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Article *in* Medicinal Chemistry Research · November 2023

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REVIEW ARTICLE

Kaempferia diterpenoids and flavonoids: an overview on phytochemistry, biosynthesis, synthesis, pharmacology, and pharmacokinetics

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Received: 19 September 2023 / Accepted: 27 October 2023

Abstract
Kaempferia species have contained various crucial ethnobotanical features, and are being used as traditional folk medicines in some Southeast Asia. This review tends to highlight important information (phytochemistry, biosynthesis, synthesis, pharmacology, and pharmacokinetics) of *Kaempferia* principal phytochemical classes diterpenoids and flavonoids. The electronic sources, e.g., Google Scholar, Sci-Finder, and Web of Science, and the most meaningful keywords "*Kaempferia*", "diterpenoids", and "flavonoids" have been more often utilized for searching the literature. More than 190 phytochemicals type diterpenoids (153 compounds) and flavonoids (42 compounds) have been separated from *Kaempferia* species. Isopiramanes and flavones are representative compounds. *Kaempferia* diterpenoids and flavonoids established great attention due to their pharmacological values such as antioxidative, anti-inflammatory, antimicrobial, antiviral, and antimalarial activities, especially anticancer. They also protected against harms to the neuron, skin, and liver. Pharmacokinetic studies revealed that metabolism of *Kaempferia* flavonoids might be related to the transformation of hydroxyl groups. Advances in chromatographic separations to obtain huge amounts of *Kaempferia* isolated compounds are expected. Future in vivo and clinical investigations on the components of *Kaempferia* should be carried out to provide accurate dosage and normative recommendations.

Keywords Kaempferia · Diterpenoids · Flavonoids · Phytochemistry · Pharmacology

Introduction

Medicinal plants have provided for global healthcare requirements from ancient time period [1–3]. Since the beginning of time, natural products made from plants have benefited the pharmaceutical sector. People in the world currently rely on traditional medicines to treat minor illnesses [4, 5]. Due to their interdependence and a profusion of secondary metabolites, medicinal plants exhibit a variety of pharmacologically chemical compounds [4–6]. Geographic zones, climate changes, and other natural elements that have great impacts on the biosynthetic pathways are some of the reasons that have contributed to variances in secondary metabolites [6].

Kaempferia is one of the most important genera in the ginger family Zingiberaceae with about 52 accepted species [7]. Almost *Kaempferia* species are annual rhizomatous plants found available in Southeast Asia, China, India, and Bangladesh [7]. Similar to the other ginger plants, species in the genus *Kaempferia* themselves come with a lot of benefits in use. *Kaempferia pandurata*, with local names as Temu kunci in Indonesia or Krachai in Thailand, has been traditionally utilized as a spice, in particular, its young rhizomes were very well-known for seasoning vegetables [8]. *K. galanga*, sometimes referred to as Kencur, Karchoor, or aromatic ginger, is advised for cough and colds, fever, headaches, skin rashes, arthritis, vertigo, gastroenteritis, pancreas diseases, antidotes for snake venom, inflammation, blood vomiting, and mouth sores [9]. By this mean, the fresh and dried parts of *Kaempferia* species, especially the

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Published online: 21 November 2023

rhizomes, were also the selective materials in phytochemical investigations. Many experimental attempts had been carried out, resulting in the isolation of a vast number of secondary metabolites. Among isolated compounds, diterpenoids and flavonoids are likely to be the main chemical classes [10–21]. Remarkably, these chemical classes are also responsible for various featured pharmacological values, such as anticancer, anti-inflammation, and neuroprotective and hepatoprotective activities [22–25]. To date, there have been several reviewed assessments about the single plants [26–28]. However, an overview highlighted natural occurence and the pharmacological role of *Kaempferia* diterpenoids and flavonoids still remained unknown. The ultimate aim of this review is to highlight natural observation and pharmacological values of these two phytochemical classes. Besides that, biosynthetic pathways of diterpenoids and synthetic steps of flavonoids were comprehensively reviewed. Structure-activity relationship was also mentioned. Pharmacokinetic progress of *Kaempferia* flavonoids is also discussed.

Phytochemistry

Phytochemical investigations on *Kaempferia* species resulted in the isolation of various chemical classes, in which diterpenoids and flavonoids can be seen as the main classes. Table 1 provides a list of 195 isolates type diterpenoids **1–153** and flavonoids **149–195**. Their name was set in the order of alphabetic words, as well as similar subclasses will be placed close each other. Herein, these metabolites were the results of chromatographic separation and NMR (nuclear magnetic resonance)-structural elucidation. Significantly, the rhizomes were the main material for phytochemical studies.

Diterpenoids

Diterpenoids-derived from *Kaempferia* plants can be divided into abietanes **1–15**, clerodanes **16–22**, labdanes **23–39**, isopiramanes **40–148**, and decalin–fused dihydropyrans **149–153** (Table 1 and Fig. 1). *Kaempferia* abietanes **1–15** were only found in *K. angustifolia*, *K. elegans*, and *K. roscoeana* [29–31]. Among these isolates, elegansols A–E (**6–10**), kaempfolienol (**11**), and roscotanes A-D (**12–15**) were previously undescribed compounds separates from *K. elegans* rhizome, *K. angustifolia* rhizome, and *K. roscoeana* whole plant, respectively [29–31]. Clerodanes **16–22** were only found in *K. pulchra* rhizome, in which propadane C (**21**) was a new compound in literature [32].

The next chemical class of *Kaempferia* ditepernoids is labdanes **23–39**. *K. candida*, *K. roscoeana*, especially *K. elegans* are species reported to contain labdanes. Kaempcandiol (**29**) and propadanes A-B (**37–38**) were new isolates derived from *K. candida* root and rhizome and *K. elegans* rhizome, respectively, whereas the remaining labdanes were found in the genus *Kaempferia* for the first time [29, 32, 33].

Isopiramane derivatives are likely the main class of *Kaempferia* diterpenoids with more than 100 isolates (Table 1). Isopiramanes can be observed in *K. elegans*, *K galanga*, *K. koratensis*, *K. marginata*, *K. pulchra*, *K. roscoeana*, and *K. saraburiensis*. Various compounds were identified as new compounds, including 1α-acetoxysandaracopimaradien-2α-ol (**40**), (1 *S*,5 *S*,9 *S*,10 *S*,11 *R*,13 *R*)-1,11-dihydroxypimara-8(14),15-diene (**50**), 1α,2α-dihydroxypimara-8(14),15-dien-7-one (**51**), 1α,14α-dihydroxyisopimara-8(9),15-diene (**52**), galangols A-D (**56–59**), 1α-hydroxy-14α-methoxyisopimara-8(9),15-diene (**60**), (5 *S*,6 *R*,9 *S*,10 *S*,13 *R*)-6-hydroxypimara-8(14),15-diene-1-one (**63**), kaemgalangols A-F (**69-74**), kaempulchraols A-W (**61** and **75–96**), koratanes A-B (**97–98**), marginaols A-M (**99–111**), marginols A-K (**112–122**), roscoranes A-D (**124–127**), shanpanootols A-H (**133–140**), saraburanes A-B (**141–142**), saraburol (**143**), (1 *R*,2 *S*,5 *S*,7 *S*,9 *R*,10 *S*,13 *R*)-1,2,7-trihydroxypimara-8(14),15-diene (**144**), (1 *R*,2 *S*,5 *S*,9 *S*,10 *S*,11 *R*,13 *R*)-1,2,11-trihydroxypimara-8(14),15-diene (**145**), and (1 *S*,5 *S*,7 *R*,9 *R*,10 *S*,11 *R*,13 *R*)-1,7,11-trihydroxypimara-8(14),15-diene (**146**) [9, 14, 15, 17, 20, 21, 25, 29, 34–43]. The CH_2Cl_2 extract of *K. elegans* rhizome also contained five new decalin-fused dihydropyrans elegansins A-E (**149–155**) [30].

Flavonoids

Kaempferia flavonoids included flavones **154–176**, flavanones **177–183**, flavans **184–185**, flavenes **186–187**, and chalcones **188–195** (Table 1 and Fig. 2). Taking flavones **154–176** into consideration, they can be seen as the representatives since various metabolites were isolated frequently, including 5,3'-dihydroxy-3,7,4'-trimethoxyflavone (**155**), 5,4'-dihydroxy-7-methoxyflavone (**156**), 5,7-dimethoxyflavone (**157**), 5-hydroxy-3,7-dimethoxyflavone (**159**), 5-hydroxy-7,4'-dimethoxyflavone (**160**), techtochrysin (**161**), 5-hydroxy-3,7,4'-trimethoxyflavone (**162**), retusine (**164**), 3,5,7,3',4'-pentamethoxyflavone (**168**), 3,5,7,4'-tetramethoxyflavone (**172**), 5,7,3',4'-tetramethoxyflavone (**173**), 3,5,7-trimethoxyflavone (**175**), and 5,7,4'-trimethoxyflavone (**176**) (Table 1). *Kaempferia* flavones were highly concentrated in the rhizomes of some plants such as *K. angustiflora*, *K. elegans*, *K. galanga*, *K. parviflora*, *K. pulchra*, and *K. rotunda*. It is also successful to estimate the qualification of the presentative flavones in *Kaempferia* species. For instance, *K. parviflora* rhizomes, which were collected from Thailand, were associated with high percentages of flavones **156** (1.3%), **173** (1.01%), and **1.76** (1.6%) [44]. Seven flavanones **177–183** were also found in

Table 1 Diterpenoids and flavonoids from *Kaempferia* plants

No	Compounds	Plants	References
Abietanes			
1	Abieta-8,11,13-trien-7α-ol	*K. elegans* rhizome, and *K. roscoeana* whole plant	[29, 30]
2	Abieta-8,11,13-trien-11-ol	*K. elegans* rhizome	[30]
3	*ar*-Abietatriene	*K. elegans* rhizome, and *K. roscoeana* whole plant	[29, 30]
4	7-Dehydroabietanone	*K. roscoeana* whole plant	[29]
5	12-Deoxyroyleanone	*K. elegans* rhizome	[30]
6	Elegansol A	*K. elegans* rhizome	[30]
7	Elegansol B	*K. elegans* rhizome	[30]
8	Elegansol C	*K. elegans* rhizome	[30]
9	Elegansol D	*K. elegans* rhizome	[30]
10	Elegansol E	*K. elegans* rhizome	[30]
11	Kaempfolienol	*K. angustifolia* rhizome	[31, 49]
12	Roscotane A	*K. roscoeana* whole plant	[29]
13	Roscotane B	*K. roscoeana* whole plant	[29]
14	Roscotane C	*K. roscoeana* whole plant	[29]
15	Roscotane D	*K. roscoeana* whole plant	[29]
Clerodanes			
16	Cleroda-2,4(18),14-trien-13-ol	*K. pulchra* rhizome	[32]
17	Dysoxydensin E	*K. pulchra* rhizome	[32]
18	(+)-13-epi-2α-hydroxykolavelool (13-*epi*-roseostachenol)	*K. pulchra* rhizome	[32]
19	(–)-2*β*-hydroxykolavelool	*K. pulchra* rhizome	[32]
20	(–)-Kolavelool	*K. pulchra* rhizome	[32]
21	Propadane C	*K. pulchra* rhizome	[32]
22	13-*epi*-Roseostachenone	*K. pulchra* rhizome	[32]
Labdanes			
23	Anticopalic acid	*K. elegans* rhizome	[32]
24	Anticopalol	*K. elegans* rhizome	[32]
25	Aromaticane J	*K. candida* root and rhizome	[33]
26	Calcaratarin A	*K. pulchra* rhizome	[32]
27	Coronadiene	*K. candida* root and rhizome	[33]
28	(+)-15,16-Epoxy-8(17),13(16),14-labdatriene	*K. elegans* rhizome	[32]
29	Kaempcandiol	*K. candida* root and rhizome	[33]
30	(12*Z*,14 *R*)-Labda-8(17),12-dien-14,15,16-triol	*K. roscoeana* whole plant	[29]
31	Labda-8(17),13(14)-diene-15,16-olide	*K. elegans* rhizome	[32]
32	(+)-Labda-8(17),13(Z)-diene-15,16-diol	*K. elegans* rhizome	[32]
33	8(17)-Labden-15-ol	*K. elegans* rhizome	[32]
34	Longpene A	*K. candida* root and rhizome	[33]
35	Methyl anticopalate	*K. elegans* rhizome	[32]
36	13-Oxo-14,15-bis-nor-labd-8(17)-ene	*K. elegans* rhizome	[32]
37	Propadane A	*K. elegans* rhizome	[32]
38	Propadane B	*K. elegans* rhizome	[32]
39	(+)-Pumiloxide	*K. elegans* rhizome	[32]
Isopiramanes			
40	1*α*-Acetoxysandaracopimaradien-2*α*-ol	*K. marginata* rhizome	[34, 58]
41	2*α*-Acetoxysandaracopimaradien-1α-ol	*K. galanga* rhizome, and *K. marginata* rhizome	[34–36,59]
42	6*β*-Acetoxysandaracopimaradien-1*α*,9*α*-diol	*K. galanga* rhizome, and *K. marginata* rhizome	[37–39,77]
43	6*β*-Acetoxysandaracopimaradiene-9*α*-ol-1-one	*K. galanga* rhizome, and *K. marginata* rhizome	[38, 39]
44	6*β*-Acetoxysandaracopimaradiene-9*α*-ol	*K. galanga* rhizome	[39]
45	Boesenberol F	*K. marginata* rhizome	[38]
46	Boesenberol I	*K. galanga* rhizome, *K. koratensis* rhizome, and *K. saraburiensis* whole plant	[25, 40–42]
47	Boesenberol J	*K. galanga* rhizome, *K. koratensis* rhizome, *K. marginata* rhizome, and *K. saraburiensis* whole plant	[25, 35, 38, 40–42]
48	Curcumrinol A	*K. koratensis* rhizome, and *K. saraburiensis* whole plant	[25, 40]
49	Curcumrinol B	*K. galanga* rhizome, and *K. koratensis* rhizome	[25, 42]

