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A comprehensive review on phytochemistry and pharmacology of genus *Kopsia*: monoterpene alkaloids – major secondary metabolites

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Kopsia belongs to the family Apocynaceae, which was originally classified as a genus in 1823. *Kopsia* consists of medicinal plants that can be traditionally used to treat rheumatoid arthritis, pharyngitis, tonsillitis, and dropsy. More than one hundred and twenty-five publications have been documented relating to the phytochemical and pharmacological results, but a systematic review is not available. The goal of this study is to compile almost all of the secondary metabolites from the plants of genus *Kopsia*, as well as the coverage of their pharmacological research. The document findings were conducted *via* reliable sources, including Web of Science, Sci-Finder, Science Direct, PubMed, Google Scholar, and publishers, while four words "*Kopsia*", "monoterpene alkaloids", "Phytochemistry" and "Pharmacology" are key factors to search for references. Most *Kopsia* secondary metabolites were collected. A total of four hundred and seventy-two, including four hundred and sixty-six monoterpene alkaloids, five triterpenoids, and one sterol, were summarized, along with their resource. *Kopsia* monoterpene alkaloids presented in various skeletons, but aspidofractinines, eburnamines, and chanofruticosinates are the three major backbones. Mersinines and pauciflorines are new chemical classes of monoterpene alkaloids. With the rich content of monoterpene alkaloids, *Kopsia* constituents were also the main objects in pharmacological studies since the plant extracts and isolated compounds were proposed for anti-microbial, anti-inflammatory, anti-allergic, anti-diabetic, anti-manic, anti-nociceptive, acetylcholinesterase (AChE) inhibitory, cardiovascular, and vasorelaxant activities, especially cytotoxicity.

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1. Introduction

Natural products are chemical substances created by living organisms and found in nature. In the medicinal chemistry field, this concept is usually limited to secondary metabolites.[1] The pharmacological studies on potential bioactive agents tend to find that lead molecules for drug development could arise from natural resources.

Kopsia belongs to the subfamily Rauvolfioideae of the family Apocynaceae.[2] This genus, containing about 30 species, is widely distributed in Southeast Asia, China, Australia, and some islands of the Western Pacific.[3,4] *Kopsia* plants are recognized as a fertile reservoir of novel and bioactive secondary metabolite type alkaloids. Therefore, they have been traditionally used in each country. Chinese folk medicine deals with the use of parts of *K. officinalis* Tsiang & P. T. Li to treat rheumatoid arthritis, pharyngitis, tonsillitis, and dropsy.[4] In Malaysia, the roots of four species, *K. larutensis* King & Gamble, *K. macrophylla* Hook.f., *K. singapurensis* Ridl., and *K. paucifora* Hook.f., were applied as a poultice to ulcerate noses in tertiary syphilis.[2,5] *Kopsia* constituents are also well-known in pharmacological discoveries, in which they have a wide spectrum of pharmacological effects such as anticancer and anti-manic activities.[6,7]

Recently, the search for bioactive molecules from the genus *Kopsia* has drawn lots of interest to natural product chemists and pharmacists.[8–13] Although there have been a variety of experimental studies, an overview of phytochemical and pharmacological assessments is not available now. The current review provides notes on basic knowledge about phytochemical research and sheds light on the pivotal role of *Kopsia* constituents in pharmacological examinations. More than one hundred twenty-five relevant publications have been used, as well as the data collection is from the 1950s to now.

2. Phytochemistry

Since the 1950s, a large number of phytochemical studies on *Kopsia* plants have been published. To some extent, this current paper provides basic knowledge about the isolation processes of *Kopsia* secondary metabolites. The results related to experimental reports are primarily based on chromatographic

