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The Genus *Alpinia*: A Review of Its Phytochemistry and Pharmacology

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ABSTRACT

Genus *Alpinia* consists of over 250 species, which are widely distributed in south and southeast Asia. Many plants of genus *Alpinia* have been used for thousands of years to treat digestive system diseases and as anti-inflammatory drugs. Phytochemical research on this genus has led to the isolation of different kinds of diarylheptanoids, terpenes triterpenoids, phenylbutanoids, lignans, and flavonoids. Experimental evidences revealed that both the crude extracts and pure constituents isolated from the genus *Alpinia* exhibit a wide range of bioactivities such as anti-cancer, anti-oxidant, anti-bacterial, anti-viral, cardiovascular, and digestive system protective effects. Here, we summarize the phytochemistry and pharmacology investigation of the genus *Alpinia*, which can provide reference for further research and drug development.

Key words: Genus Alipinia, phytochemistry, pharmacology, a review

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INTRODUCTION

Genus *Alpinia* is a large genus of the Zingiberaceae family, which is widely distributed in many tropical regions of Asia, including China, India and Indonesia. This genus consist of almost 250 species, of which about 50 species are distributed in east and southwest China. Plants of this genus have been utilized as traditional medicines, food and spices in many countries such as China, Japan and India. *A. katsumada* Hayatai, *A. galangal (L.)* Willd., *A. oxyphylla* Miq., *A. officinarum* Hance, A. *blepharocalyx* K. Schum. and *A. japonica* (Thunb.) Miq. have been used as important and precious Traditional Chinese Medicines (TCMs) in ancient China. Fruits, seeds, leaves and rhizomes of these herbs have been manufactured into medicines and used for the treatment of influenza and vomiting (Figure 1).

Recently, investigations of the genus *Alpinia* have been focused on its biological activities against harmful microbes to deadly diseases such as cancer and fatal viral infections. Phytochemical studies have resulted in the isolation of diarylheptanoids, terpenes, and other compounds from the plant. This review intends to provide a comprehensive insight into the phytochemistry and pharmacology of the genus *Alpinia*.

PHYTOCHEMICAL INVESTIGATIONS

Majority of the compounds isolated from this genus show multiple medical potential and usually possess novel chemical structures. So far, about 200 compounds have been isolated and identified from 45 species of the genus *Alpinia*, including diarylheptanoids, terpenes, flavonoids, phenylpropanoids, volatile oil, lignin, and so on. Based on our comprehensive review, the conclusion can be drawn that, diarylheptanoids, terpenes and flavonoids are abundant in this genus.

1. Diarylheptanoids

Phytochemical investigations showed that diarylheptanoids are the major compounds in the genus *Alpinia*. To date more than 100 diarylheptanoids including 5 characteristic subtypes: linear-diarylheptanoids, cyclic-diarylheptanoids, dimeric-diarylheptanoids, chalcone/flavanone- diarylheptanoids and novel-diarylheptanoids have been found. Linear-diarylheptanoids and chalcone/flavanone- diarylheptanoids are the most common diarylheptanoids in this genus. All these compounds have the same characteristic skeleton of two aromatic rings joined by a heptane chain. Their structures are shown in Figure [2–7], and their detailed names are listed in Table 1.

1.1 Linear-Diarylheptanoids

Linear-diarylheptanoids mainly occur in plants of the genus *Alpinia*, *Curuma*, *Zingiber* (Zingiberaceae), and *Alnus* (Betulaceae). A small amount of these compounds are found

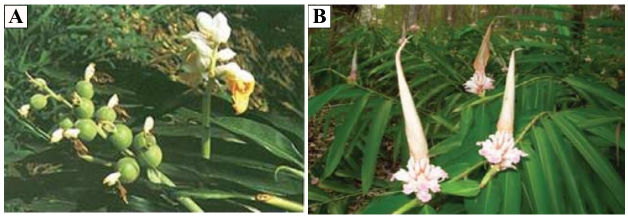


Figure 1. **A** the aerial parts of *A. katsumadai* Hayata including fruits and flowers **B** the aerial parts of *A. oxyphylla* Miq. including flowers

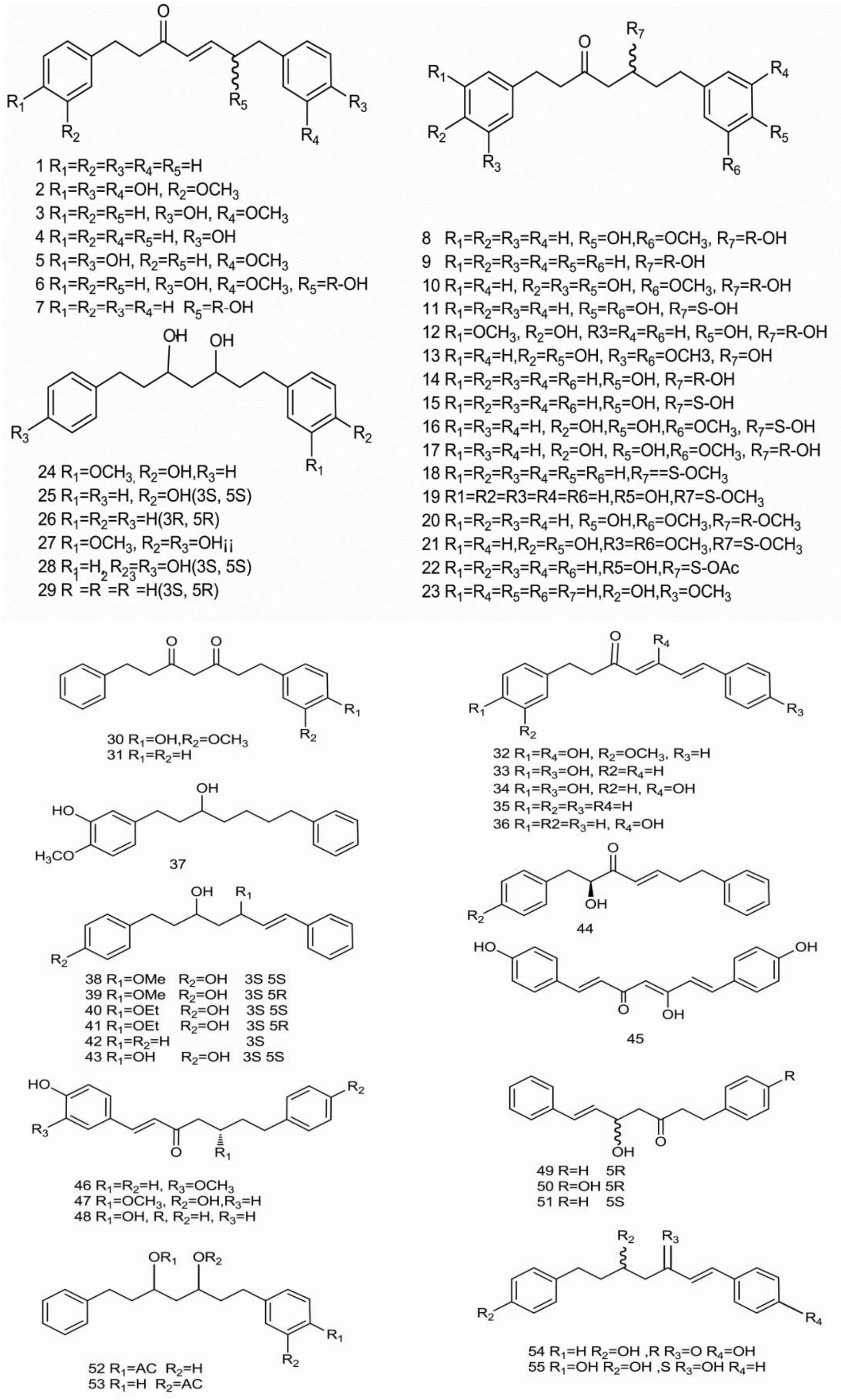


Figure 2. Structures of linear-diarylheptanoids isolated from *Alpinia* plants

Table 1. Detailed names of all kinds of diarylheptanoids of the genus *Alpinia*.