Table 1 (continued)

No	Compounds	Plants	References
50	(1*S*,5*S*,9*S*,10*S*,11*R*,13*R*)-1,11-Dihydroxypimara-8(14),15-diene	*K. galanga* rhizome, and *K. marginata* whole plant and rhizome	[17, 35–37, 42, 58]
51	1*α*,2*α*-Dihydroxypimara-8(14),15-dien-7-one ((1*R*,2*S*,5*S*,7*S*,9*R*,10*S*,13*R*)-1,2-Dihydroxypimara-8(14),15-diene-7-one)	*K. galanga* rhizome, *K. marginata* whole plant, *K. pulchra* rhizomes, and *K. roscoeana* whole plant	[21, 29, 35, 36]
52	1*α*,14*α*-Dihydroxyisopimara-8(9),15-diene	*K. galanga* rhizome, and *K. marginata* rhizome	[37, 39]
53	7*β*,9*α*-Dihydroxyisopimara-8(14),15-diene (Sandaracopimaradiene-7*β*,9*α*-diol)	*K. galanga* rhizome, and *K. pulchra* rhizome	[17, 35, 39]
54	6*β*,14*α*-Dihydroxyisopimara-8(9),15-diene	*K. galanga* rhizome	[39]
55	6*β*,14*β*-Dihydroxyisopimara-8(9),15-diene	*K. galanga* rhizome	[39]
56	Galangol A	*K. galanga* rhizome	[42]
57	Galangol B	*K. galanga* rhizome	[42]
58	Galangol C	*K. galanga* rhizome	[42]
59	Galangol D (Sandaracopimaradiene-9*α*-ol)	*K. galanga* rhizome, and *K. koratensis* rhizome	[25, 41, 42]
60	1*α*-Hydroxy-14*α*-methoxyisopimara-8(9),15-diene	*K. galanga* rhizome	[39]
61	1*α*-Hydroxyisopimara-8(14),15-diene (Sandaracopimaradien-1α-ol, Kaempulchraol I)	*K. galanga* rhizome, *K. marginata* rhizome and whole plant, *K. pulchra* rhizome, and *K. roscoeana* whole plant	[14, 17, 29, 35, 36, 41, 42, 58]
62	(2*R*)-*ent*-2-Hydroxyisopimara-8(14),15-diene (*ent*-Sandaracopimaradien-2-ol)	*K. galanga* rhizome, *K. marginata* rhizome, and *K. pulchra* rhizome	[16, 17, 35]
63	(5*S*,6*R*,9*S*,10*S*,13*R*)-6-Hydroxypimara-8(14),15-diene-1-one (6*β*-Hydroxypimara-8(14),15-diene-1-one)	*K. galanga* rhizome, and *K. marginata* whole plant	[35, 36, 41, 42]
64	7*α*-Hydroxyisopimara-8(14),15-diene	K. *elegans* rhizome, *K. galanga* rhizome, *K. pulchra* rhizome, and *K. roscoeana* whole plant	[15, 17, 29, 30, 58]
65	9*α*-Hydroxyisopimara-8(14),15-dien-7-one	*K. pulchra* rhizome	[17]
66	Isopimara-8(9),15-dien-7-one	*K. roscoeana* whole plant	[29]
67	(–)-Isopimara-8(14),15-diene ((–)-Sandaracopimaradiene)	K. *elegans* rhizome, *K. roscoeana* whole plant, and *K. saraburiensis* rhizome	[29, 30, 35, 36, 39–41]
68	Isopimara-8(14),15-diene-7-oxo-2*α*-ol	*K. marginata* rhizome	[58]
69	Kaemgalangol A	*K. galanga* rhizome, and *K. marginata* rhizome	[35, 41, 43]
70	Kaemgalangol B	*K. galanga* rhizome	[35]
71	Kaemgalangol C	*K. galanga* rhizome, and *K. marginata* rhizome	[35, 38]
72	Kaemgalangol D	*K. galanga* rhizome	[35]
73	Kaemgalangol E	*K. galanga* rhizome	[9]
74	Kaemgalangol F	*K. galanga* rhizome	[9]
75	Kaempulchraol A	*K. pulchra* rhizome, and *K. saraburiensis* whole plant	[17, 25, 40]
76	Kaempulchraol B	*K. galanga* rhizome, *K. koratensis* rhizome, *K. marginata* rhizome, *K. pulchra* rhizome, and *K. saraburiensis* whole plant	[17, 25, 35, 38]
77	Kaempulchraol C	*K galanga* rhizome, *K. koratensis* rhizome, *K. marginata* rhizome, *K. pulchra* rhizome, and *K. saraburiensis* whole plant	[17, 25, 38, 40, 42]
78	Kaempulchraol D	*K. marginata* rhizome, *K. pulchra* rhizome, and *K. saraburiensis* whole plant	[17, 38, 40]
79	Kaempulchraol E	*K. galanga* rhizome, *K. marginata* rhizome, and *K. pulchra* rhizome	[17, 35, 38, 41]
80	Kaempulchraol F	*K. galanga* rhizome, and *K. pulchra* rhizome	[17, 35, 42]
81	Kaempulchraol G	*K. pulchra* rhizome, and *K. saraburiensis* whole plant	[17, 40]
82	Kaempulchraol H	*K. pulchra* rhizome	[17]
83	Kaempulchraol J	*K. marginata* rhizome, and *K. pulchra* rhizome	[14, 58]

Table 1 (continued)

No	Compounds	Plants	References
84	Kaempulchraol K	*K. marginata* rhizome, and *K. pulchra* rhizome	[14, 17, 37, 38]
85	Kaempulchraol L	*K. marginata* rhizome, *K. pulchra* rhizome, and *K. saraburiensis* whole plant	[14, 17, 38, 40, 41]
86	Kaempulchraol M	*K. pulchra* rhizome	[14]
87	Kaempulchraol N	*K. pulchra* rhizome, and *K. galanga* rhizome	[14, 17, 20, 35]
88	Kaempulchraol O	*K. pulchra* rhizome and *K. galanga* rhizome	[14, 17, 20, 35]
89	Kaempulchraol P	*K. koratensis* rhizome, *K. galanga* rhizome, and *K. pulchra* rhizome	[15, 17, 25, 35]
90	Kaempulchraol Q	*K. pulchra* rhizome, and *K. galanga* rhizome	[15, 17, 35]
91	Kaempulchraol R	*K. pulchra* rhizome	[15, 17]
92	Kaempulchraol S	*K. pulchra* rhizome	[15, 17]
93	Kaempulchraol T	*K. pulchra* rhizome	[15, 17]
94	Kaempulchraol U	*K. pulchra* rhizome	[17]
95	Kaempulchraol V	*K. pulchra* rhizome	[17]
96	Kaempulchraol W	*K. marginata* rhizome, and *K. pulchra* rhizome	[17, 38]
97	Koratane A	*K. koratensis* rhizome	[25]
98	Koratane B	*K. koratensis* rhizome	[25]
99	Marginaol A	*K. marginata* rhizome	[58]
100	Marginaol B	*K. marginata* rhizome	[58]
101	Marginaol C	*K. marginata* rhizome	[58]
102	Marginaol D	*K. marginata* rhizome	[58]
103	Marginaol E	*K. marginata* rhizome	[58]
104	Marginaol F	*K. marginata* rhizome	[58]
105	Marginaol G	*K. marginata* rhizome	[58]
106	Marginaol H	*K. marginata* rhizome	[58]
107	Marginaol I	*K. marginata* rhizome	[58]
108	Marginaol J	*K. marginata* rhizome	[58]
109	Marginaol K	*K. marginata* rhizome	[58]
110	Marginaol L	*K. marginata* rhizome	[58]
111	Marginaol M	*K. marginata* rhizome	[37]
112	Marginol A	*K. galanga* rhizome, and *K. marginata* rhizome	[35, 38]
113	Marginol B	*K. marginata* rhizome	[38]
114	Marginol C	*K. marginata* rhizome	[38]
115	Marginol D	*K. marginata* rhizome	[38]
116	Marginol E	*K. marginata* rhizome	[38]
117	Marginol F	*K. marginata* rhizome	[38]
118	Marginol G	*K. marginata* rhizome	[38]
119	Marginol H	*K. marginata* rhizome	[38]
120	Marginol I	*K. marginata* rhizome	[43]
121	Marginol J	*K. marginata* rhizome	[43]
122	Marginol K	*K. marginata* rhizome	[43]
123	(5β,9β,10α,13α)-Pimara-6,8(14) 15-trien-18-oic acid	*K. marginata* rhizome	[38]
124	Roscorane A	*K. roscoeana* whole plant	[29]
125	Roscorane B	*K. koratensis* rhizome, and *K. roscoeana* whole plant	[25, 29]
126	Roscorane C	*K. pulchra* rhizome, *K. roscoeana* whole plant	[21, 29]
127	Roscorane D	*K. roscoeana* whole plant	[29]
128	8(14),15-Sanderacopimaradiene-1α,9α-diol (Sandaracopimaradien-1α,9α-diol)	*K. galanga* rhizome, *K. marginata* rhizome, and *K. saraburiensis* whole plant	[35, 38–41]
129	Sandaracopimaradien-9α-ol-1-one	*K. galanga* rhizome	[35]
130	Sandaracopimaradiene-1α,2α-diol	*K. marginata* rhizome, *K. galanga* rhizome, and *K. roscoeana* whole plant	[34–36, 40, 42, 58]
131	Sandaracopimaradien-6β,9α-diol-1-one	*K. galanga* rhizome, and *K. marginata* rhizome	[35, 38, 41]
132	Sandaracopimaradien-1,6,9-triol	*K. marginata* rhizome	[38]
133	Shanpanootol A	*K. pulchra* rhizome	[20]
134	Shanpanootol B	*K. pulchra* rhizome	[20]
135	Shanpanootol C	*K. pulchra* rhizome	[20]
136	Shanpanootol D	*K. pulchra* rhizome	[20]

Table 1 (continued)