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approaches, such as silica gel chromatography or HPLC procedure (high performance chromatography column), whereas the NMR structural elucidation of isolated compounds is due to the most utilization of spectral methods, such as 1D/2D-NMR, mass spectroscopy (MS), ultraviolet-visible (UV-Vis), optical rotation (OR), infrared (IR), circular dichroism (CD) and comparisons with previous literature. Among recorded thirty species, nineteen plants, including *K. arborea*, *K. dasyrachis*, *K. deverrei*, *K. flavida*, *K. fruticosa*, *K. grandifolia*, *K. griffithii*, *K. hainanensis*, *K. jasminiflora*, *K. lancibracteolata*, *K. lapidilecta*, *K. larutensis*, *K. macrophylla*, *K. officinalis*, *K. pauciflora*, *K. profunda*, *K. singapurensis*, *K. teoi*, and *K. terengganensis*, have been most widely utilized for phytochemical investigations. More than four hundred seventy metabolites were collected and tabulated in Table 1 and Fig. 1–9. Significantly, four hundred sixty-six isolated compounds have been categorized as monoterpene alkaloids, in which they have induced a diversity of chemical skeletons, including aspidofractinines **1–204**, chanofruticosinates **205–241**, aspidospermines **242–248**, danuphyllines **249–252**, eburnamines **253–301**, akuammilines **302–322**, sarpagines **323–326**, aspidophyllines **327–331**, strychnos **332–356**, stemmadenine **357**, mersinines **358–378**, pauciflorines **379–390**, skytanthines **391–400**, rhazinilams **401–409**, lundurines **410–426**, aspidospermas **427–431**, catharinensines **432–436**, leuconoxines **437–442**, pericines **443–446**, alstonines **447–449**, quebrachamines **450–452**, arbophyllinines **453–454**, arboflorines **455–456**, andrasinines **457–458**, corynantheines **459–460**, carbolines **461–462**, arbophyllidine **463**, mersicarpine **464**, azepane-fused tetrahydro-β-carboline **465**, and andranginine **466**. In each group, the name of the compound was alphabetically ordered in an arrangement. The similar chemical classes will be placed close to each other.

2.1. Aspidofractinines

Aspidofractinines are the largest phytochemical class of isolated alkaloids from the genus *Kopsia*. As shown in Table 1, more than two hundred aspidofractinines have been isolated to date, and they derive from various parts of *K. arborea*, *K. dasyrachis*, *K. fruticosa*, *K. grandifolia*, *K. griffithii*, *K. hainanensis*, *K. hainanensis*, *K. jasminiflora*, *K. larutensis*, *K. macrophylla*, *K. officinalis*, *K. pauciflora*, *K. profunda*, *K. singapurensis*, and *K. teoi*.[4,7–59,61–79,81] From Fig. 1, *Kopsia* aspidofractinines **1–204** occurred in both monomer and dimer forms, but they did not bind to sugar units. Aspidofractinines **1–204** have been generally associated with the esterification at nitrogen N-1 and carbon C-16, carbonylation at carbon C-5, expoxydation at carbons C-11 and C-12, and hydroxylation, or methoxylation at carbons C-11, C-12, C-16, C-17, and C-18. It was found that 5,22-dioxokopsane (**17**), kopsamine (**39**), kopsamine *N*-oxide (**40**), kopsanone (**41**), kopsifine (**73**), kopsilongine (**91**), kopsininic acid (**117**), kopsinilam (**124**), kopsinine (**126**), kopsinine-*N*(4)-oxide (**127**), pleiocarpine (**189**), and (−)-venalstonine (**201**) might be seen as characteristic metabolites in the group of *Kopsia* aspidofractinines. For instance, compound **126** was recorded to appear in *K. arborea* twig and stem bark, *K. dasyrachis* stem, *K. fruticosa* stem bark, *K. jasminiflora* stem bark, *K. grandifolia* stem bark, *K. griffithii* leaf and stem bark, *K. hainanensis* leaf, stem, stem bark and twig, *K. larutensis* stem, stem bark and leaf, *K. officinalis* root, stem, twig, leaf and fruit, *K. singapurensis* stem bark and leaf, *K. pauciflora* stem, stem bark and leaf, and *K. teoi* stem bark, whereas its *N*(4)-oxide (**127**) presented in *K. dasyrachis* stem, *K. griffithii* stem bark, *K. hainanensis* stem and leaf, *K. officinalis* fruit and leaf, *K. pauciflora* stem, and *K. singapurensis* bark.[5–7,9–11,13–19,21–25,28,29,32,36,42,43,48,51,65,66,68–72]