No.	Chemical name	Parts of plants	Plant source	Ref.
	Linear- diarylheptanoids			
1	(4*E*)-1,7-diphenyl-4-en-3-heptanone	rhizomes	*A. officinarum*	[1]
2	(4*E*)-7-(3,4-dihydroxylphenyl)-1-(4-hydroxyl -3-methoxyphenyl)-4-en-3-heptanone	rhizomes	*A. officinarum*	[2]
3	7-(4-hydroxyl-3-methoxyphenyl)-1-phenyl-4-en-3-heptanone	rhizomes	*A. officinarum*	[1]
		rhizomes	*A. galanga*	[3]
		rhizomes	*A. conchigera*	[4]
4	7-(4-hydroxylphenyl)-1-phenyl-4-en-3-heptanone	rhizomes	*A. officinarum*	[1]
5	(*E*)-7-(4-hydroxy-3-methoxyphenyl)-1-(4-hydroxyphenyl) hept-4-en-3-one	rhizomes	*A. officinarum*	[5]
6	(4*E*, 6*R*)-6-hydroxy-7-(4-hydroxy-3-methoxyphenyl)-1-phenyl-4- en-3-heptanone	rhizomes	*A. officinarum*	[6]
7	(4*E*, 6*R*)-6-hydroxy-1,7-diphenyl-4-en-3-heptanone	rhizomes	*A. officinarum*	[6]
8	(*R*)-5-hydroxy-7-(4-hydroxy-3-methoxyphenyl)-1- phenyl-3-heptanone	rhizomes	*A. officinarum*	[5]
		rhizomes	*A. galanga*	[3]
		rhizomes	*A. conchigera*	[4]
9	(5*R*)-1,7-diphenyl-5-hydroxy-3-heptanone	rhizomes	*A. officinarum*	[4]
		rhizomes	*A. katsumadai*	[5]
10	(5*R*)-1-(3,4-dihydroxyphenyl)-5-hydroxy-7-(4-hydroxy-3-methoxy- phenyl)-3- heptanone	rhizomes	*A. officinarum*	[2]
11	(5*S*)-7-(3,4-dihydroxyphenyl)-5-hydroxy-1- phenyl -3 - heptanone	rhizomes	*A. officinarum*	[2]
12	(5*R*)-1-(4-hydroxy-3-methoxy-phenyl)-5-hydroxy-7-(4-hydroxy phenyl)-3- heptanone	rhizomes	*A. officinarum*	[7]
13	1,7-bis(4-hydroxy-3-methoxy-phenyl)-5-hydroxy-3-heptanone	rhizomes	*A. officinarum*	[8]
14	(*R*)-5-hydroxy-7-(4-hydroxyphenyl)-1-phenylheptan-3-one		*A. officinarum*	[9]
15	(*S*)-5-hydroxy-7-(4-hydroxyphenyl)-1-phenylheptan-3-one	rhizomes	*A. officinarum*	[5]
16	(5*S*)-1-(4-hydroxyphenyl)-5-hydroxy-7-(4-hydroxy-3 -methoxy-phenyl)-3- heptanone	rhizomes	*A. officinarum*	[5]
17	(5*R*)-1-(4-hydroxyphenyl)-5-hydroxy-7-(4-hydroxy- 3-methoxy-phenyl)-3- heptanone	rhizomes	*A. officinarum*	[7]
18	(5*S*)-1,7-diphenyl-5-methoxy-3-heptanone	rhizomes	*A. officinarum*	[5]
19	(*S*)-7-(4-hydroxyphenyl)-5-methoxy-1-phenylheptan-3-one	rhizomes	*A. officinarum*	[5]
20	(*R*)-7-(4-hydroxy-3-methoxy phenyl)-5-methoxy-1-phenylheptan-3-one	rhizomes	*A. officinarum*	[5]
21	(*S*)-7-(4-hydroxy-3-methoxyphenyl)- 1-(4-hydroxyphenyl)-5-methoxy-heptan-3-one	rhizomes	*A. officinarum*	[5]
22	5(*S*)-acetoxy-7-(4-dihydroxyphenyl)-1-phenyl-3-heptanone	rhizomes	*A. officinarum*	[10]
23	1-(4-hydroxy-3-methoxyphenyl)-7-phenylheptan-3-one	rhizomes	*A. officinarum*	[11]
		rhizomes	*A. oxyphylla*	[12]
24	1-(4-hydroxy-3-methoxyphenyl) -7-phenyl-3,5-heptanediol	rhizomes	*A. officinarum*	[7]
25	(3*S*,5*S*)-1-(4-hydroxyphenyl)-7-phenyl-3,5-heptanediol	rhizomes	*A. officinarum*	[7]
26	(3*R*,5*R*)-1-(4-hydroxy-3-methoxyphenyl) -7-phenyl-3,5-heptanediol	rhizomes	*A. officinarum*	[5]
27	1-(4-hydroxyphenyl)-7-(4-hydroxy-3-methoxy-phenyl)-3,5- heptanediol	rhizomes	*A. officinarum*	[13]
28	(3*S*,5*S*)-3,5-dihydroxy-1,7-bis(4-hydroxyphenyl)heptane	seeds	*A. blepharocalyx*	[14]
29	(3*S*,5*R*)-3,5-dihydroxy-1,7-diphenyl-heptane	seeds	*A. katsumadai*	[15]
30	1-(4-hydroxy-3-methoxyphenyl)-7-phenylheptane-3,5-dione	rhizomes	*A. officinarum*	[11]
31	1,7-diphenylheptane-3,5-dione	rhizomes	*A. conchigera*	[4]
32	(4*Z*,6*E*)-5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-7-phenylhepta-4,6-dien-3-one	rhizomes	*A. officinarum*	[16]
33	1,7-bis(4-hydroxyphenyl)-hepta-4E,6E-dien-3-one	seeds	*A. blepharocalyx*	[14]
34	5-hydroxy-1,7-bis(4-hydroxyphenyl)-hepta-4E,6E-dien-3-one	seeds	*A. blepharocalyx*	[14]
35	(4*Z*,6*E*)-1,7-diphenyl-hepta-4,6-dien-3-one	seeds	*A. katsumadai*	[15]
36	(4*Z*,6*E*)-5-hydroxy-1,7-diphenyl-hepta-4,6-dien-3-one	seeds	*A. katsumadai*	[15]
37	3-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-7-phenylheptanol	rhizomes	*A. oxyphylla*	[12]
38	(3*S*,5*S*)-3-hydroxy-5-methoxy-1-(4-hydroxyphenyl)-7-phenyl-6E- heptene	seeds	*A. blepharocalyx*	[14]
39	(3*S*,5*R*)-3-hydroxy-5-methoxy-1-(4-hydroxyphenyl)-7-phenyl-6E- heptene	seeds	*A. blepharocalyx*	[14]
40	(3*S*,5*S*)-3-hydroxy-5-ethoxy-1-(4-hydroxyphenyl)-7-phenyl-6E- heptene	seeds	*A. blepharocalyx*	[14]
41	(3*S*,5*R*)-3-hydroxy-5-ethoxy-1-(4-hydroxyphenyl)-7-phenyl-6E- heptene	seeds	*A. blepharocalyx*	[14]
42	(*S*,*E*)-3-hydroxy-1,7-diphenyl-6E-heptene		*A. katsumadai*	[17]
43	(3*S*,5*S*)-3,5-dihydroxy-1,7-diphenyl-1E-heptene	seeds	*A. katsumadai*	[15]
44	(*S*,*E*)-2-hydroxy-1,7-diphenylhept-4-en-3-one	rhizomes	*A. officinarum*	[5]
45	1,7-bis(4-hydroxyphenyl)-3-hydroxy-1,3,6-heptatrien-5-one	seeds	*A. blepharocalyx*	[18]
46	(*E*)-1-(4-hydroxy-3-methoxyphenyl)-7-phenylhept-1-en-3-one	rhizomes	*A. oxyphylla*	[12]
47	(3*S*)-methoxy-1,7-bis(4-hydroxyphenyl)-6*E*-hepten-5-one	seeds	*A. blepharocalyx*	[14]

Table 1. (Continued)