No	Compounds	Plants	References
137	Shanpanootol E	*K. pulchra* rhizome	[20]
138	Shanpanootol F	*K. pulchra* rhizome	[20]
139	Shanpanootol G	*K. koratensis* rhizome, and *K. pulchra* rhizome	[21, 34]
140	Shanpanootol H	*K. pulchra* rhizome	[21]
141	Saraburane A	*K. saraburiensis* whole plant	[40]
142	Saraburane B	*K. koratensis* rhizome, and *K. saraburiensis* whole plant	[34, 40]
143	Saraburol	*K. saraburiensis* whole plant	[40]
144	(1*R*,2*S*,5*S*,7*S*,9*R*,10*S*,13*R*)-1,2,7-Trihydroxypimara-8(14), 15-diene	*K. marginata* whole plant and rhizome, and *K. pulchra* rhizome	[21, 36, 58]
145	(1*R*,2*S*,5*S*,9*S*,10*S*,11*R*,13*R*)-1,2,11-Trihydroxypimara-8(14),15-diene	*K. marginata* whole plant, *K. roscoeana* whole plant, and *K. pulchra* rhizome	[14, 17, 18, 36, 40]
146	(1*S*,5*S*,7*R*,9*R*,10*S*,11*R*,13*R*)-1,7,11-Trihydroxypimara-8(14),15-diene (1α,7α,11α-Trihydroxypimara-8(4), 15-diene)	*K. koratensis* rhizome, and *K. marginata* whole plant and rhizome	[25, 36, 58]
147	Virescenol B	*K. marginata* rhizome	[38]
148	Virescenol C	*K. marginata* rhizome	[38]
Decalin-fused dihydropyrans			
149	Elegansin A	*K. elegans* rhizome	[30]
150	Elegansin B	*K. elegans* rhizome	[30]
151	Elegansin C	*K. elegans* rhizome	[30]
152	Elegansin D	*K. elegans* rhizome	[30]
153	Elegansin E	*K. elegans* rhizome	[30]
Flavonoids			
Flavones			
154	5,4'-Dihydroxy-3,7,3'-trimethoxyflavone	*K. parviflora* rhizome	[70, 85]
155	5,3'-Dihydroxy-3,7,4'-trimethoxyflavone	*K. parviflora* rhizome	[12, 61, 66, 68, 69, 71, 72, 74]
156	5,4'-Dihydroxy-7-methoxyflavone	*K. parviflora* rhizome	[12, 68, 71, 72, 74]
1 57	5,7-Dimethoxyflavone	*K. parviflora* rhizome	[10–12, 23, 45, 61, 62, 65–74, 76, 81, 85, 86, 89–94]
158	2",2"-Dimethylpyrano-[5",6":8,7]-flavone	*K. pulchra* rhizome	[32]
159	5-Hydroxy-3,7-dimethoxyflavone	*K. angustiflora* rhizome, *K. elegans* rhizome, *K. galanga* rhizome, *K. parviflora* rhizome, *K. pulchra*, and *K. rotunda* rhizome	[10–12, 22–24, 44, 46, 48, 60–63, 65, 66, 68–72, 74, 76, 79, 80, 82, 85, 86, 91–94]
160	5-Hydroxy-7,4'-dimethoxyflavone	*K. angustiflora* rhizome, *K. elegans* rhizome, *K. galanga* rhizome, *K. marginata* rhizome, *K. parviflora* rhizome, *K. pulchra*, and *K. rotunda* rhizome	[12, 22–24, 44, 46, 60, 61, 63, 65, 66, 68–72, 74, 76, 79, 80, 85, 86, 92]
161	5-Hydroxy-7-methoxyflavone (techtochrysin)	*K. angustiflora* rhizome, *K. elegans* rhizome, *K. galanga* rhizome, *K. marginata* rhizome, *K. parviflora* rhizome, *K. pulchra*, and *K. rotunda* rhizome	[12, 22–24, 44, 46, 60–63, 65, 66, 68–72, 74, 76, 79, 80, 82, 85, 91–94]
162	5-Hydroxy-3,7,4'-trimethoxyflavone	*K. angustiflora* rhizome, *K. elegans* rhizome, *K. galanga* rhizome, *K. marginata* rhizome, *K. parviflora* rhizome, *K. pulchra*, and *K. rotunda* rhizome	[10–12, 22–24, 44, 46, 48, 60–63, 66, 68–72, 74, 76, 79, 80, 82, 85, 86, 91, 92, 94]
163	5-Hydroxy-7,3',4'-trimethoxyflavone	*K. parviflora* rhizome	[12, 24, 66, 74]
164	5-Hydroxy-3,7,3',4'-tetramethoxyflavone (retusine)	*K. angustiflora* rhizome, *K. elegans* rhizome, *K. galanga* rhizome, *K. marginata* rhizome, *K. parviflora* rhizome, *K. pulchra*, and *K. rotunda* rhizome	[12, 22–24, 46, 60, 61, 63, 65, 66, 68–72, 74, 76, 79, 80, 85, 91–95]
165	4'-Hydroxy-5, 7-dimethoxyflavone	*K. parviflora* rhizome	[66, 69, 70, 85]
166	Isorhamnetin 3-*O*-[β-rhamnopyranosyl-(1→6)-β-glucopyranoside]	*K. parviflora* rhizome	[66]
167	Kaempferol	*K. parviflora* rhizome	[24]

Table 1 (continued)

No	Compounds	Plants	References
168	3,5,7,3',4'-Pentamethoxyflavone	*K. angustiflora* rhizome, *K. elegans* rhizome, *K. galanga* rhizome, *K. marginata* rhizome, *K. parviflora* rhizome, *K. pulchra*, and *K. rotunda* rhizome	[10–12, 23, 24, 46, 61, 66–74, 76, 85, 86, 89–91, 93, 94]
169	Quercetin 3-*O*-[*β*-rhamnopyranosyl-(1 → 6)-*β*-glucopyranoside]	*K. parviflora* rhizome	[66]
170	Syringetin 3-*O*-rutionside	*K. parviflora* rhizome	[12]
171	Tamarixetin 3-*O*-rutionside	*K. parviflora* rhizome	[12]
172	3,5,7,4'-Tetramethoxyflavone	*K. angustiflora* rhizome, *K. elegans* rhizome, *K. galanga* rhizome, *K. marginata* rhizome, *K. parviflora* rhizome, *K. pulchra*, and *K. rotunda* rhizome	[10–12, 22, 23, 44, 46, 61, 63, 66–68, 70–72, 82, 85, 89, 91, 93–95]
173	5,7,3',4'-Tetramethoxyflavone	*K. angustiflora* rhizome, *K. elegans* rhizome, *K. galanga* rhizome, *K. marginata* rhizome, *K. parviflora* rhizome, *K. pulchra*, and *K. rotunda* rhizome	[12, 44, 46, 61, 66, 69, 74, 76, 91, 93]
174	Tilianine	*K. parviflora* rhizome	[12]
175	3,5,7-Trimethoxyflavone	*K. angustiflora* rhizome, *K. elegans* rhizome, *K. galanga* rhizome, *K. marginata* rhizome, *K. parviflora* rhizome, *K. pulchra*, and *K. rotunda* rhizome	[12, 22–24, 44–46, 60, 61, 63, 65–72, 74, 79, 80, 82, 85, 86, 89, 91, 92]
176	5,7,4'-Trimethoxyflavone	*K. angustiflora* rhizome, *K. elegans* rhizome, *K. galanga* rhizome, *K. marginata* rhizome, *K. parviflora* rhizome, *K. pulchra*, and *K. rotunda* rhizome	[10–12, 23, 24, 44, 46, 57, 61, 65–74, 76, 82, 85, 86, 89–95]
Flavanones			
177	(2*R*,3*R*)-(−)-Aromadendrin trimethyl ether	*K. parviflora* rhizome	[12]
178	5,7-Dihydroxyflavanone (Pinocembrin)	*K. elegans* rhizome, *K. galanga* rhizome, *K. pandurata* rhizome, and *K. parviflora* rhizome	[46, 47]
179	3,7-Dimethoxyflavanone	*K. parviflora* rhizome	[24]
180	5,7-Dimethoxyflavanone (Dimethylpinocembrin)	*K. elegans* rhizome, *K. galanga* rhizome, and *K. parviflora* rhizome	[45, 46]
181	5-Hydroxy-7-methoxyflavanone (Pinostrobin)	*K. pandurata* rhizome	[47]
182	*trans*-3-Hydroxy-5,7-dimethoxyflavanone	*K. parviflora* rhizome	[24]
183	Taxifolin	*K. parviflora* rhizome	[24]
Flavans			
184	Kaempferiaoside A	*K. parviflora* rhizome	[12]
185	(2*R*,3*S*,4*S*)-3-*O*-[*α*-L-Rhamnopyranosyl-(1→6)-*β*-D-glucopyranosyl]-3'-*O*-methyl-*ent*-epicatechin-(2*α*→*O*→3,4*α*→4)-(5a*S*,10b*S*)-5a,10b-dihydro-1,3,5a,9 tetrahydroxy-8-methoxy-6*H*- benz[*b*]indeno[1,2-*d*]furan-6-one	*K. parviflora* rhizome	[12, 48, 66]
Flavenes			
186	Kaempferiaoside C	*K. parviflora* rhizome	[13]
187	Kaempferiaoside D	*K. parviflora* rhizome	[13]
Chalcones			
188	2'-Hydroxy-4,4',6'-trimethoxychalcone	*K. angustifolia* rhizome and *K. rotunda* rhizome	[31, 49, 50]
189	(+)-Panduratin A	*K. pandurata* rhizome	[51–53]
190	(−)-Panduratin A	*K. pandurata* rhizome	[53]
191	Flavokawain B	*K. elegans* rhizome, *K. galanga* rhizome, and *K. parviflora* rhizome	[46]
192	Cardamonin	*K. elegans* rhizome, *K. galanga* rhizome, and *K. parviflora* rhizome	[46]
193	(−)-Isopanduratin A	*K. pandurata* rhizome	[54]
194	(+)-4-Hydoxypanduratin A	*K. pandurata* rhizome	[52]
195	(−)-4-Hydoxypanduratin A	*K. pandurata* rhizome	[54]

the rhizomes of *Kaempferia* species. It is frequent to isolate pinocembrin (**178**) and dimethylpinocembrin (**180**), which have the same resource as *K. angustiflora*, *K. elegans*, *K. galanga*, *K. marginata*, *K. parviflora*, *K. pulchra*, and *K. rotunda* [45–47]. The rest isolates, including (2*R*,3*R*)-(−)-aromadendrin trimethyl ether (**177**), 3,7-dimethoxyflavanone (**179**), *trans*-3-hydroxy-5,7-dimethoxyflavanone (**182**), and taxifolin (**183**) from *K. parviflora*, and pinostrobin (**181**) from *K. pandurata* [12, 24, 47].

Four new compounds **184–185** and **186–187** can be classified as flavans and flavenes, respectively. They together composed of *α*-L-rhamnopyranosyl-(1→6)-*β*-D-glucopyranosyl unit at carbon C-3 (Fig. 2). Kaempferiaosides A and C-D (**184** and **186–187**) were first isolated from the MeOH extract of *K. parviflora* rhizome, whereas (2*R*,3*S*,4*S*)-3-*O*-[*α*-L-rhamnopyranosyl-(1→6)-*β*-D-glucopyranosyl]-3'-*O*-methyl-*ent*-epicatechin-(2*α*→*O*→3,4*α*→4)-(5a*S*,10b*S*)-5a,10b-dihydro-1,3,5a,9-tetrahydroxy-8-methoxy-6*H*-benz[*b*]indeno[1,2-*d*]furan-6-one (**185**) was detected in its CH_2Cl_2 extract [12, 13, 48].

Additional results of phytochemical investigations on *Kaempferia* plants are the identification of chalcones **188–195** (Table 1 and Fig. 2). *Kaempferia* chalcones can be found in the rhizomes of *K. angustifolia*, *K. elegans*, *K. galanga*, *K. pandurata*, *K. parviflora*, and *K. rotunda* [31, 46, 49–54]. They included 2'-hydroxy-4,4',6'-trimethoxychalcone (**188**), (±)-panduratins A (**189–190**), flavokawain B (**191**), cardamonin (**192**), (−)-isopanduratin A (**193**), and (±)-4-hydoxypanduratins A (**194–195**) (Table 1).

Biosynthesis and synthesis

Biosynthesis

As shown in Fig. 3, biosynthesis of *Kaempferia* diterpenoids was proposed starting from (*E,E,E*)-geranylgeranyl diphosphate (GGPP) [9]. The GGPP is first cyclized to form a cationic intermediate that is directly cyclized to generate isopimara-8(14),15-diene and sandaracopimaradiene via the reactions with enzymes *Aspergillus niger* and *Neosartorya fischeri*. By these enzymatic catalyzes, hydroxylation of carbons C-1 and C-7 of sandaracopimaradiene afforded compound **74**. Dehydration of kaemgalangol provided 1-hydroxy-isopimara-6(7),8(14),15-triene. This compound then can undergo a sequence of hydration and C-2 hydroxylation to afford compound **99**. In the meantime, compound **73** could be produced from 1-hydroxy-isopimara-6(7),8(14),15-triene through a sequence of enzymatic dehydration, C1 hydroperoxyration with lipoxygenase (LOX), and hydroxylation at carbons C-2, C-6, and C-7.

Biosynthesis of marginols I-K (**107–109**) was proposed starting from sandaracopimaradien-6β,9α-diol-1-one (Fig. 4) [43]. A sequence of retro-aldol and intramolecular ketal formation generated marginol I (**107**). Methylation of compound **107** provided marginol J (**108**). On the other hand, compound **107** might undergo a sequence of oxidation, 1,10-Grebe-type fragmentation, and ketone formation to afford marginol K (**109**).

Synthesis

With the ultimate aim to improve biological activities, Yenjai and partners proposed the synthetic steps to modify carbonyl group C-4 of *Kaempferia* flavonoids [55]. Catalytic hydrogenation of 5,7-dimethoxyflavone (**157**) using palladium on charcoal as a catalyst provided 5,7-dimethoxyflavanone (Fig. 5). The reaction of 5,7-dimethoxyflavanone with $NH_2OH.HCl$ in KOH afforded 5,7-dimethoxyflavanone oxime (**196**). Treatment of **157** with HBr in the presence of acetic acid gave 5,7-dihydroxyflavone. A similar result was obtained by the reaction of 5,7-dimethoxyflavanone with HBr, and AcOH to form 5,7-dihydroxyflavanone. The oximes **197–198** can be synthesized from the corresponding 5,7-dihydroxyflavone and 5,7-dihydroxyflavanone by treatment with hydroxylamine hydrochloride in KOH.

