanoids, 71
flavanones, 66 phenolics, seven steroids, eight alkaloids, six stilbenes, and 11 others (Fig. 11). Among 207 terpenoids, 17 are monoterprenoids, 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.148

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.38,39,231,248–250

In addition, they also showed antiulcer,25 antiplatelet,17,18 antihepatoprotective,225 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. jiangfeng 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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Notes and references