No.	Chemical name	Parts of plants	Plant source	Ref.
48	(3*R*)-3-hydroxy-l-phenyl-7-(4-hydroxyphenyl)-6*E*-hepten-5-one	seeds	*A. katsumadai*	[20]
49	5*R*-hydroxy-l,-7-diphenyl-hepta-6-en-3-one	aerial parts	*A. katsumadai*	[19]
50	5*R*-hydroxy-l-(4'-hydroxyphenyl)-7-phenyl-hepta-6-en-3-one	aerial parts	*A. katsumadai*	[19]
51	5*S*-hydroxy-l,-7-diphenyl-hepta-6-en-3-one	seeds	*A. rafflesiana* *A. mutica*	[21]
52	3-(acetyloxy)alpinikatin	seeds	*A. katsumadai*	[22]
53	5-(acetyloxy)alpinikatin	seeds	*A. katsumadai*	[22]
54	(-)-(R)-4''-hydroxyyashabushiketol	seeds	*A. katsumadai*	[20]
55	(3S,5S)-alpinikatin	seeds	*A. katsumadai*	[20]
	Cyclic- Diarylheptanoids			
56	(3S,7R)-5,6-Dehydro-1,7-bis(4-hydroxyphenyl)-de- Omethylcentrolobine	seeds	*A. blepharocalyx*	[23]
57	(3S,7S)-5,6-dehydro-4¢¢-de-O-methylcentrolobine	seeds	*A. blepharocalyx*	[23]
58	(3S,5S,6S,7R)-5,6-Dihydroxy-1,7-bis(4-hydroxyphenyl)-de-O-methylcentrolobine	seeds	*A. blepharocalyx*	[23]
59	(3S,5R,6S,7R)- 5,6-dihydroxy-1,7-bis(4-hydroxyphenyl)-de-O-methylcentrolobine	seeds	*A. blepharocalyx*	[23]
60	(3S,5S,6R,7R)- 5,6-dihydroxy-1,7-bis(4-hydroxyphenyl)-de-O-methylcentrolobine	seeds	*A. blepharocalyx*	[23]
61	Alpinoid D	rhizomes	*A. officinarum*	[5]
62	3,6-furan-1,7-diphenylheptane	rhizomes	*A. officinarum*	[5]
	Dimeric-Diarylheptanoids			
63	blepharocalyxins A	rhizomes	*A. blepharocalyx*	[23]
64	blepharocalyxins B	rhizomes	*A. blepharocalyx*	[23]
65	blepharocalyxins C	rhizomes	*A. blepharocalyx*	[24]
66	blepharocalyxins D	rhizomes	*A. blepharocalyx*	[24]
67	blepharocalyxins E	rhizomes	*A. blepharocalyx*	[24]
68	alpinoid A	rhizomes	*A. galangal* Willd.	[6]
69	officinaruminane A	rhizomes	*A. galangal* Willd.	[10]
70	alpinin A	rhizomes	*A. galangal* Willd.	[25]
71	alpinin B	rhizomes	*A. officinarum*	[26, 27]
72	alpinin C	rhizomes	*A. officinarum*	[26, 27]
73	alpinin D	rhizomes	*A. officinarum* Hance	[26, 27]
	Chalcone/flavanone- Diarylheptanoids			
74	deoxycalyxin A	rhizomes	*A. pinnanensis*	[28]
75	calyxins A	rhizomes	*A. blepharocalyx*	[24]
76	calyxin B	rhizomes	*A. pinnanensis*	[28]
77	epicalyxin B	rhizomes	*A. pinnanensis*	[28]
78	calyxin H	rhizomes	*A. katsumadai* Hayata	[29]
79	epicalyxin H	rhizomes	*A. katsumadai* Hayata	[29]
80	calyxin C	rhizomes	*A. blepharocalyx*	[24]
81	calyxin D	rhizomes	*A. blepharocalyx*	[24]
82	calyxins E	rhizomes	*A. blepharocalyx*	[24]
83	epicalyxin F	rhizomes	*A. blepharocalyx*	[30]
84	calyxins F	rhizomes	*A. blepharocalyx*	[30]
85	6-hydroxycalyxin F	rhizomes	*A. blepharocalyx*	[30]
86	calyxin G	rhizomes	*A. blepharocalyx*	[30]
87	epicalyxin G	rhizomes	*A. blepharocalyx*	[30]
88	calyxin I	rhizomes	*A. blepharocalyx*	[30]
89	epicalyxin I	rhizomes	*A. blepharocalyx*	[31]
90	calyxin J	rhizomes	*A. blepharocalyx*	[31]
91	epicalyxin J	rhizomes	*A. blepharocalyx*	[31]
92	calyxin K	rhizomes	*A. blepharocalyx*	[31]
93	epicalyxin K	rhizomes	*A. blepharocalyx*	[32]
94	calyxin L	rhizomes	*A. blepharocalyx*	[32]
95	calyxin M	rhizomes	*A. blepharocalyx*	[32]
96	epicalyxin M	rhizomes	*A. blepharocalyx*	[32]
97	alpinnanin A	rhizomes	*A. blepharocalyx*	[32]
98	alpinnanin B	rhizomes	*A. blepharocalyx*	[32]
99	alpinnanin C	rhizomes	*A. pinnanensis*	[28]
100	katsumadain A	rhizomes	*A. pinnanensis*	[28]
101	katsumadain B	rhizomes	*A. pinnanensis*	[28]
102	katsumadain C	rhizomes	*A. katsumadai* Hayata	[33]
103	7-epi-katsumadai C	rhizomes	*A. katsumadai* Hayata	[33]

Table 1. (Continued)

No.	Chemical name	Parts of plants	Plant source	Ref.
104	ent-alpinnanin B	rhizomes	*A. katsumadai* Hayata	[33]
105	ent-alpinnanin A	rhizomes	*A. katsumadai* Hayata	[20]
106	alpinnanin B	rhizomes	*A. katsumadai* Hayata	[20]
107	ent-calyxin H	rhizomes	*A. katsumadai* Hayata	[20]
108	calyxin N	rhizomes	*A. katsumadai* Hayata	[34]
109	ent-calyxin N	rhizomes	*A. katsumadai* Hayata	[34]
110	calyxin O	rhizomes	*A. katsumadai* Hayata	[34]
111	ent-calyxin N	rhizomes	*A. katsumadai* Hayata	[34]
112	calyxin P	rhizomes	*A. katsumadai* Hayata	[34]
113	9''-epicalyxin P	rhizomes	*A. katsumadai* Hayata	[34]
114	calyxin Q	rhizomes	*A. katsumadai* Hayata	[34]
115	calyxin R	rhizomes	*A. katsumadai* Hayata	[34]
116	calyxin S	rhizomes	*A. katsumadai* Hayata	[34]
117	5-epicalyxin S	rhizomes	*A. katsumadai* Hayata	[34]
	Novel-Diarylheptanoids			
118	Katsumadains A	seeds	*A. katsumadai*	[35]
119	Katsumadains B	seeds	*A. katsumadai*	[35]
120	neocalyxins A	seeds	*A. pinnanensis*	[28]
121	neocalyxins B	seeds	*A. pinnanensis*	[28]
122	officinaruminane B	seeds	*A. officinarm* Hance	[10]

from the plants of the genus *Centrolobium* (Leguninocae) and genus *Acer* (Aceraceae).

In *Alpinia* plants, over 50 linear-diarylheptanoids have been isolated and their structures are shown below in Figure 2. Nearly all of these compounds have a hydroxyl or ketone carbonyl group at C-3 position of the core structure, while the C-1, C-4, C-6 are assigned C=C bond.

1.2 Cyclic- Diarylheptanoids

Five different cyclic-diarylhptanoids bearing a tetrahydro-pyran ring have been isolated from the seeds of *A. blepharocalyx* (56–60), and 3 cyclic-diarylhptanoids bearing a furan ring have been obtained from the rhizome of *A. galangal* Willd (61–62). The structures are shown in Figure 3.

1.3 Dimeric-Diarylheptanoids

Belpharocalyxins A-E (63–67) have been isolated from *A. blepharocalyx*. Two symmetrically dimeric-diarylheptanoids have been isolated from rhizomes of *A. galangal* Willd (68–69). One unique dimeric-diarylheptanoid bearing a rare pyridine ring has also been isolated from this plant (70). Recently, two new dimeric-diarylheptanoids have been isolated from the rhizomes of *A. officinarum* and *A. officinarum* Hance (71–73). All structures of these compounds are shown in Figure 4.

1.4 Chalcone/flavanone- Diarylheptanoids

Many researchers call this type of diarylheptanoids "calyxin". *A. blepharocalyx* is the main source of calyxin compounds (74–98) and only about 8 compounds were obtained from *A. pinnanensis* (74, 76–79, 99–101). Recently, these kind of compounds were also found in *A. katsumadai* Hayata (78–79, 103–107, 108–117). Chalcone /flavanone- diarylheptanoids are referred to as such because of the attachment of a chalcone or flavanone moiety at C-5 or C-7 position. To solve the configuration challenges of calyxins G, F, L, M, research based on their synthetic pathways were developed to overcome these challenges[36–37].