Taking phytochemical studies into account, a new bisindole alkaloid arbolodinine A (**1**) was isolated from *K. arborea* stem bark.[8] Based on NMR, MS, and ECD data, compound **1** was a product by the combination of two apidofractinine units, and its biosynthetic pathway was structurally formulated from precursor **126**. Aspidofractinine (**2**) can be found in *K. arborea* stem bark, *K. hainanensis* twigs and leaves, and *K. officinalis* stem,[9–11] but aspidofractinine-1,3-dicarboxylic acid (**4**) was only detected in *K. officinalis* stem.[11] (2β,5β)-Aspidofractinin-16-ol (**3**) was a new 16-alcohol derivative found in *K. officinalis* leaves for the first time, and then was detected in *K. hainanensis* twigs and leaves.[9,12,13] Compounds **5–9** have shared the same feature of carbomethoxylation at nitrogen N-1,[14–19] in which *N*-carbomethoxy-11-hydroxy-12-methoxykopsinaline (**5**) and *N*-carbomethoxy-11-methoxy-12-hydroxykopsinaline (**6**) were two new metabolites in nature.[14–16] Dasyrachine (**10**) containing isokopsine skeleton was one of the new metabolites present in the 95% EtOH extract of *K. dasyrachis* stem.[18] In contrast to compounds **5–9**, the next compounds decarbomethoxykopsine (**11**), decarbomethoxyisokopsine (**12**), decarbomethoxykopsifine (**13**), *N*(1)-decarbomethoxykopsamine (**14**), N_a-demethoxycarbonyl-12-methoxykopsine (**15**), and 10-demethoxykopsidasinine (**16**) are associated with the decarbomethoxylation at nitrogen N-1.[10,11,16,18–26] Among them, compounds **13**, **15**, and **16** were new in nature. 11,12-Dimethoxykopsamine (**18**) was a known metabolite found in *K. dasyrachis* leaves, but 11,12-dimethoxykopsinaline (**19**) was a new one in the stem bark of *K. pauciflora* stem bark.[22,30] Similarly, 16-*epi*-kopsinine (**20**), 16-*epi*-kopsinilam (**21**), 16-*epi*-17α-hydroxy-$\Delta^{14,15}$-kopsinine (**22**), 14,15-β-epoxykopsingine (**23**), *N*(1)-formylkopsininic acid (**24**), *N*(1)-formylkopsininic acid-*N*(4)-oxide (**25**), fruticosamine (**26**), fruticosiamine A (**27**), and fruticosine (**28**) were new aspidofractinines, and found in genus *Kopsia* for the first time.[11,20,24,31–37,39–42] The known metabolite 11-hydroxykopsilongine (**29**) has been detected in both the fruit and leaf of *K. officinalis*,[13,25] while 11-hydroxykopsingine (**30**), 5β-hydroxykopsinine (**31**), and 15-hydroxykopsamine (**32**) were first isolated from polar extracts of *K. teoi* leaf, *K. jasminiflora* stem bark, and *K. singapurensis* root, respectively.[24,34,35] Two known compounds **33** and **34** were products of 15α and 17α-hydroxylation of kopsinine, respectively (Fig. 1). In the meantime, the structure of the new metabolite **35** is closely related to kopsinine by 17α-OH and olefinic double bond at carbons C-14 and C-15.[44] For a long time, Ruangrungsi *et al.* (1987) successfully isolated two new aspidofractinines, named jasminiflorine (**36**) and kopsijasmine (**89**), from the MeOH extract of *K. jasminiflora* leaves, whereas

Table 1 Monoterpene alkaloids and non-alkaloidal constituents from the genus *Kopsia*