From Fig. 6, the structural modifications of *Kaempferia* flavones also tend to create new nitro and amino derivatives [56]. Nitration of compound **157** by a mixture of HNO_3 and H_2SO_4 at room temperature afforded 5,7-dimethoxy-8-nitroflavone (**199**) as a major product, along with 5,7-dimethoxy-6-nitroflavone (**200**). Reduction of **199** under H_2 flow and Pd/C gave 8-amino-5,7-dimethoxyflavone (**201**), and 8-amino-5,7-dimethoxyflavanone (**202**). Treatment of **201** with HBr in AcOH at a higher temperature furnished 8-amino-5-hydroxy-7-methoxyflavone (**203**), and 6-amino-5-hydroxy-7-methoxyflavone (**204**). Compound **204** was formed from **201** via Wessely-Moser rearrangement. The same procedure was applied for **202** to synthesize 8-amino-5-hydroxy-7-methoxyflavanone (**205**) and 6-amino-5-hydroxy-7-methoxyflavanone (**206**).

Pharmacology

Anticancer activity

New diterpenoid **11** and chalcone **188** were reported to inhibit HL-60 and MCF-7 cancer cells with the IC_{50} values of 6.24–24.22 µg/mL, but failed to control HT-29 and HeLa cancer cells ($IC_{50} > 30$ µg/mL) [31, 49]. Diterpenoid **20** was strongly cytotoxic against CCRF-CEM, MDA-MB-231-pcDNA, and HCT116 ($p53^{+/+}$) cancer cells with the IC_{50} values of 35.38, 61.6, and 42.77 µM, respectively [35].

Diterpenoids **47**, **59**, **77**, and **130** were cytotoxic against KB cells with the corresponding IC_{50} values of 20.92, 6.31, 11.43, and 38.22 µg/mL [42]. As compared to doxorubicin (IC_{50} 8.53 µg/mL), diterpenoids **77** (IC_{50} 18.17 µg/mL) and **130** (IC_{50} 47.4 µg/mL), compound **59** (IC_{50} 11.75 µg/mL) also strongly suppressed cytotoxic activity against MCF-7 cells [42]. Compound **49** moderately controlled K562 cells (IC_{50} 37.5 µg/mL) and HL-60 cells (IC_{50} 18.9 µg/mL), while compound **80** was only active to PSN-1 cells with the IC_{50} value of 12.3 µg/mL (46). Clerodanes **19–20** and isopimarane **78** were also cytotoxicity towards HL-60 with the IC_{50} value of 9.58, 8.97, and 38.4 µM, respectively [32, 40].

Diterpenoids **47–48**, **59**, **75–77**, **97–98**, and **142** were moderate cytotoxicity towards MOLT-3, HL-60, and T-47D cancer cells with the IC_{50} values of 42.10–56.57 µM, but they showed weak or inactive to MRC-5 cancer cells [25]. In another report, diterpenoids **59**, **61**, and **85** moderately inhibited HSC-2 cancer cells with the IC_{50} values of 53.3–69.9 µM better than those to HeLa cancer cells (IC_{50} 74.2–76.5 µM) (45). The isolated diterpenoids **61**, **83–86**, and **145** were cytotoxic towards A549 cancer cells with the IC_{50} values of 33.1–93.1 µM, as well as compound **61** with the IC_{50} values of 39.9–87.5 µM possessed moderate activity against HeLa, PANC-1, PSN-1, MDA-MB-231, and TIC-3 [14].

Flavone **161** was comparable to the standard arctigenin (IC_{50} 0.8 µM) against PANC1 pancreatic cancer cells, whereas flavones **157**, **172**, and **175–176** exerted the IC_{50} value of 16–85.5 µM, but flavones **159–160**, **162**, **164**, and **168** did not show activity [23]. It suggests that flavones without substitution at carbons C-3 and C-4' are appropriate for PANC1 treatment. At the concentration of 30 µM, methoxyflavones **157** and **168** promoted the sensitivity of doxorubicin to A549 cancer cells [10].

Flavone **176** at 100 µM induced DNA fragmentation and apoptosis in HCT-15 cancer cells better than two analogs **164** and **172** (79). It is further evidence that compound **176** (20 µg/mL) changed cellular morphology, activated caspase 3, and induced death in HuCCA-1 and RMCCA-1 cancer cells [57]. (–)-Panduratin A (**190**) at 2.5–20 µM inhibited proliferation and induced G2/M phase arrest and apoptosis in PC3 and DU145 prostate cancer cells (85). The mechanism involved the upregulation of Fas, $p21^{WAF/Cip1}$ and $p27^{Kip1}$, and the inhibition of cdks, cyclins and cdc2/cdc25C [53].

Two synthetic oximes **196** and **198** strongly controlled HepG2 and T47D cancer cells with the IC_{50} value of 22.94–41.66 µg/mL, but the natural compound **157** was inactive [55]. It suggested the oxime group at carbon C-4 is better than carbonyl group. In the same manner, the addition of amino groups would help to increase cytotoxicity to KB cancer cells, in which the IC_{50} values of amino-flavonoids **201–202** and **204–206** ranged from 5.84 to 45.09 µg/mL, but their precursor **157** failed to show activity [56].

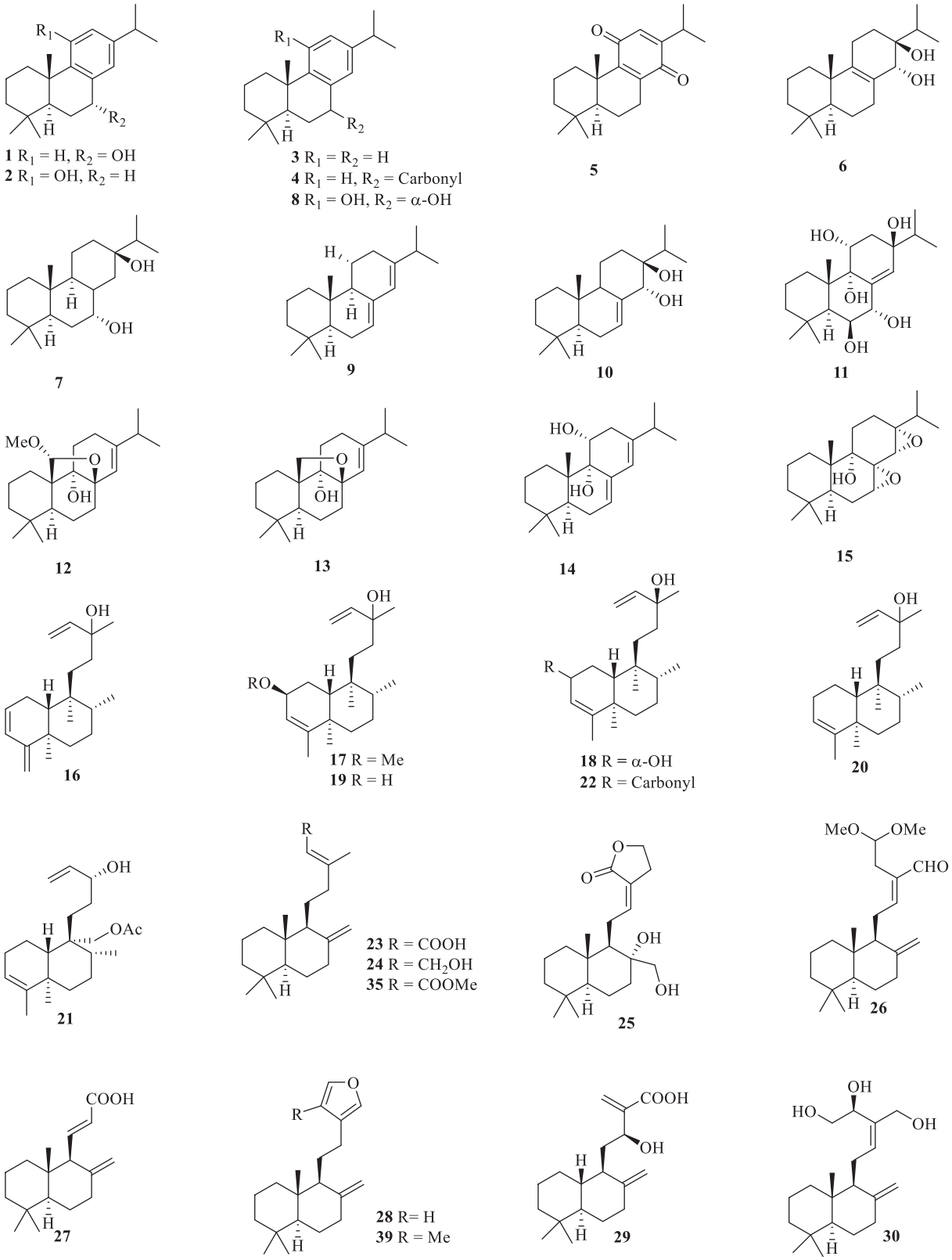
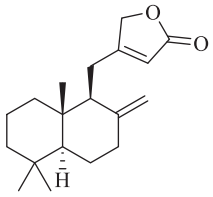


Fig. 1 Diterpenoids from *Kaempferia*



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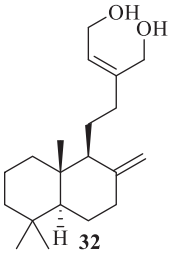

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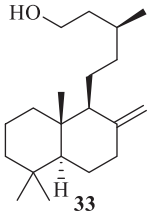

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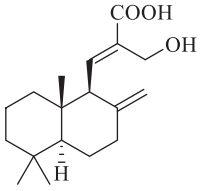

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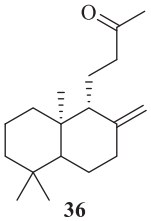

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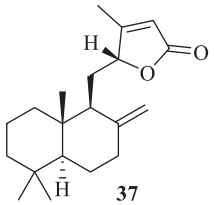

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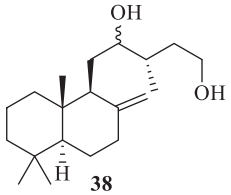

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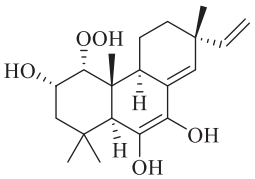

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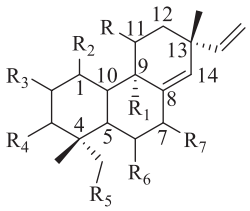