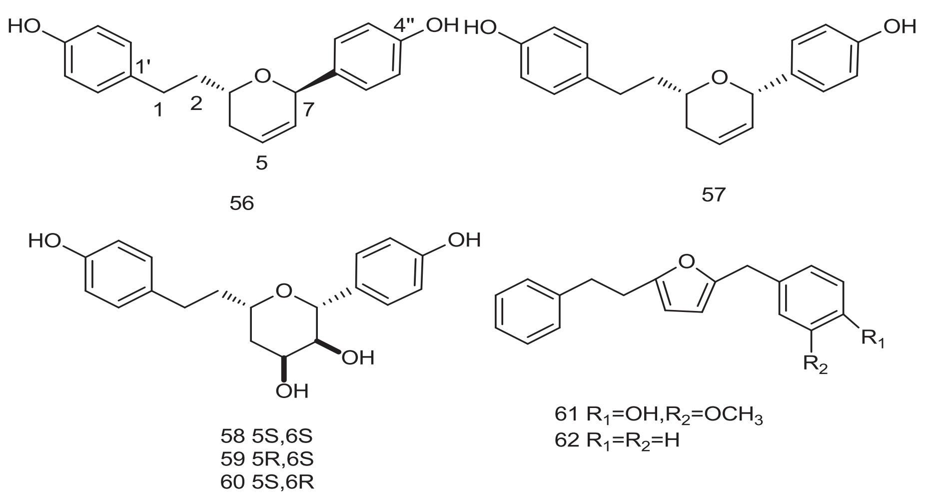


Figure 3. Structures of cyclic- diarylheptanoids isolated from *Alpini* plants

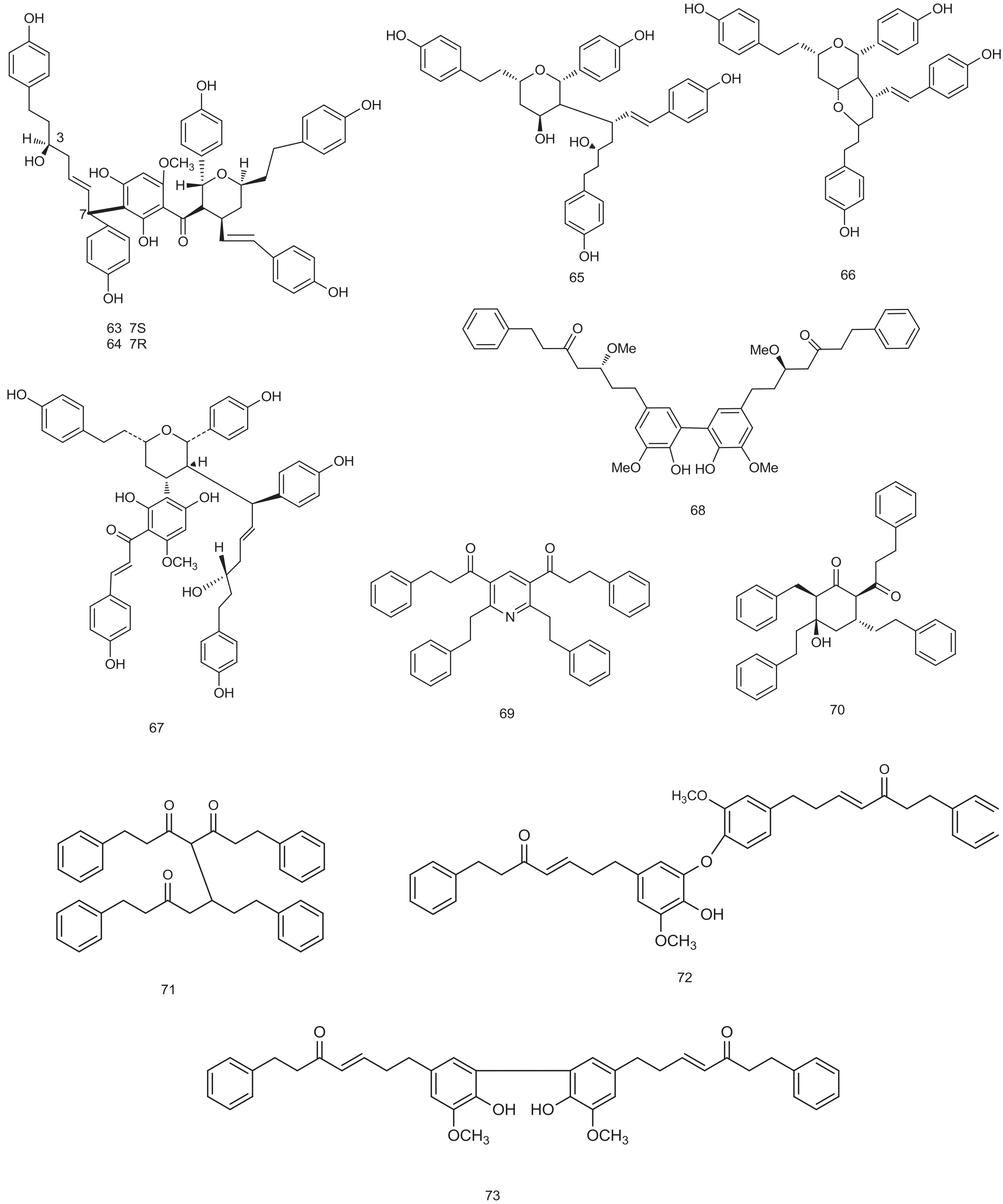


Figure 4. Structures of dimeric-diarylheptanoids isolated from plants in the genus *Alpinia*

Structures of chalcone /flavanone- diarylheptanoids are listed in Figure 5.

1.5 Novel-Diarylheptanoids

In addition, some novel diarylheptanoids with unusual skeletons have been found in *A. katsumadai*, *A. pinnanensis* and *A. officinarm* Hance, their structures are shown in Figure 7.

2. Diterpenoid

Monoterpenes and sesquiterpenes are not often systematically studied in isolation research. Most of them have been identified by HPLC/GC-MS chemical fingerprint analysis from volatile oils. Diterpenoids, especially eudesmane-type diterpenoids have been proven to be the most common subtype in this genus.

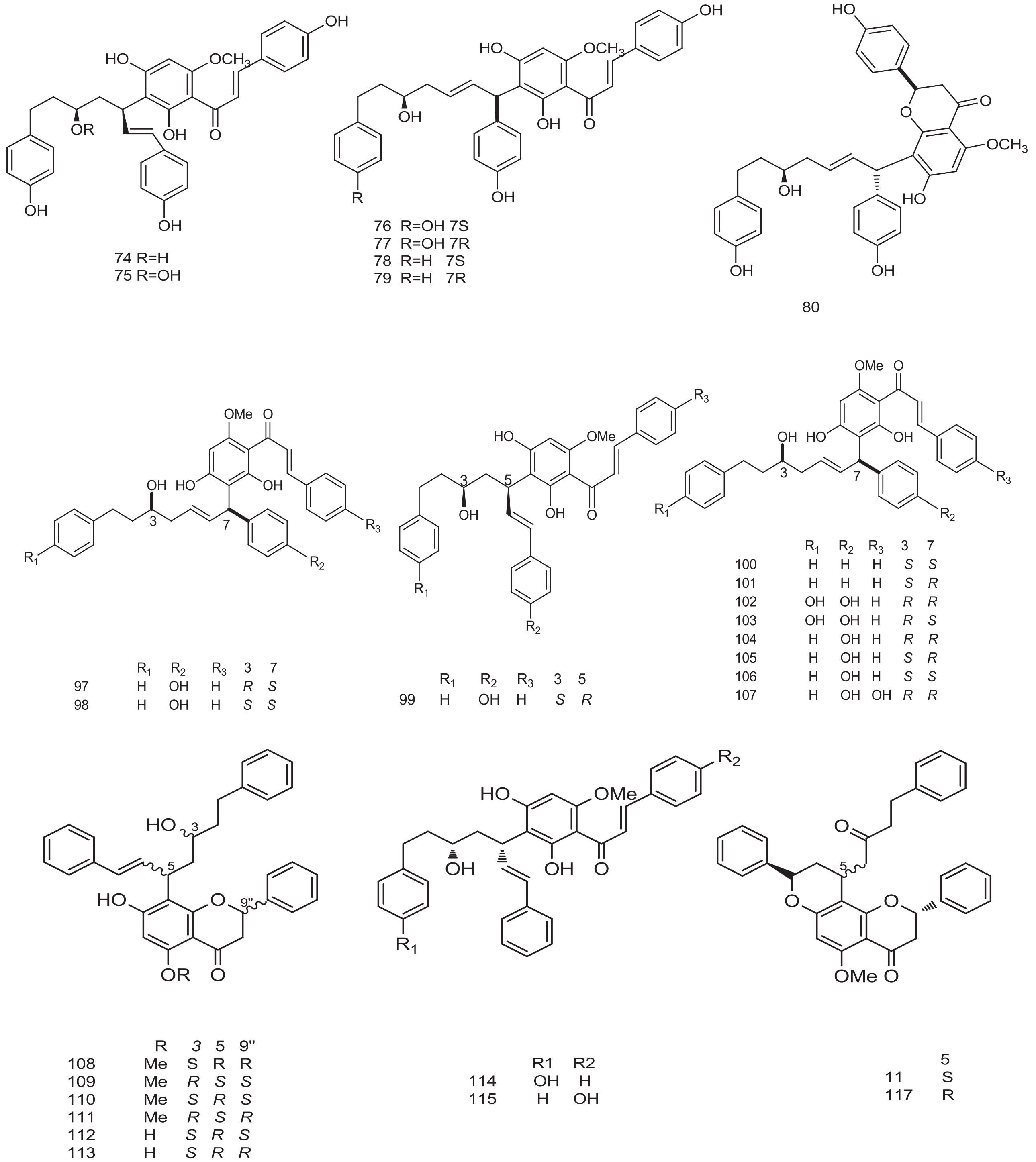


Figure 5. Structures of chalcone /flavanone- diarylheptanoids isolated from plants in the genus *Alpinia*

Diterpenoids are another kind of major compounds found in plants of the genus *Alpinia*. The main category is the eudesmane subtype, in which three kinds of core structures have been isolated from 9 plants of the genus. Most of them are shown in Table 2.