No.	Compounds	Species	References
Aspidofractinines			
1	Arbolodinine A	*K. arborea* stem bark	8
2	Aspidofractinine	*K. arborea* stem bark, *K. hainanensis* twig and leaf, *K. officinalis* stem	9–11
3	(2β,5β)-Aspidofractinin-16-ol	*K. hainanensis* twig and leaf, *K. officinalis* leaf	9, 12 and 13
4	Aspidofractinine-1,3-dicarboxylic acid	*K. officinalis* stem	11
5	*N*-Carbomethoxy-11-hydroxy-12-methoxykopsinaline	*K. griffithii* leaf, *K. officinalis* twig, leaf and fruit	14–16
6	*N*-Carbomethoxy-11-methoxy-12-hydroxykopsinaline	*K. officinalis* fruit	14
7	*N*(1)-Carbomethoxy-11, 12-dimethoxykopsinaline	*K. griffithii* leaf, *K. officinalis* fruit	14, 15 and 17
8	*N*-Carbomethoxy-12-methoxykopsinaline	*K. officinalis* fruit	14
9	*N*-Carbomethoxy-5,22-dioxokopsane	*K. dasyrachis* stem, *K. pauciflora* stem	18 and 19
10	Dasyrachine	*K. arborea* stem bark, *K. dasyrachis* stem	10 and 18
11	Decarbomethoxykopsine (demethoxycarbonylkopsin)	*K. fruticosa* leaf, *K. officinalis* leaf and twig	16 and 20
12	Decarbomethoxyisokopsine	*K. fruticosa* leaf	20
13	Decarbomethoxykopsifine	*K. arborea* twig, *K. dasyrachis* stem, *K. officinalis* stem, *K. pauciflora* stem and stem bark	11, 18, 19, 21 and 22
14	*N*(1)-Decarbomethoxykopsamine	*K. arborea* stem bark, *K. hainanensis* stem and leaf, *K. pauciflora* leaf, *K. singapurensis* leaf	7, 10, 22 and 23
15	N_a-Demethoxycarbonyl-12-methoxykopsine	*K. jasminiflora* stem bark, *K. officinalis* leaf and twig	16, 24 and 25
16	10-Demethoxykopsidasinine	*K. jasminiflora*	26
17	5,22-Dioxokopsane	*K. hainanensis* stem bark and twig, *K. macrophylla* bark, *K. officinalis* root, stem, twig and fruit, *K. pauciflora* stem bark	11, 12, 14, 16, 19 and 27–29
18	11,12-Dimethoxykopsamine	*K. dasyrachis* leaf	30
19	11,12-Dimethoxykopsinaline	*K. pauciflora* stem bark	22
20	16-*epi*-Kopsinine	*K. fruticosa* stem bark, *K. officinalis* stem, *K. singapurensis* leaf	11, 31 and 32
21	16-*epi*-Kopsinilam	*K. jasminiflora* stem bark	24
22	16-*epi*-17α-Hydroxy-$\Delta^{14,15}$-kopsinine	*K. teoi* stem bark and leaf	33
23	14,15-β-Epoxykopsingine	*K. teoi* leaf	34
24	*N*(1)-Formylkopsininic acid	*K. singapurensis* root	35 and 36
25	*N*(1)-Formylkopsininic acid-*N*(4)-oxide	*K. singapurensis* root	35 and 36
26	Fruticosamine	*K. fruticosa* leaf, *K. jasminiflora* leaf	20 and 37–41
27	Fruticosiamine A	*K. fruticosa* leaf	41
28	Fruticosine	*K. jasminiflora* leaf, *K. fruticosa* leaf, *K. officinalis* twig	20 and 37–42
29	11-Hydroxykopsilongine	*K. officinalis* fruit and leaf	13 and 25
30	11-Hydroxykopsingine	*K. teoi* leaf	34
31	5β-Hydroxykopsinine	*K. jasminiflora* stem bark	24
32	15-Hydroxykopsamine	*K. singapurensis* root	35 and 36
33	15α-Hydroxykopsinine	*K. arborea* stem bark; *K. fruticosa* leaf and stem bark, *K. singapurensis* bark	10, 31 and 36
34	17α-Hydroxykopsinine	*K. teoi* stem bark	43
35	17α-Hydroxy-$\Delta^{14,15}$-kopsinine	*K. singapurensis* stem bark and leaf; *K. teoi* stem and stem bark	23, 32, 34 and 44–48
36	Jasminiflorine	*K. jasminiflora* leaf	40
37	Kopsamidine A	*K. arborea* stem bark	10
38	Kopsamidine B	*K. arborea* stem bark	10
39	Kopsamine	*K. arborea* twig and stem bark, *K. dasyrachis* stem and leaf, *K. officinalis* stem, root, leaf and fruit, *K. griffithii* leaf, *K. pauciflora* stem and stem bark, *K. singapurensis* leaf and root, *K. teoi* stem bark	10, 13–15, 17–19, 21, 25, 30, 36, 43, 49 and 50
40	Kopsamine *N*-oxide	*K. arborea* stem bark; *K. dasyrachis* stem and leaf, *K. officinalis* fruit, *K. griffithii* leaf, *K. pauciflora* stem, *K. singapurensis* root	10, 14, 15, 17–19, 30, 36, 49 and 51
41	Kopsanone	*K. arborea* stem bark; *K. fruticosa* stem bark, *K. jasminiflora* stem bark, *K. hainanensis* stem bark, *K. pauciflora* stem and stem bark, *K. officinalis* fruit	10, 14, 19, 22, 24, 29 and 31
42	Kopsaporine	*K. singapurensis* stem bark, *K. teoi* stem and stem bark	32, 34, 44 and 45
43	Kopsiafrutine A	*K. fruticosa* aerial part	52
44	Kopsiafrutine B	*K. fruticosa* aerial part	52
45	Kopsiafrutine C	*K. fruticosa* aerial part	52
46	Kopsiafrutine D	*K. fruticosa* aerial part	52
47	Kopsiafrutine E	*K. fruticosa* aerial part	52
48	Kopsiahainanin A	*K. hainanensis* twig and leaf	53
49	Kopsiahainanin B	*K. hainanensis* twig and leaf	53
50	Kopsiahainanin C	*K. hainanensis* twig and leaf	53