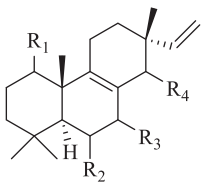

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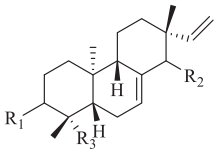
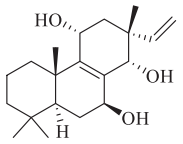
41 R = R_1= R_4 = R_5 = R_6= R_7 = H, R_2 = α-OH, R_3 = α-OAc
42 R = R_3 = R_4 = R_5 = R_7 = H, R_1 = OH, R_2 = OH, R_6 = β-OAc
43 R= R_3 = R_4 = R_5 = R_7 = H, R_1 = OH, R_2 = Carbonyl, R_6 = β-OAc
44 R= R_2 = R_3 = R_4 = R_5 = R_7 = H, R_1=OH, R_6 = β-OAc
45 R= α-OH, R_1 = OH, R_2 = R_3 = R_4 = R_5 = R_6 = H, R_7 = β-OH
46 R= R_3 = R_4 = R_5 = R_6 = H, R_1 = OH, R_2 = Carbonyl, R_7 = α-OH
47 R= R_3 = R_4= R_5 = R_7 = H, R_1 = OH, R_2 = Carbonyl, R_6 = β-OH
50 R= R_2= α-OH, R_1 = R_3= R_4= R_5= R_6 = R_7 = H
51 R = R_1 = R_4= R_5 = R_6 = H, R_2= α-OH, R_3 = OH, R_7 = Carbonyl
53 R= R_2 = R_3 = R_4 = R_5 = R_6= H, R_1=OH, R_7 = β-OH
58 R= R_3 = R_4 = R_5 = H, R_1=OH, R_2= R_7 = α-OH, R_6 = β-OH
59 R = R_2 = R_3 = R_4 = R_5 = R_6 = R_7 = H, R_1= OH
61 R= R_1 = R_3 = R_4 = R_5 = R_6 = R_7 = H, R_2 = α-OH
62 R= R_1 = R_2 = R_4= R_5 = R_6 = R_7 = H, R_3= β-OH
63 R= R_1= R_3= R_4 = R_5 = R_7 = H, R_2= Carbonyl, R_6 = β-OH
64 R = R_1 = R_2 = R_3 = R_4 = R_5 = R_6= H, R_7= α-OH
65 R = R_2 = R_3 = R_4 = R_5 = R_6 = H, R_1=OH, R_7 = Carbonyl
66 R = R_1 = R_2 = R_3 = R_4 = R_5 = R_6= H, R_7 = Carbonyl
67 R = R_1 = R_2 = R_3 = R_4 = R_5 = R_6= R_7 = H
68 R= R_1= R_2 = R_4= R_5 = R_6 = H, R_3= α-OH, R_7 = Carbonyl
74 R = R_1 = R_3 = R_4= R_5 = R_6 = H, R_2= α-OH, R_7 = β-OH
79 R = R_1 = R_3 = R_4 = R_5 = R_7 = H, R_2 = α-OH, R_6 = β-OH
80 R = R_1 = R_3 = R_5 = R_6 = R_7 = H, R_2 = R_4= α-OH
82 R = R_1 = R_3 = R_5 = R_7 = H, R_2 = R_4= α-OH, R_6 = β-OH
83 R = R_1 = R_3 = R_4 = R_5 = R_6 = H, R_2 = α-OH, R_7 = Carbonyl
84 R = R_2 = R_3 = R_5 = R_7 = H, R_1 = OH, R_4= α-OH, R_6 = β-OAc
85 R = R_2 = R_3 = R_4 = R_5 = R_7 = H, R_1 = OMe, R_6 = β-OH
86 R= R_4 = R_5 = R_6 = R_7 = H, R_1 = OH, R_2 = R_3 = α-OH
89 R= R_1 = R_2 = R_3 = R_4 = R_5 = R_7 = H, R_6 = β-OH
90 R = R_1 = R_3 = R_4 = R_5 = R_7 = H, R_2 = OAc, R_6 = β-OH
91 R = R_2 = R_3 = R_4 = R_5 = R_6 = H, R_1= OH, R_7 = α-OAc

48 R_1 = H, R_2 = R_4 = α-OH, R_3=β-OH
49 R_1 = H, R_2 = α-OH, R_3 = R_4 = β-OH
52 R_1 = α-OH, R_2 = R_3 = H, R_4 = α-OH
54 R_1= R_3 = H, R_2 = β-OH, R_4 = α-OH
55 R_1= R_3 = H, R_2 = β-OH, R_4 = β-OH
56 R_1= R_3 = H, R_2= α-OH, R_4 = β-OAc
57 R_1= R_2 = β-OH, R_3 = H, R_4 = α-OH
60 R_1=α-OH, R_2 = R_3 = H, R_4 = α-OMe
69 R_1 = R_2 = R_3 = H, R_4 = Carbonyl
70 R_1= α-OH, R_2 = R_4 = β-OH, R_3 = H
71 R_1= α-OH, R_2= β-OH, R_3 = H, R_4 = α-OMe
72 R_1= α-OH, R_2 = β-OH, R_3 = H, R_4 = α-OEt
75 R_1 = H, R_2 = β-OH, R_3 = H, R_4 = α-OMe
76 R_1= R_3 = H, R_2 = β-OH, R_4 = β-OMe
77 R_1= R_3 = H, R_2 = β-OH, R_4 = α-OH
78 R_1= R_3 = H, R_2 = R_4= β-OH
81 R_1= R_3 = H, R_2 = β-OH, R_4 = Carbonyl
87 R_1= R_4 = α-OH, R_2 = β-OH, R_3 = H
88 R_1 = α-OH, R_2 = β-OH, R_3 = H, R_4 = β-OMe
92 R_1 = R_2 = H, R_3= Carbonyl, R_4 = α-OH
94 R_1 = R_2 = R_3 = H, R_4 = α-OH
105 R_1= R_4 = α-OH, R_2 = β-OAc, R_3 = H
106 R_1=α-OH, R_2=β-OAc, R_3=H, R_4=β-OH
107 R_1 = α-OH, R_2= R_3= H, R_4 = α-OAc
108 R_1= α-OH, R_2=H, R_3=H, R_4= β-OAc
109 R_1= R_3 = H, R_2 = β-OAc, R_4 = α-OAc
110 R_1= α-OH, R_2= β-OAc, R_3 = H, R_4 = β-OAc
111 R_1 = α-OH, R_2 = β-OAc, R_3 = H, R_4 = α-OAc
115 R_1 = Carbonyl, R_2 = β-OH, R_3 = H, R_4 = α-OH
135 R_1 = α-OH, R_2 = β-OAc, R_3 = H, R_4 = α-OMe
136 R_1= R_4 = α-OH, R_2 = β-OAc, R_3 = H

93 R = R_1= R_2 = R_3 = R_4 = R_5 = H, R_6= β-OH, R_7 = α-OAc
95 R = R_2 = R_3 = R_4 = R_5 = H, R_1 = OH, R_6 = β-OH, R_7 = β-OAc
96 R = R_2 = R_3 = R_4 = R_5 = H, R_1 = OH, R_6 = R_7 = β-OH
97 R = R_2 = R_3 = R_4 = R_5 = H, R_1= OH, R_6= β-OH, R_7 = α-OH
98 R = R_1 = R_3 = R_4 = R_5 = R_6= H, R_2 = R_7 = α-OH
99 R = R_1= R_4 = R_5 = R_7 = H, R_2 = OH, R_3= α-OH, R_6= β-OH
100 R = OH, R_1= R_3 = R_5 = R_6 = R_7 = H, R_2 = R_4= α-OH
101 R = R_4 = β-OH, R_1 = R_3 = R_5 = R_6 = R_7 = H, R_2= Carbonyl
102 R = R_2 = α-OH, R_1 = R_3 = R_5 = R_6 = R_7 = H, R_4=β-OH
103 R= R_2 = R_7 = α-OH, R_1 = R_3 = R_5 = R_6 = H, R_4 = β-OH
104 R= α-OH, R_1 = R_3 = R_5 = R_6 = H, R_2 = R_7 = Carbonyl, R_4 = β-OH
117 R = R_3 = R_4 = R_5 = H, R_1= OH, R_2 = Carbonyl, R_6 = β-OH, R_7 = α-OH
118 R = R_3 = R_4 = R_5 = R_6 = H, R_1 = OH, R_2= Carbonyl, R_7 = α-OAc
125 R = R_2 = α-OH, R_1 = R_3 = R_4 = R_5 = R_7 = H, R_6 = β-OH
126 R = R_1= R_4 = R_5 = H, R_2 = R_6 = β-OH, R_3 = R_7 = α-OH
127 R = R_1 = R_4 = R_6 = R_7 = H, R_2 = R_3= α-OH, R_5 = OH
128 R = R_3 = R_4 = R_5 = R_6 = R_7 = H, R_1 = OH, R_2 = α-OH
129 R = R_3 = R_4 = R_5 = R_6 = R_7 = H, R_1 = OH, R_2 = Carbonyl
130 R = R_1 = R_4 = R_5 = R_6 = R_7 = H, R_2= R_3= α-OH
131 R = R_3 = R_4 = R_5 = R_7 = H, R_1= OH, R_2= Carbonyl, R_6 = β-OH
132 R = R_3 = R_4 = R_5 = R_7 = H, R_1 = OH, R_2 = α-OH, R_6 = β-OH
139 R = R_1 = R_3 = R_4 = R_5 = H, R_6 = β-OH, R_2= R_7 = α-OH
140 R = R_1= R_4 = R_5 = R_6 = H, R_2 = R_3= R_7 = α-OH
142 R = R_1 = R_2 = R_3 = R_4 = R_5 = H, R_6 = β-OH, R_7 = α-OH
144 R = R_1 = R_4 = R_5 = R_6 = H, R_2= R_3= α-OH, R_7 = β-OH
145 R= R_2 = R_3= α-OH, R_1 = R_4= R_5 = R_6 = R_7 = H
146 R = R_2 = R_7 = α-OH, R_1 = R_3= R_4 = R_5 = R_6 = H



112 R_1 = α-OH, R_2 = H, R_3 = CHO
113 R_1= H, R_2 = α-OH, R_3 = COOH
114 R_1 = H, R_2 = α-OAc, R_3 = COOH



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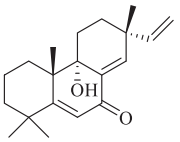

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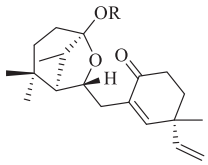
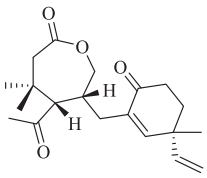


120 R = H
121 R = Me



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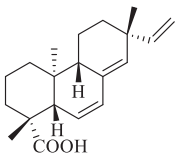

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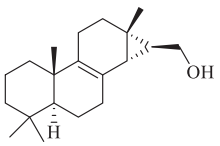

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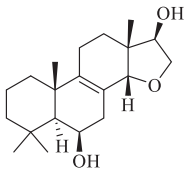

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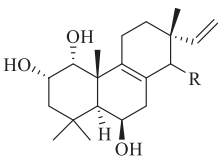
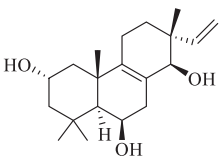


134 R = Carbonyl
137 R = β-OH



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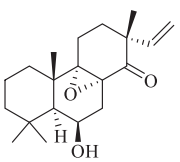

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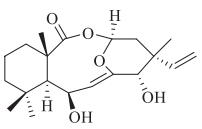

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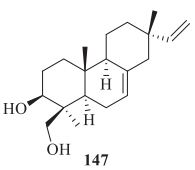

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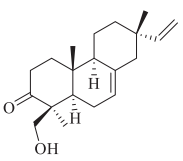

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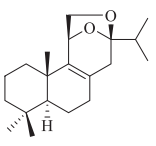

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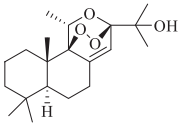

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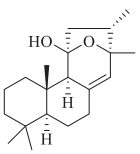

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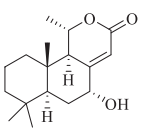

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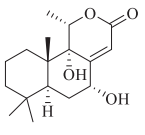
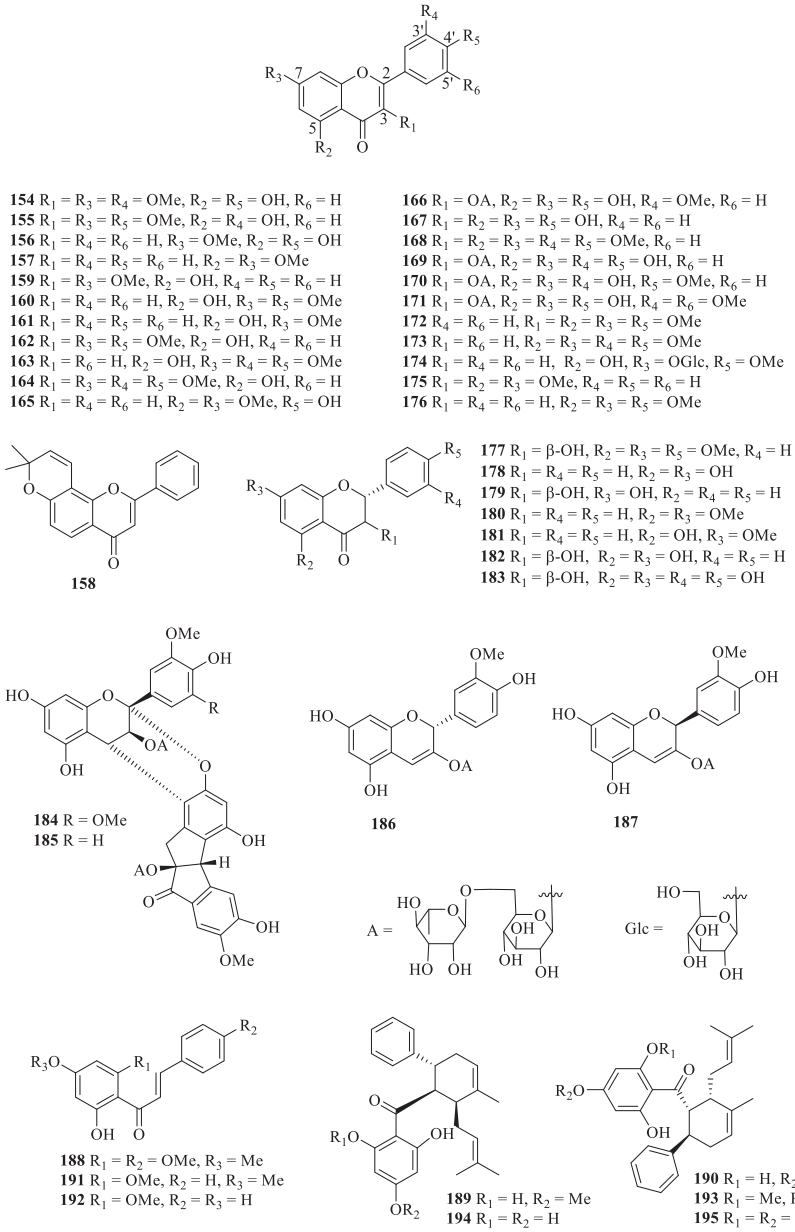


153

Fig. 2 Flavonoids from *Kaempferia*



P-glycoprotein (P-gp), a drug transporter belongs to the ATP-binding cassette superfamily, confers multidrug resistance on cells by releasing a number of structurally and pharmacologically varied cancer chemotherapeutic drugs with the help of ATP hydrolysis [11]. The EtOH extract of *K. parviflora* rhizome containing the major flavone **168** remarkably enhanced the accumulation of rhodamine 123 and daunorubicin, and P-gp substrates in LLC-GA5-COL150 cells, but not in LLC-PK1 cells [11].