There are also cytotoxic novel diterpenes that can be found in *A. katsumadai*, *A. japonica* Miq., *A. calcarata*, *A. Zerumbet.*[45], *A. galanga* Wild.[46], *A. flabellate*[47], *A. pahangensis* Ridley[48], and structures of these compounds can be found in Figure 8.

3. Phenylpropanoid

So far, phenylpropanoids have been proven to exist in four species of the genus *Alpinia*. Structures of these phenylpropanoids are listed below in Table 3.

4. Lignin

Currently, only two plants (*A. galanga*[49] and *A. officinarum* Hance[50–51]) are known to have these kind of constituents (Figure 9).

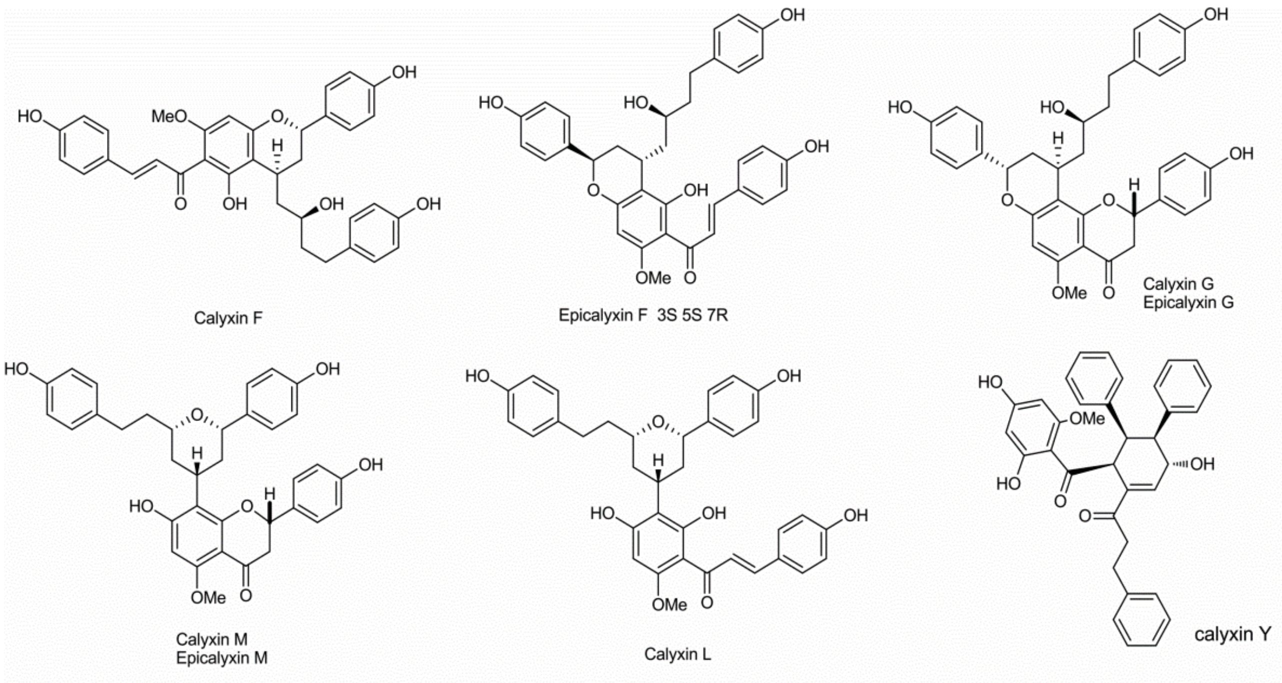
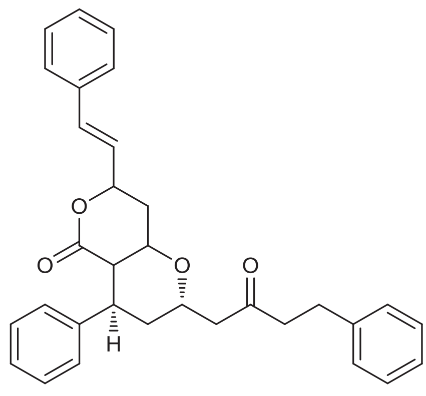


Figure 6. Structures involved in synthetic pathway research.



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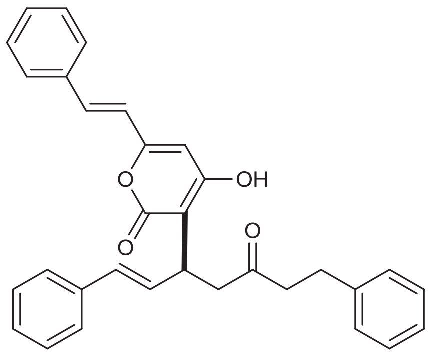

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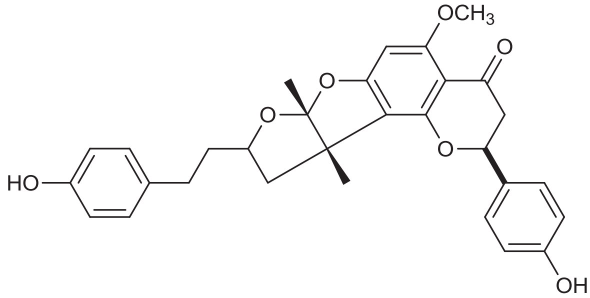

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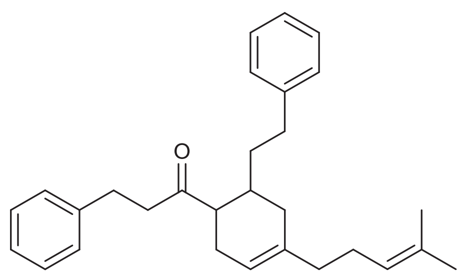

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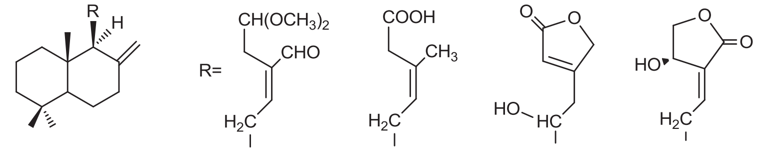
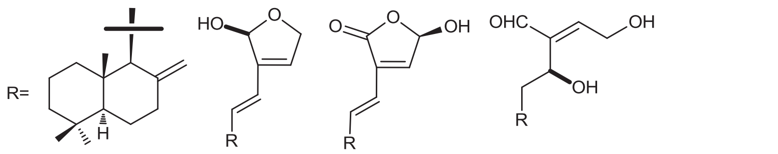
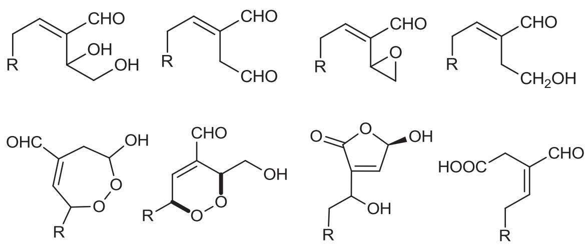
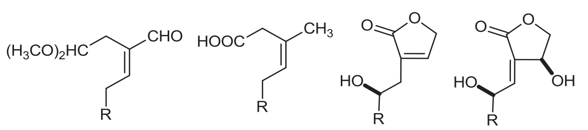
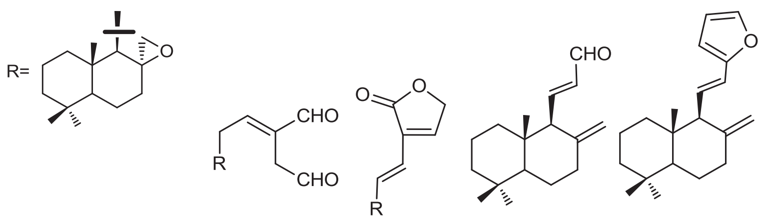
Figure 7. Structures of novel- diarylheptanoids isolated from plants in genus *Alpinia*

Table 2. Diterpenoids of the genus *Alpinia*.

Core structure	Parts	Plants	Reference
	rhizomes	*A. japonica* Miq.	[38]
	the aerial parts	*A. Chinensis.* *A. officinarum*	[39] [40]
	rhizomes	*A. galangal* *A. calcarata.*	[41] [42]
	the aerial parts	*A. Zerumbet.* *A. speciosa* K. Schum.	[43] [44]
	the aerial parts rhizomes	*A. speciosa* K. Schum. *A. katsumadai*	[44] [19]

5. Flavonoids

Flavonoids and their glycosides isolated from the genus *Alpinia* show significant bioactivities. Characteristic flavonoids such as tectochrysin and chrysin have been isolated from *A. oxyphylla* Miq.[54]. Galangin has been isolated from *A. officinarum* Hance, which shows significant anti-oxidant activity[45]. Twenty-five flavonoids have been obtained from the genus *Alpinia*.

6. Volatile oil

Volatile oil is considered to be an important components of the genus *Alpinia* and mainly consists of various terpenoids[62]. Some studies have reported that volatile oil from the genus *Alpinia* has various pharmacological properties, such as anti-hypertensive, anti-nociceptive, anxiolytic, antimicrobial, antipsychotic, and anti-oxidant attributes[62]. Phytomedicine manufacturers often use active marker substances for qualitative and quantitative control[62], therefore, detailed knowledge of the volatile profiles is required for these evaluations. GC-MS becomes the most common and appropriate approach to qualitative and quantitative analysis nowadays. Over 64 constituents have been identified from the volatile oil of *A. oxyphylla* Miq, including a high content of mini monoterpene and diterpenoid[63]. Thirty-seven components make up 80% of the essential oil from *A. katsumadai* Hayata[62]. Fresh rhizomes of *A. calcarata* were subjected to a hydro distillation process to obtain the essential oil which was characterized by GC-MS, and contained the derivatives of 2-octanone, camphene, 1,8-cineole, α fenchyl acetate, 2 hexanone, 4 methyl- 2- hexanone, and other minor compounds[64]. Chemical constituents of the essential oil from *A. blepharocalyx* rhizomes have been determined and mainly consist of amphor (23.13 %), sabinene (11.27 %), α-pinene (9.81 %) and eucalyptol (8.86 %) followed by camphene (8.05 %), sylvestrene (5.61 %) and α-phellandrene (5.00 %)[65]. A new method, GC-FID, coupled with chemometrics, for quantitative and chemical fingerprinting analysis of *A. oxyphylla* volatile oil has also been used. The compounds

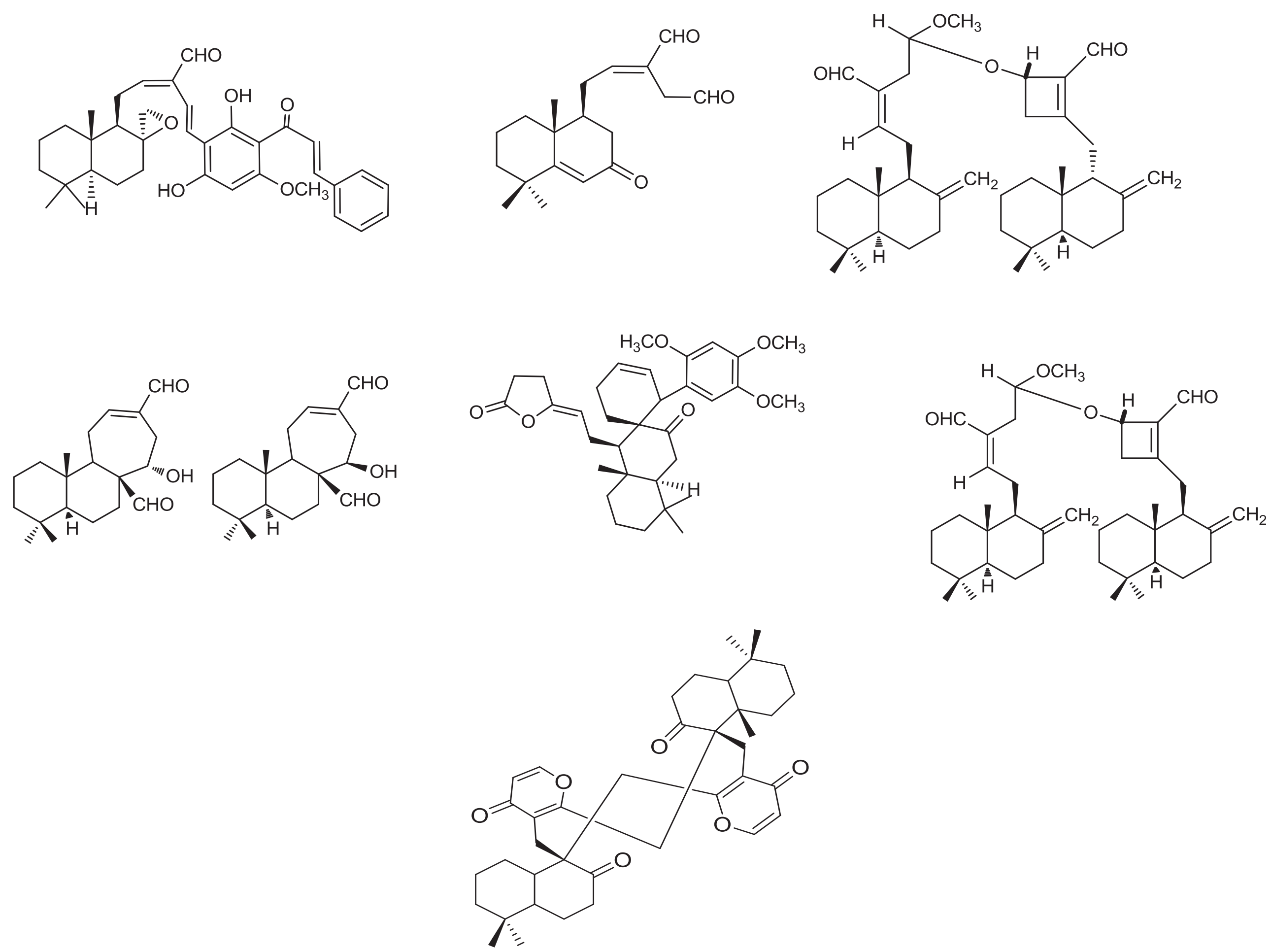


Figure 8. Structures of novel cytotoxic diterpenes isolated from the genus *Alpinia*

p-cymene and nootkatone were detected and are present in large quantities[66].

7. Others

Some other kinds of chemical constituents have also been isolated from plants of the genus *Alpinia*. It has been reported that some glycosides were found in the genus *Alpinia*. Some glycosides from the rhizomes of smaller galangal have been isolated and identified, and these contained trans-2-and trans-3-hydroxy-1,8-cineole glucosides, n-butyl-beta-D-fructopyranoside and alpinoside A[67–68]. Additionally, labdane diterpene glycosides from the stems of *Alpinia densespicata* were isolated and exhibited moderate NO inhibitory activities[69–70]. Apart from glycosides, a novel katsumadain dimer named katsumadain C (Figure 10) has been isolated from *A. katsumadai*[34]. A plant growth inhibitor, dihydro-5, 6-dehydrokawain, has been isolated from *A. speciosa* leaves (Figure 10). In addition, polysaccharides, sitosterol and daucosterol have also been identified[71–74].

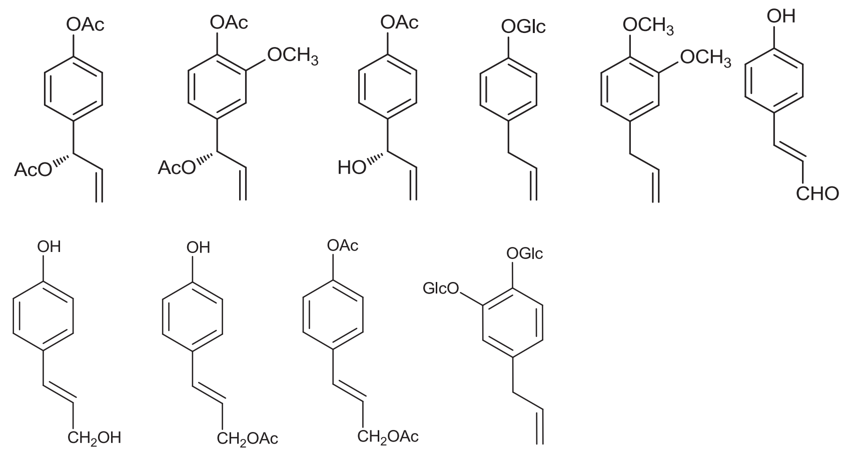
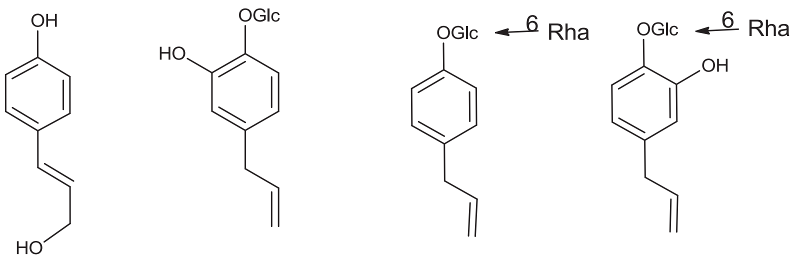
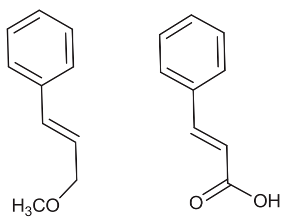
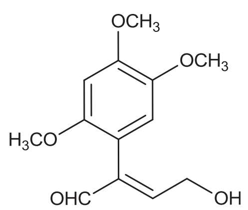
BIOLOGICAL ACTIVITY

1. Anti-cancer activity

Different experiments and assays have been carried out on species of *Alpinia* to determine their anti-cancer activities.