Antiinflammatory activity

Among tested diterpenoids, compounds **42–43**, **52**, and **54** exerted good antiinflammatory activity against NO (nitric oxide) production in LPS (lipopolysaccharide)-mediated RAW264.7 cells with the IC_{50} value of 7.7–12.1 μM, when caffeic acid phenethyl ester was used as a standard (IC_{50} 5.6 μM) [39]. Compounds **42–43** also suppressed iNOS (inducible nitric oxide synthase) and COX-2 (cyclooxygenase-2) mRNA expressions [39]. The structural effects were deduced from oxygenation at carbons C-1, C-6, and α-OH at C-14. New diterpenoids **69**, **120**, and **122** generated the IC_{50} value of 81.93-87.70 μM against NO production, but their analog **121** was inactive with $IC_{50} > 100$ μM [43]. New diterpenoids **76–78** exhibited preventions against NO production and IL-6, COX-2, and NF-κB expressions [19]. Diterpenoids **61, 64, 85, 89–91, 93**, **96**, **113**, **115–118**, and **131** inhibited NO production with IC_{50} values of

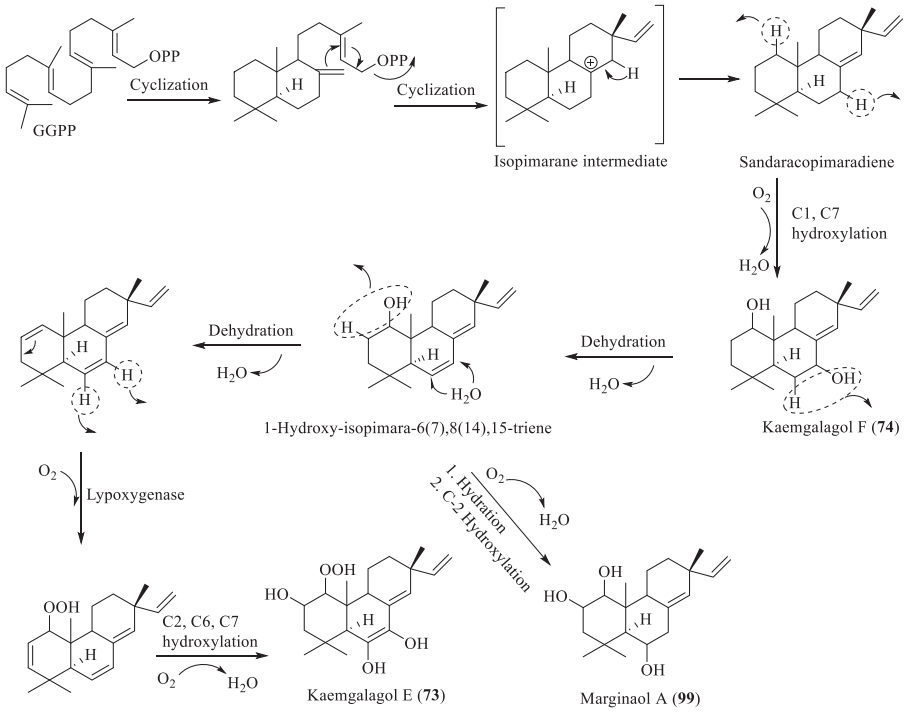


Fig. 3 Biosynthesis pathway of kaemgalangols E-F (**73–74**) and marginaol A (**99**)

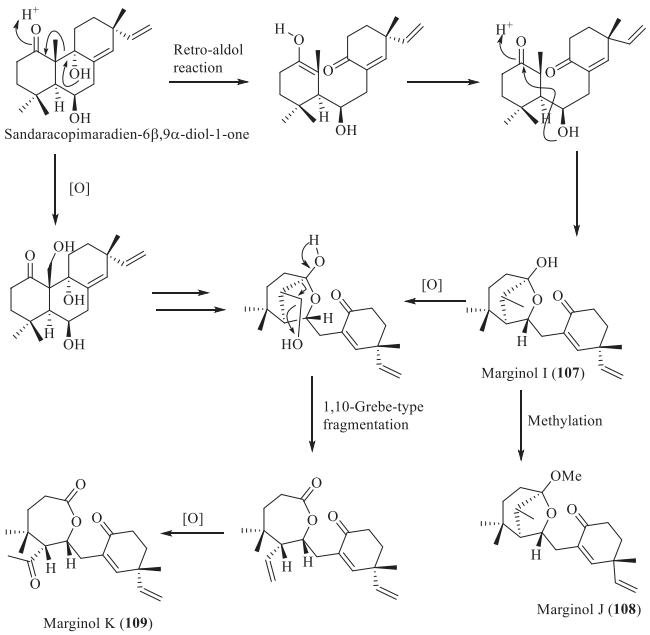


Fig. 4 Biosynthesis pathway of marginaols I-K (**107–109**)

30–100 μM (Table S1) [18, 38]. Especially, diterpenoids **89–90**, **93**, and **177** possessed the IC_{50} values of 39.88, 36.05, 32.79, and 68.51 μM, respectively, which were comparable to that of standard compound L-NMMA monoacetate (IC_{50} 65.50 μM) [18, 38].

Serial new diterpenoids marginaols G-M **105–111** were very strong against NO production with the IC_{50} values of 5.5–15.4 μM, in comparison with that of the standard compound dexamethasone (IC_{50} 4.7 μM), and their analog marginaol B **100** (IC_{50} 28.1 μM) [37, 58].

Due to the role of 2-OH group, diterpenoid **130** (ID_{50} 50 μg/ear) is better than its analog **41** (ID_{50} 330 μg/ear) in the model of TPA (12-*O*-tetradecanoylphorbol-13-acetate)-stimulated rat ear edema [59].

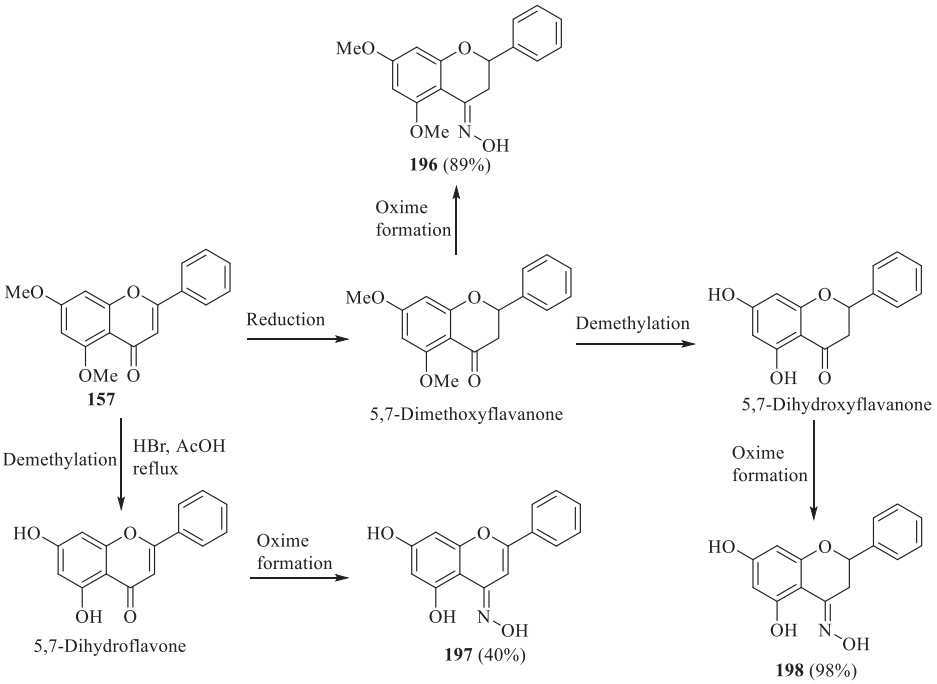


Fig. 5 Proposed synthesis of target *Kaempferia* flavonoid oximes

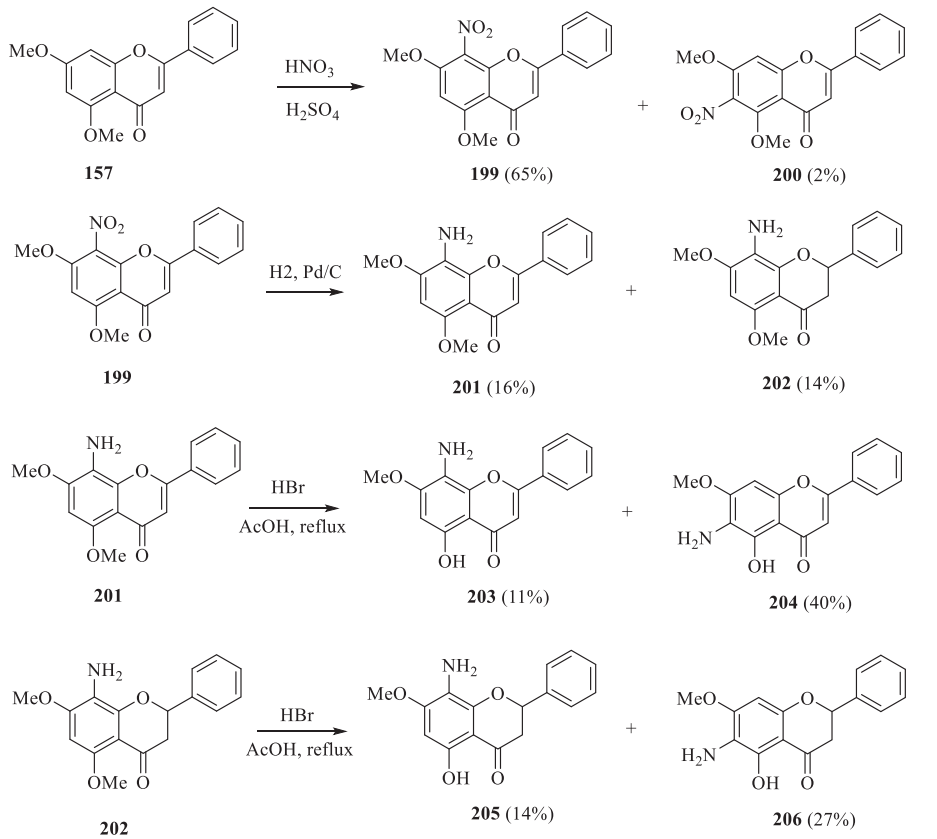


Fig. 6 Proposed synthesis of target *Kaempferia* nitro and amino flavonoids

Kaempferia flavones have been also objects in anti-inflammatory examinations. Flavone **164** showed the best activity against NO production with the IC_{50} value of 16.1 μM, followed by **159–160** and **175** [22]. The activity of compound **164** is four times higher than that of L-nitroarginine (an iNOS inhibitor) [22]. Furthermore, metabolite **164** exerted the IC_{50} value of 16.3 μM against inflammatory mediator PGE_2 (prostaglandin 2) [60]. As compared with the standard caffeic acid phenethyl ester (IC_{50} 3.7 μM), three flavones **157**, **173**, and **176** strongly inhibited NO production with the IC_{50} values of 15–26 μM [61]. However, in contrast to **157** (inactive), flavones **173** and **176** were recorded to suppress TNF-α (tumor necrosis factor-α) in LPS-activated RAW264.7 cells with the IC_{50} values of 292 and 206 μM, respectively [61]. In the same way, both four diterpenoids **40–41, 60**, and **130** inhibited NO production with the IC_{50} values of 38.6–51.9 μM, as well as only metabolite **130** protected against TNF-α with an IC_{50} value of 48.3 μM [34]. The active results of compound **130** over **40–41** can be explained by hydroxylation at carbons C-1 and C-2.

Antimicrobial activity

Abietane **3** exhibited the most antimicrobial activity against bacteria *Straphylococcus epidermidis* and *Bacillus cereus* with the MIC/MBC (minimum inhibitory concentration/minimum bactericidal concentration) values of 25/75 and 25/50 μg/mL, respectively [29]. Labdanes **23–24** possessed the corresponding MIC/MBC values of 12.5/18.75 and 12.5/200 μg/mL for *S. epidermidis*; 12.5/25 and 6.25/200 μg/mL for *E. faecalis*; and 3.13/6.25 and 6.25/6.25 μg/mL for *B. cereus*, while compound **33** demonstrated the selection towards *B. cereus* with an MIC/MBC value of 6.25/25 μg/mL [32].

Ditepenoid **130** exhibited remarkable activity against *S. aureus*, with a MIC value of 16 μg/mL, whereas diterpenoids **56** and **49** showed moderate antibacterial activities against *B. cereus*, *B. subtilis*, *S. aureus*, and *Pseudomonas aeruginosa* with the MIC values of 32–64 μg/mL [42]. Parallel with this, the other diterpenoids **47**, **58–59**, and **61** were found to exhibit antimicrobial activity at different levels (Table S1) [42]. At 200 μM, flavone **159** acted as suppressor of Ca^{2+} signal-stimulated cell cycle regulation in the yeast *Saccharomyces cerevisiae* [62].

4'-Methoxylation did not promote antimicrobial activity since flavone **175** showed the same MIC value of 250 μg/mL against *Trichophyton rubrum*, *T. mentagrophytes*, and *Microsporum gypseum*, but its analog **172** failed to do so (inactive, MIC > 250 μg/mL) [63]. In addition, it is found that diterpenoids **130** and **145** and flavones **172** and **176** were active in antifungal assay against *Candida albicans* with the MIC values of 49.9, 17.5, 39.71, and 17.63 μg/mL, respectively [36, 44]. Natural product **157** failed to control fungus *C. albicans*, but its synthetic oxime **197** exerted the IC_{50} value of 48.98 μg/mL [55].

Chalcone **189** established the same MIC value of 4.0 mg/L against four oral bacteria *Streptococcus mutans*, *S. salivarius*, *S. sanguis*, and *S. sobrinus* [8]. Compound **189** also exhibited the MIC value of 1 μg/mL against the oral biofilm bacterium *Actinomyces viscosus*, as well as inhibited 50% biofilm formation at a MIC value of 8 μg/mL [64]. Also, compound **189** with 4-methoxylation is better than its analog **194** in antimicrobial activity against *B. subtilis*, *S. aureus*, and *S. typhi* [52].

Antiviral and antimalarial activities

The Vpr (viral protein R) is a small basic protein that is well conserved in HIV (human immune virus) and SIV (simian immunodeficiency virus) [17]. Among tested diterpenoids, isopimara-8(9),15-dienes **76**, **78**, **81**, and **94** as well as isopimara-8(14),15-dienes **90**, **93**, and **96** inhibited the proliferation of TREx-HeLa-Vpr cells at a concentration of 1.56–6.25 μg/mL (% cell viability > 96%) [17]. Apparently, the presence of β-OH groups at carbons C-6 and C-14 of isopimara-8(9),15-diene and α-OAc groups at carbons C-1 and C-7 of isopimara-8(14),15-diene increased the inhibitory capacity. At the concentration of 5 μM, the viability of TREx-HeLa-Vpr cells was found as follows: diterpenoid **135** (152%) > **137** (149.9%) > the positive control damnacanthal (143.94%) > **136** (143.79%) > **140** (136.42%) > **51** (135.25%) > **133** (131.75%) > **25** (135%) > **34** (134%) > **29** (131%) > **27** (129%) > **127** (114.48%) > **138** (114.48%) > **139** (114.84%) > **144** (112.40%) > **134** (111.93%) (20,21,34). From this evidence, the transformation of compound **133** from isopimara-8(9),15-diene and the presence of carbonyl group at C-14 of compound **134** could lead to a reduction of activity, but carbonyl group at C-7 of compound **51** increases activity.

Diterpenoids **59** and **61** inhibited the growth of *Mycobacterium tuberculosis* H37Ra with the same MIC value of 25 μg/mL, whereas diterpenoids **41** and **77** also exerted the MIC value 50 μg/mL [36, 42]. Flavones **157** and **161** were accompanied by the IC_{50} values of less than 20 μM against HIV-1 protease, while their analogs **159–160**, **162**, **164**, and **175–176** exerted the IC_{50} values of 66.11–160.07 μM [65]. It generally concluded that 4'-methoxylation would not enhance activity.

Diterpenoids **50** and **145** were associated with the corresponding IC_{50} values of 3.2 and 8.8 μg/mL against *P. falciparum* [36]. Meanwhile, 5-methoxylation would enhance antiplasmodial activity of flavones **173** (IC_{50} 4.06 μg/mL) and **176** (IC_{50} 3.70 μg/mL) against *P. falciparum*, in comparison with flavone **160** (inactive) [44].

Antidiabetic and anti-allergenic activities

α-Glucosidase inhibitory activity of *Kaempferia* flavones is dependent on the functional groups. Flavones **173** and **176** without 3-methoxylation are better than analogs **168** and **172** (Table S1) [66]. Flavones **168**, **172**, and **176** overcome derivatives **160**, **162**, and **164** due to 5-methoxylation [66]. 3',4'-Dimethoxyflavones **168** and **173** are more active than 4'-methoxyflavones **172** and **176** [66]. Additionally, flavones **157**, **159**, **161**, and **175** without substituent in ring B have IC_{50} values of more than 140 μM [66].

With the IC_{50} value of less than 10 μg/mL, flavones **168**, **172**, and **176** were superior to the standard aminoguanidine (IC_{50} 165.5 μg/mL) in anti-glycation activity, but their analogs **157** and **176** were inactive with the $IC_{50} > 50$ μg/mL [67]. It turns out that methoxylation seems a good way to improve activity. Lipase can be seen as a family of enzymes that catalyzed the hydrolysis of lipids. Flavones **159–162** exhibited pancreatic lipase inhibitory activity with the IC_{50} value of 291, 220, 291, and 536 mg/mL, respectively [68].

It is also found that *Kaempferia* flavones are appropriate for anti-allergenic activity, in which 5-hydroxyflavones **155**, **159–162**, and **164** strongly inhibited antigen-mediated degranulation in RBL-2H3 cells with the IC_{50} value of <15 μM, 5-methoxyflavones **157** and **176** showed moderate activity with $15 < IC_{50} < 100$ μM, and less active flavone **175** with $IC_{50} > 100$ μM (Table S1) [69]. Especially, the inhibitory effects of two flavones **155** and **162** (at 100 μM) were accompanied by the suppression of degranulation due to Ca^{2+} influx, phosphorylation of Syk and PLCγ1, and translocation of FcεRI to the cell surface (Fig. 7) [69].

Antioxidative activity

The addition of methoxy group would enhance activity since *Kaempferia* flavones **155**, **157**, **159–162**, **164**, **168**, **172**, and **175–176** showed significant antioxidative activity with the ORAC (oxygen radical absorbance capacity) values of 0.79–8.47 μM TE/L (trolox equivalent per liter), at 10.0 μM [70]. Flavanones **178** and **181** showed weak antioxidative activity to quench DPPH (2,2-diphenyl-1-picrylhydrazyl) radicals with the IC_{50} values 5816 and 6268 μmol/L, respectively [47].

It suggests that the medium polar extracts of *K. rotunda* seem better than the non/weak or strong polar extracts in antioxidative treatments [50]. Especially, their chalcone **188** successfully captured DPPH radicals with the IC_{50} value of 142 μg/mL, when BHT (butylated hydroxytoluene) was used as a positive control (IC_{50} 49 μg/mL) [50]. Chalcone **191** showed the best antioxidative activities of 493.89, 185.41, and 17.57 μM TE/g DW (trolox equivalent per g of dried weight) in ABTS (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)), DPPH, and FRAP (ferric reducing antioxidant power), respectively [46].

Anti-obesity and anti-mutagenic activities

At the concentration of 30 μM, methoxylated flavones **168** and **173** induced adipogenesis on 3T3-L1 preadipocytes by regulating GATA-2/3 transcription factors at an early stage [71]. In addition, flavones **168** and **176** suppressed adipocyte hypertrophy by activation of ATGL (adipose tissue triglyceride lipase) and HSL (hormone-sensitive lipase) independent of PPARγ transcription [72].

Kaempferia flavones are likely to be outstanding agents for antimutagenicity against *Salmonella typhimurium* TA98 strain since flavones **155**, **157**, **159–162**, **164**, **172–173**, and **175–176** exerted the IC_{50} values of 0.40–1.07 nmol/plate, and were lower than that of the standard hemin (IC_{50} 7.82 nmol/plate) [66]. In addition, 5-methoxylated flavones **157** and **175–176** gave lower IC_{50} values than 5-hydroxylated flavone **164** (Table S1) [66].

Neuroprotective activity

A recent report indicated that flavonoids **159–164**, **167–168**, **175–176**, **179**, and **182–183** inhibited AChE (acetylcholinesterase) enzyme with the IC_{50} values ranging from 72.05 to 205.41 μM, as compared with that of the standard galantamine (IC_{50} 5.78 μM) [24]. 3,5,7,3',4'-Pentamethoxyflavone (**168**) enhanced AChE activity at 20 μM, while 5,7-dimethoxyflavone (**157**) and 5-hydroxy-7,4'-dimethoxyflavone (**160**) would help neurite outgrowth in PC12 cells at 40 μM [73]. At 0.1 mg/mL, the inhibitory percentages of flavones **157**, **160**, **168**, **172**, and **176** against BChE (butyrylcholinesterase) enzyme ranged from 16.5 to 84.6%, when galanthamine was used as a positive control (95.5%) [74].

BACE1 (Beta-site amyloid precursor protein cleaving enzyme 1) is responsible for the Aβ (β-amyloid peptide) formation that represents a neuropathological hallmark of Alzheimer's disease [75]. Flavones **157**, **168**, and **176** acted as non-competitive inhibitors that may bind to β-secretase sub-site with the K_i (inhibition constant) values of 0.2, 0.26, and 0.19 mM, respectively [75]. The CRE (cAMP-response element) is essential for formation of long-term memory [76]. It turns out that flavones **157**, **168**, **173**, and **176** might be potential agents for preventing and recovering memory cognition since they increased CRE-mediated transcription [76].

Skin protective activity

The gel containing diterpenoid **18** (0.25%, w/w) protected HDF (human dermal fibroblasts) cells via suppressing NO

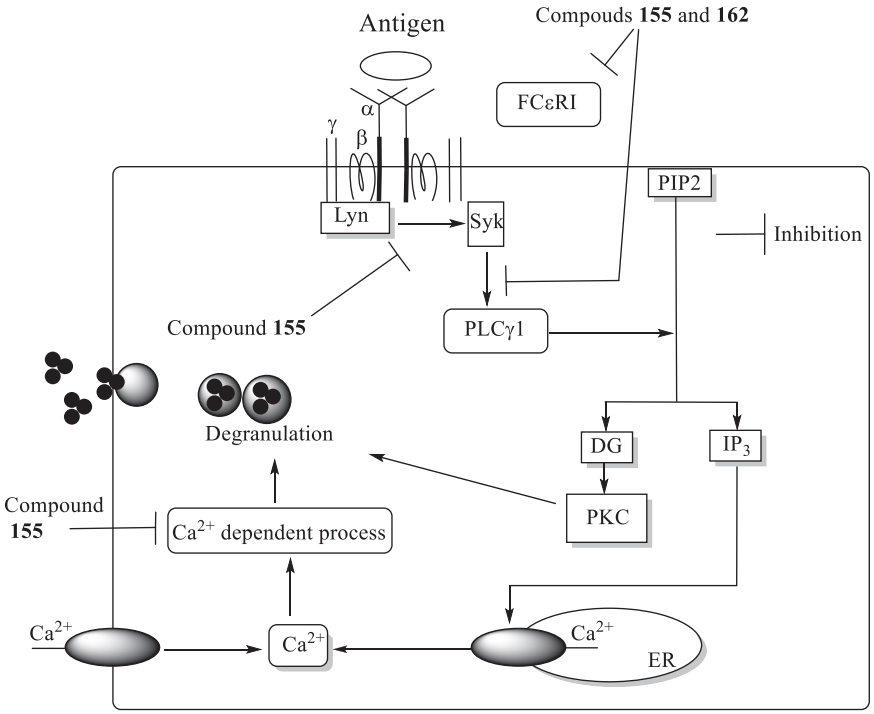


Fig. 7 The inhibitory effects of flavones **155** and **162** on antigen-stimulated degranulation in RBL-2H3 cells. DG Diacylglycerol, ER Endoplasmic reticulum, IP3 Inositol trisphosphate, ITAM Immunoreceptor tyrosine-based activation motif, PIP2 Phosphatidylinositol 4,5-bisphosphate, PKC Protein kinase, PLC Phospholipase C

production and H_2O_2-induced oxidative stress, as well as increased collagen content in HDF cells [77]. Significantly, flavonoids **155, 157, 163–164, 168, 172–177**, and **185** with the IC_{50} values of 2.9–35.3 μM exerted melanogenesis inhibitory activity in B16 4A5 cells better than that of the standard compound arbutin (IC_{50} 174 μM) [78]. Flavones **160** and **175** remarkably decreased the IBMX (3-isobutyl-1-methylxanthine)-induced melanogenesis in B16F10 cells (flavone **160**: 25 μM (2.25-fold), 50 μM (1.88-fold), and 100 μM (1.78 -fold)), and (flavone **175**: 50 μM (2.16-fold), and 100 μM (1.56-fold)), compared to that in the IBMX-stimulated group [79].