One study showed that the 80% aqueous acetone extract from the rhizomes of *A. officinarum* has been found to inhibit melanogenesis in theophylline-stimulated murine B16 melanoma 4A5 cells, and galangin is the representative constituent of the species, which may induce BEL-7402 cells apoptosis through the mitochondrial pathway[75–76]. In addition, among the constituents isolated from the extract, four diarylheptanoids inhibit melanogenesis with IC_{50} (half maximal inhibitory concentration) values between 10–48μM, and three of them inhibit mRNA expression of tyrosinase and tyrosinase-related proteins-1 and proteins -2, and the protein level of a microphthalmia associated transcription factor. Meanwhile, diarylheptanoids from *A. officinarum* cause distinct but overlapping effects on the translatome of B-Llymphoblastoid cells[77]. The diarylheptanoids isolated from the seeds of *A. blepharocalyx* have an interesting structure: a chalcone or a flavanone moiety attached to a diarylheptanoid skeleton, such as epicalyxin F and blepharocalyxins C-E, which exerts a pronounced antiproliferative effect against human HT-1080 fibrosarcoma and highly liver-metastatic murine colon 26-L5 carcinoma[78]. Cellular viabilities in the presence and absence of experimental agents have been determined using the standard MTT assay. Evidences show that the attachment of a chalcone moiety enhances the antiproliferative activity of diaryalheptanoids[79]. Some other constituents have been

Table 3. Phenylpropanoids of the genus *Alpinia*.

Plant	Structure	Part	Reference
A. galangal		rhizomes	[49]
A. officinarum Hance		rhizomes	[50-52]
A. tonkinensis		rhizomes	[53]
A. flabellate		leaves	[47]

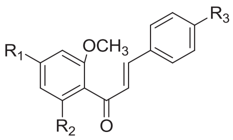
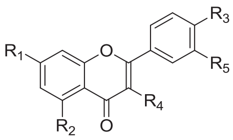
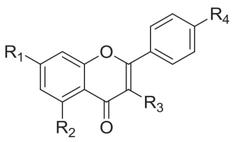
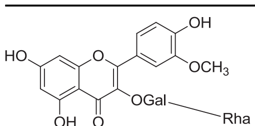
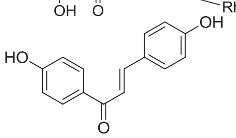
known to show inhibitory effects toward cancer cell lines. The compounds isolated from *A. katsumadai Hayata* (alnustone) show significant inhibitory effects on the growth of Bel 7402 and L0-2 cells[80]. Diterpenes from *A. galangal* exert significant cytotoxic activities[81].

Apart from cell line based tests, the methanolic extract of dried fruits of *A. oxyphylla* has been shown to significantly ameliorate 12-O-tetradecanoylp horbol-13-acetate (TPA)-induced skin tumor promotion as well as ear edema in female ICR mice[82]. The leaf extract of *A. nigra* (2 mg/disc) show mild antibacterial activity compared to tetracycline (50 mg/disc). In the brine shrimp lethality bioassay, the LC_{50} (lethal concentration 50) value of the extract was found to be 57.12 mg/mL, implying a promising cytotoxic effect[83].

2. Anti-oxidant activity

Methanol extracts of many *Alpinia* species show significant anti-oxidant activities. Among them, high anti-oxidant activities have been shown in leaves of *A. zerumbet*, *A. zerumbet* variegata and *A. purpurata* by using DPPH and RP assays, which are related to high TPC values. In spite of lower TPC values, the leaves and flowers of *A. galanga* show highest chelating and β-carotene bleaching abilities[84]. Furthermore, the flavonoids (galangin) from *A. officinarum*

Table 4. Flavonoids from the genus *Alpinia*.

Core structure	Substituent	Plant	Part	Reference
	R_1=OHR_2=OHR_3=OH R_1=OHR_2=OHR_3=H R_1=$OCH_3$$R_2$=OH$R_3$=H R_1=OHR_2=$OCH_3$$R_3$=OH R_1=OHR_2=OHR_3=OH	*A. katsumadai* *A. speciosa* *A. conchigera* *A. blepharocalyx* *A. blepharocalyx*	rhizomes rhizomes rhizomes seeds seeds	[55] [19] [56] [57] [18] [20] [4] [14] [14]
	R_1=OHR_2=OHR_3=H R_4=HR_5=H R_1=OHR_2=$OCH_3$$R_3$=H R_4=HR_5=H R_1=OHR_2=OCH_3 R_3=OHR_4=HR_5=H R_1=$OCH_3$$R_2$=OCH3 R_3=$OCH_3$$R_4$=OH$R_5$=H R_1=$OCH_3$$R_2$=OH R_3=$OCH_3$$R_4$=H$R_5$=OH R_1=$OCH_3$$R_2$=OCH3 R_3=$OCH_3$$R_4$=OH$R_5$=H	*A. katsumadai* *A. katsumadai* *A. katsumadai* *A. tonkinensis* Gagnep *A. tonkinensis* Gagnep *A. tonkinensis* Gagnep	Seeds seeds seeds rhizomes rhizomes rhizomes	[58] [21] [58] [55] [58] [57] [57] [57]
	R_1=OHR_2=OH R_3=OHR_4=H R_1=OHR_2=OH R_3=OHR_4=OCH_3 R_1=OHR_2=OH R_3=OHR_4=OH R_1=OHR_2=OH R_3=HR_4=H R_1=$OCH_3$$R_2$=OH R_3=HR_4=H R_1=$OCH_3$$R_2$=OH R_3=OHR_4=H R_1=$OCH_3$$R_2$=OH R_3=OHR_4=OCH_3 R_1=$OCH_3$$R_2$=$OCH_3$ R_3=OHR_4=OCH_3 R_1=$OCH_3$$R_2$=OH R_3=$OCH_3$$R_4$=OH R_1=OHR_2=OH R_3=$OCH_3$$R_4$=OH	*A. conchigera* *A. officinarum* Hance A. *tonkinensis* Gagnep *A. oxyphylla* Miq *A. oxyphylla* Miq *A. oxyphylla* Miq *A. flabellate* A. *tonkinensis* Gagnep A. *tonkinensis* Gagnep A. *tonkinensis* Gagnep	rhizomes rhizomes rhizomes seeds seeds seeds leaves rhizomes rhizomes rhizomes	[4] [6] [59] [60] [52] [12] [44] [46] [46] [61] [57] [52] [57] [52] [57]
		*A. officinarum* Hance. *A. lepharocalyx*	rhizomes Seeds	[51] [14]

have been shown to possess a variety of biological activities at non-toxic concentrations in organisms. Results from different studies indicate that galangin with anti-oxidative and free radical scavenging activities can modulate enzyme activities and suppress the genotoxicity of chemicals[85].

3. Anti-bacterial activity

An anti-microbial diterpene has been isolated from *A. galanga* during the screening for phytochemical potentiators with antibiotic action; results suggest that the antifungal activity of this compound is due to a change in membrane permeability arising from membrane lipid alternation[86]. Additionally, three diarylheptanoids, trans, trans-1,7-diphenylhepta-4, 6-dien-3-one,(5R)-trans-1,7-diphenyl-5-hydroxyhept-6-en-3-one, (3S,5S)-trans-1,7-diphenylhept-1-ene-3,5-diol from *A. katsumadai,* reveal significant anti-mycobacterial activity on EtBr accumulation and efflux as well as a synergistic effect in combination with rifampicin, which should be taken into consideration when screening lipophilic plant extracts for their anti-mycobacterial and modulating activities[87].