Flavone (**175**) at the concentrations of 50 and 100 μM inhibited TNF-α-induced MMP-1/ROS (matrix metalloproteinase 1/reactive oxygen species) in normal human dermal fibroblast cells via reduction of cytokines IL-1β (interleukin-1β), IL-6, and IL-8, suppression of Akt (protein kinase B), COX-2, and MAPK (mitogen-activated protein kinase) activation, and induction of HO-1 [80].

(+)-Panduratin A (**189**) inhibited melanin synthesis (IC_{50} 9.6 μM) and tyrosinase enzyme (IC_{50} 8.2 μM) better than the standard compound kojic acid (IC_{50} values of 152 and 126 μM) [80].

Due to the role of OMe group, (–)-isopanduratin A (**193**) is superior to (–)-4-hydoxypanduratin A (**195**) in the melanin synthesis and tyrosinase activity (Table S1) [54]. Significantly, these two chalcones are also better than the standard phenylthiurea (IC_{50} 34.32 μM for melanin synthesis, and 47.6 μM for tyrosinase activity) [54].

Hepatoprotective and vasorelaxant activities

5,3'-Dihydroxy-3,7,4'-trimethoxyflavone (**155**) with the IC_{50} value of 18.4 μM is better than the standard compound silybin (IC_{50} 38.8 μM) to inhibit D-GalN-stimulated cytotoxicity in primary cultured mouse hepatocytes [12].

At 1-100 μM, dimethylpinocembrin (**180**) induced the relaxations in methoxamine-precontracted aortic rings of mice via the Ca^{2+} influx inhibition, K^+ efflux increasing, and NO-cGMP and cyclooxygenase mediations [81]. Flavones **162** and **176** at the concentration of 0.4 mg/mL had stronger antiplatelet aggregation effects (90.4 and 89.7%, respectively) than the standard compound ticagrelor (75.6%) [82].

sEH, PDE5, and aromatase inhibitory activities

sEH (soluble epoxide hydrolase) greatly affects the increase in epoxyeicosatrienoic acids levels, and the decrease in dihydroxyeicosatrienoic acids levels [83, 84]. Thereby, the inhibitory actions of this enzyme have been claimed to treat various diseases such as hypertension, stroke, dyslipidemia, and immunological disorders [85]. *Kaempferia* flavones caused the inhibition to sHE enzyme with a visible order of **154** (IC_{50} 0.9 μM) < **172** (1.1 μM) < **176** (2.3 μM) < **168** (3.3 μM) < **175** (4.5 μM) < the positive control 12-(3-adamantan-1-yl-ureido)dodecanoic acid (12.2 μM) **157** (14.1 μM) < **162** (20.3 μM) < **161** (30.4 μM) < **160** (30.9 μM) < **159** (31.7 μM) < **164** (38.6 μM) [85].

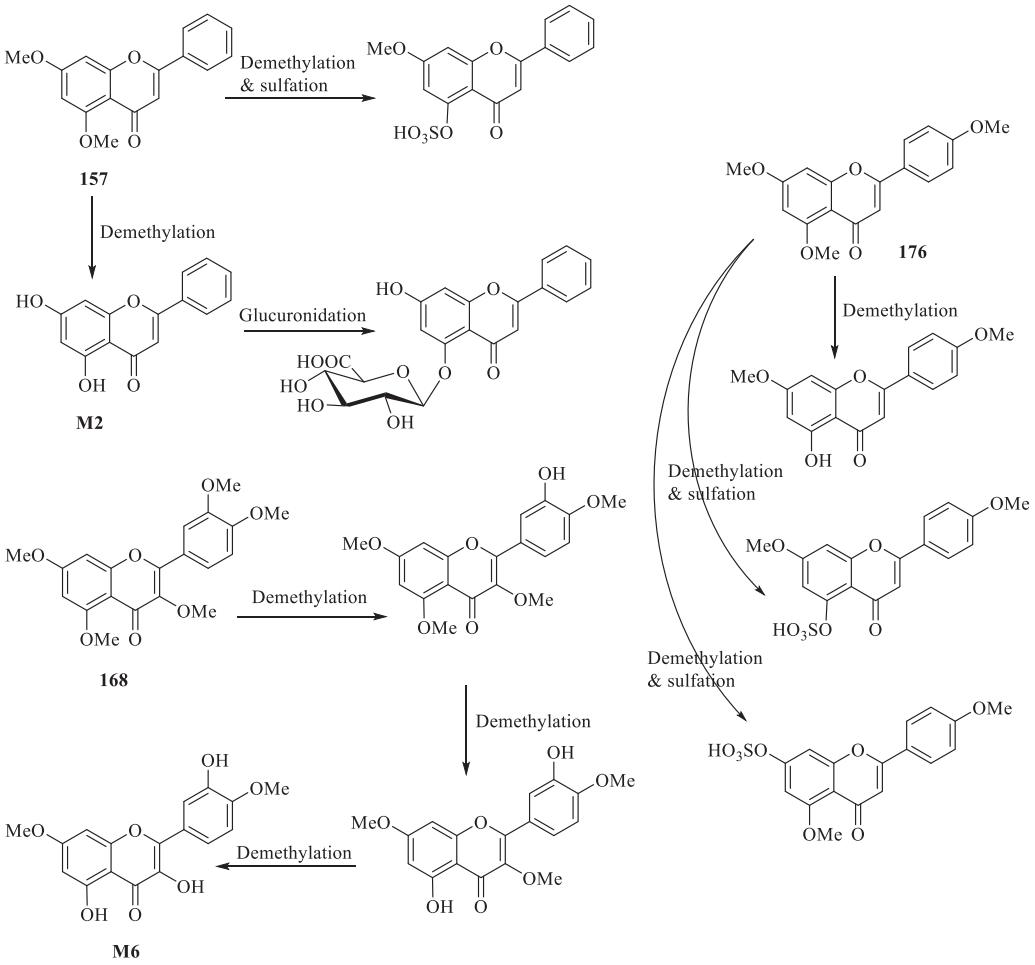


Fig. 8 Proposed metabolic pathways of flavones **157, 168**, and **176** in mice

Obviously, 3,7,3'-trimethoxylation and 5,4'-dihydroxylation would enhance the activity.

As we know, the PDE5 (phosphodiesterase 5) is an isoenzyme used for erectile dysfunction since it increased blood flow to penile tissue [86]. However, this also inhibited PDE6, which gave rise to visual disturbances [86]. Four flavones **157**, **168**, and **175–176** showed the SI (selective index) of 0.16–3.71 to PDE6/PDE5, when sildenafil was used as a positive control (SI 4.85) [86].

As we know, estrogen productive reduction could be performed by aromatase enzyme suppression [30]. Diterpenoid **2** was such an active inhibitor to this enzyme with a IC_{50} value of 3.7 μM, followed by **8** (IC_{50} 7.2 μM), **67** (IC_{50} 10.4 μM), **150** (IC_{50} 10.7 μM), and **151** (IC_{50} 11.8 μM), when ketoconazole was used as a positive control (IC_{50} 2.4 μM) [30].

Pharmacokinetic studies

After the oral administration of the EtOH extract of *K. parviflora* rhizome to mice, the maximal concentration (C_{max}) of flavones **157**, **168**, and **176** fluctuated from 0.55 to 0.88 μg/mL within 2 h treatment, together with their bioavailability of 1–4% [87]. These metabolites were concentrated in the liver and kidney, and occasionally occurred in the lung, testes, and brain [87]. It is also found that these compounds were mainly eliminated via the urine by demethylated, sulfated, and glucuronidated reactions and as demethylated reactions in the feces (Fig. 8) [87]. It has been so far observed that the C_{max} values of these flavones were changed to 0.53–2.03 μg/mL when co-administrated the EtOH extract of *K. parviflora* rhizome and sildenafil [88].

The oral bioavailability of *K. parviflora* rhizome EtOH extract-self microemulsifying complex was higher than the treatment of the single extract (26.01-, 25.38-, and 42.00-fold for **157**, **168**, and **176**, respectively) [87]. Similarly, for the *K. parviflora* rhizome EtOH extract-2-hydroxypropyl-β-cyclodextrin, the corresponding oral bioavailability values of **157**, **168**, and **176** were 22.90-, 21.63-, and 34.20-fold greater than the treatment of the single extract [87].

Conclusions and perspectives

Kaempferia species are among the oldest and most popular medicinal plants. The current review first covered all information on two major chemical classes diterpenoids and flavonoids of this genus, including natural occurrence, biosynthesis, synthesis, pharmacology and pharmacokinetics. The rhizomes were used in phytochemical separations at most. **153** Diterpenoids and 42 flavonoids have been compiled, in which isopiramanes are principal ditepernoids. Among isolated flavonoids, flavones **155–157**, **159–162**, **164**, **168**, **172–173**, and **175–176** were detected frequently. As for various natural diterpenoids, biosynthesis of *Kaempferia* diterpenoids was originated from the precursor (*E,E,E*)-geranylgeranyl diphosphate. Synthetic procedures successfully created aminoflavones and flavone oximes with the ultimate aim of pharmacological property enhancements. Importantly, diterpenoids and flavonoids derived from *Kaempferia* plants have been shown to possess a variety of pharmacological activities, comprising anticancer, antioxidative, antiinflammatory, antimicrobial, antiviral, antimalarial, antidiabetic, anti-allergenic, anti-obesity, anti-mutagenic, neuroprotective skin protective, hepatoprotective, vasorelaxant, and enzymatic and aromatase inhibitory activities. Bioavailability of *Kaempferia* flavones has been identified from 1.0 to 4.0%, and pharmacokinetic metabolism was deduced from demethylation, sulfation, and glucuronidation.

Nevertheless, there have been some scientific gaps which should be further investigated. It is expected to the continuous progresses in the phytochemical and pharmacological studies. The useful methods to obtain huge amounts of *Kaempferia* flavonoids seem better than the traditional chromatographic separations. Most pharmacological results were initial in vivo screenings, by this mean, in vitro assessments, molecular mechanisms of action, and clinical significance are needed. More pharmacokinetic studies on *Kaempferia* constituents, especially diterpenoids are necessary. The studies tend to highlight the toxicology of these phytochemicals are still unknown, as well as their synergistic combinations with other drugs for promoting pharmacology, pharmacokinetics, and bioavailability are welcome.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1007/s00044-023-03169-w.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

List of abbreviations

ABTS	2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)
AChE	Acetylcholinesterase
Akt	Protein kinase B
ATGL	Adipose tissue triglyceride lipase
BACE1	Beta-site amyloid precursor protein cleaving enzyme 1
BHT	Butylated hydroxytoluene
BChE	Butyrylcholinesterase
COX-2	Cyclooxygenase-2
DPPH	2,2-Diphenyl-1-picrylhydrazyl
FRAP	Ferric reducing antioxidant power
GGPP	(*E*,*E*,*E*)-geranylgeranyl diphosphate
HDF	Human dermal fibroblasts
HSL	Hormone-sensitive lipase
HIV	Human immune virus
IL-1β	Interleukin-1β
iNOS	Inducible nitric oxide synthase
LPS	Lipopolysaccharide
MAPK	Mitogen-activated protein kinase
MBC	Minimum bactericidal concentration
MIC	Minimum inhibitory concentration
MMP-1	Matrix metalloproteinase 1
NO	Nitric oxide
NMR	Nuclear magnetic resonance
ORAC	Oxygen radical absorbance capacity
PDE5	Phosphodiesterase 5
PGE_2	Prostaglandin 2
P-gp	P-glycoprotein
ROS	Reactive oxygen species
SIV	Simian immunodeficiency virus
sHE	Soluble epoxide hydrolase
SI	Selective index
TNF-α	Tumor necrosis factor-α
TPA	12-*O*-tetradecanoylphorbol-13-acetate
Vpr	Viral protein R

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