4. Anti-viral activity

Currently, AIDS remains a major global health issue and an investigation hotspot. Despite a number of therapeutic

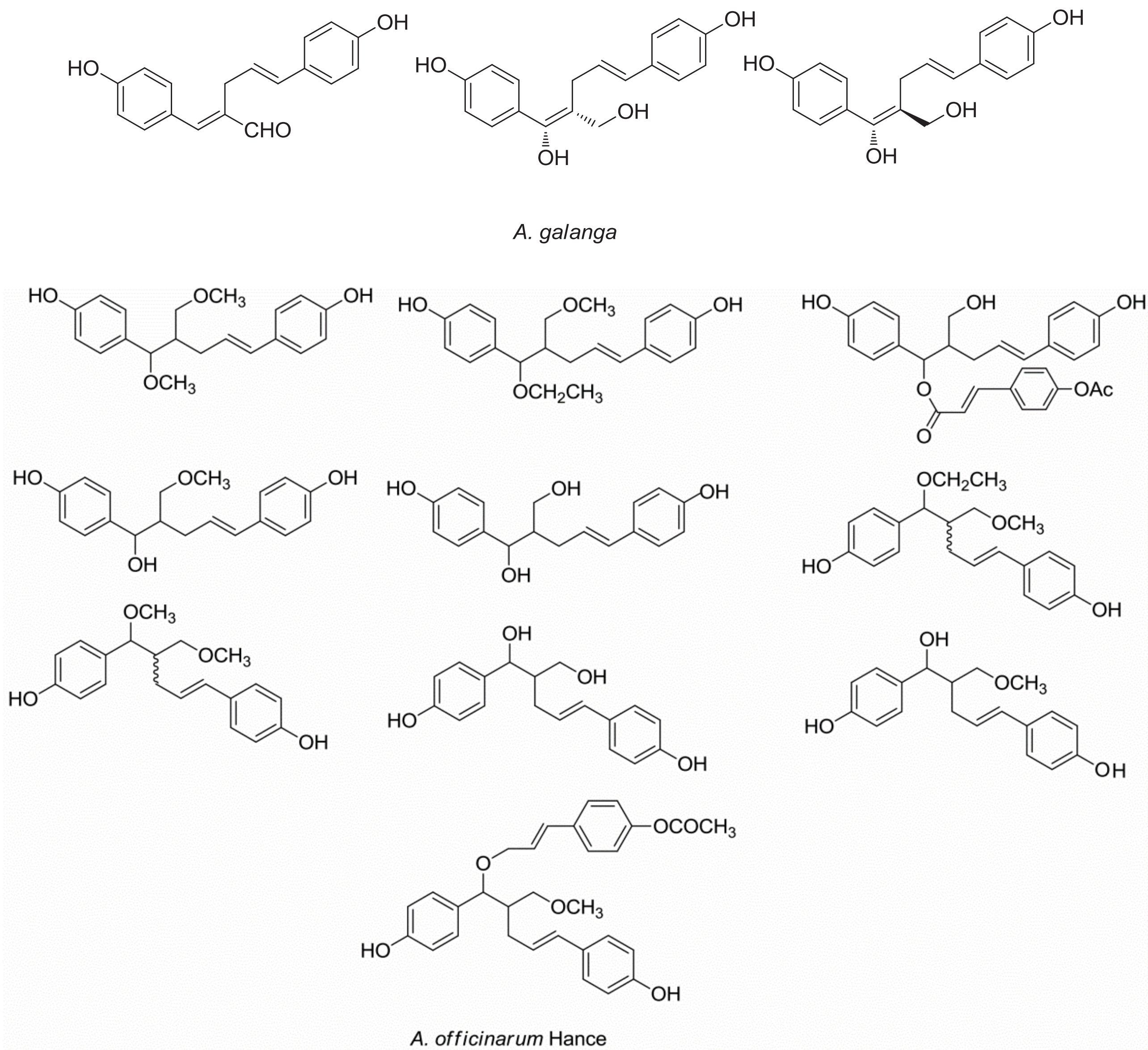


Figure 9. Structures of lignin isolated from plants of the genus *Alpinia*

advancements, there is still an urgent need to develop a new class of therapy for human immunodeficiency virus (HIV). It has been shown that 1'S -1'-acetoxychavicol acetate (ACA), which was isolated from *A. galangal,* can be a blocker in HIV-1 replication in peripheral blood mononuclear cells. Meanwhile, ACA and didanosine act synergistically to inhibit HIV-1 replication[88]. Thus, ACA may be a novel treatment for HIV-1 infection, especially in combination with other anti-HIV drugs. *Alpinia* can also show inhibitory effects toward other viruses. The anti-influenza A/PR/8/34 (H1N1) virus activities of ten diarylheptanoids isolated from *A. officinarum* have been examined using the MTT method. Results show that two of these compounds exhibit potential anti-viral activity against influenza virus *in vitro*[89].

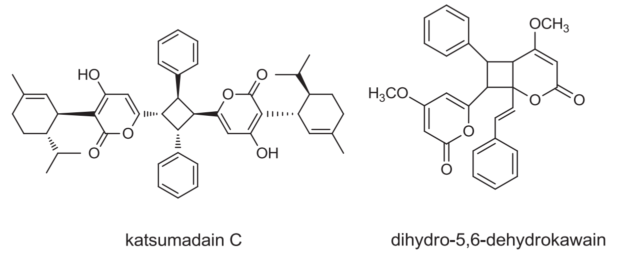


Figure 10. Structures of katsumadain C and dihydro-5, 6-dehydrokawain

5. The digestive system protection

Many Chinese herbal drugs have been used as protective agents for the digestive system, including drugs manufactured from the *Alpinia* species. Two compounds that have been isolated from *A. katsumadai* showed anti-emetic activities on copper sulfate-induced emesis in young chicks[90]. The methanol and ether extracts of *A. officinarum* showed obvious effects against ulcer induced by water-immersion stress method in mice[91]. As a kind of traditional herbal medicine in China, the volatile oil of *A. villosum* exhibits inhibition phenomenon, but non-volatile compounds exhibit promotion phenomenon[92].

6. The cardiovascular system protection

Some compounds of the *Alpinia* species have been proven to exhibit cardiovascular system protection. 5, 6-dehydrokawain, which is isolated from *A. mutica*, showed strong inhibition on platelet aggregation induced by arachidonic acid with IC_{50} values of less than 84μM[93]. Intravenous treatment with either the essential oil of *A. zerumbet* or one of its compounds, Trp-4-ol, dose-dependently decreases blood pressure in conscious deoxycorticosterone-acetate-salt hypertensive rats, and this action is significant when compared with uninephrectomized controls[94]. Cardamonin and alpinetin, isolated from *A. henryi K. Schum.*, can relax rat mesenteric arteries through multiple mechanisms. They induce both endothelium-dependent and -independent relaxation[95]. A pancreatic lipase inhibitor, 5-hydroxy-7-(4'-hydroxy-3'-methoxyphenyl)-I-phenyl-3-heptanone (HPH), from the rhizomes of *A. officinarum*, significantly lowers serum triglyceride (TG) levels in corn oil feeding-induced triglyceridemic mice, and reduces serum TG and cholesterol in Triton WR-1339-induced hyperlipidemic mice[96].

7. Anti-inflammatory and analgesic activity

The ethanolic extract and three pure components from *A. katsumadai* HAYATA seeds have been investigated for the production of inflammatory mediators and some potential underlying mechanisms in lipopolysaccharide (LPS)-induced inflammation RAW264.7 cells. The results show they possess anti-inflammatory activities via induction of HO-1 expression which is partly responsible for the anti-inflammatory effects[97]. *A. katsumadai* extract has remarkable, non-opioid receptor-mediated analgesic effects on PBQ-induced writhing and carrageenan-induced hyperalgesia that occurs via cyclooxygenase-2 inhibition[98].

CONCLUSION

All data demonstrate that *Alpinia* is a genus with rich resources. Plants of the genus *Alpinia* has a long history of being used as folk medicine not only in China, but also in other countries of Asia. In view of the reported studies on the phytochemistry, biological activities and clinical practices research, the traditional usage has been proven, but there are still many questions to be answered.

Compounds with novel skeletons have been isolated from plants of the genus *Alpinia* in our laboratory. Phytochemical research has shown that diterpenoids are the major components and diarylheptanoids are the most characteristic components of the genus *Alpinia*. Most of these compounds are obtained from the rhizomes and seeds, while compounds are found from the leaves or fruits. Therefore, the other parts of the plants of the genus *Alpinia* should be of interest to researchers in order to discover more therapeutic drugs in the field of natural product research.

As a result of pharmacological activity investigation; *in vivo* and *in vitro*, pure compounds or crude extracts revealed a large range of biological activities, especially in anti-tumor and anti-viral effects. These positive effects need further proof by way of animal experiments and clinic trials.

Our present paper has systematically reviewed the phytochemistry and pharmacology research of the genus *Alpinia* and provided comprehensive information on this genus *Alpinia*.

We hope this review points out the importance of the genus *Alpinia* and provides leads for future investigations into plants of the genus *Alpinia*.

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