Table 1 (*Contd.*)

No.	Compounds	Species	References
51	Kopsiahainanin D	*K. hainanensis* twig and leaf	53
52	Kopsiahainanin E	*K. hainanensis* twig and leaf	53
53	Kopsiahainanin F	*K. hainanensis* twig and leaf	53
54	Kopsiahainin A	*K. hainanensis* twig and leaf	54
55	Kopsiahainin B	*K. hainanensis* twig and leaf	54
56	Kopsiahainin C	*K. hainanensis* twig and leaf	54
57	Kopsiahainin D	*K. hainanensis* twig and leaf	54
58	Kopsiahainin E	*K. hainanensis* twig and leaf	54
59	Kopsiaofficine A	*K. officinalis* aerial part	55
60	Kopsiaofficine B	*K. officinalis* aerial part	55
61	Kopsiaofficine C	*K. officinalis* aerial part	55
62	Kopsiarborines A	*K. arborea* aerial part	56
63	Kopsidarine	*K. singapurensis* leaf	48
64	Kopsidasine	*K. dasyrachis* leaf	57
65	Kopsidasine-*N*-oxide	*K. dasyrachis* leaf	57
66	Kopsidasinine	*K. dasyrachis* leaf	57
67	Kopsidine A	*K. singapurensis* leaf, *K. teoi* leaf and stem bark	34, 43, 45, 48 and 58
68	Kopsidine B	*K. teoi* leaf	34, 45 and 58
69	Kopsidine C	*K. singapurensis* leaf, *K. teoi* leaf	34, 48 and 58
70	Kopsidine C *N*-oxide	*K. singapurensis* leaf	48
71	Kopsidine D	*K. singapurensis* leaf, *K. teoi* leaf	32, 34 and 58
72	Kopsidine E	*K. arborea* bark	59
73	Kopsifine	*K. arborea* stem bark, *K. dasyrachis* stem, *K. hainanensis* twig, *K. officinalis* stem, *K. pauciflora* stem and stem bark, *K. singapurensis* root	10–12, 18, 22, 49 and 60
74	Kopsiflorine	*K. arborea* stem bark; *K. dasyrachis* stem, *K. hainanensis* stem and leaf, *K. officinalis* leaf	7, 10, 12, 13, 18 and 61
75	Kopsiflorine *N*(4)-oxide	*K. dasyrachis* stem	18
76	Kopsifoline A	*K. fruticosa* leaf and aerial part, *K. singapurensis* leaf	31, 36, 52, 62 and 63
77	Kopsifoline B	*K. fruticosa* leaf	31, 62 and 63
78	Kopsifoline C	*K. fruticosa* leaf	31, 62 and 63
79	Kopsifoline D	*K. fruticosa* leaf	31 and 63
80	Kopsifoline E	*K. fruticosa* leaf	31 and 63
81	Kopsifoline F	*K. fruticosa* leaf	31 and 63
82	Kopsifoline G	*K. hainanensis* stem	64
83	Kopsihainin B	*K. hainanensis* stem	65
84	Kopsihainin C	*K. hainanensis* stem	65
85	Kopsihainin D	*K. hainanensis* twig	12
86	Kopsihainin E	*K. hainanensis* twig	12
87	Kopsihainin F	*K. hainanensis* twig	12
88	Kopsijasminine	*K. teoi* stem bark	43
89	Kopsijasmine	*K. jasminiflora* leaf	40
90	Kopsilarutensinine	*K. larutensis* stem bark and leaf	66
91	Kopsilongine	*K. arborea* twig and stem bark, *K. dasyrachis* stem, *K. griffithii* leaf and stem bark, *K. officinalis* leaf, *K. pauciflora* stem *K. singapurensis* leaf	10, 13, 15, 17–19, 21, 22 and 32
92	Kopsilongine-*N*-oxide	*K. singapurensis* leaf	32
93	Kopsiloscine A	*K. singapurensis* leaf	32
94	Kopsiloscine B	*K. singapurensis* leaf	32
95	Kopsiloscine C	*K. singapurensis* leaf and stem bark	32 and 48
96	Kopsiloscine D	*K. singapurensis* leaf	32
97	Kopsiloscine E	*K. singapurensis* leaf	32
98	Kopsiloscine F	*K. singapurensis* leaf	32
99	Kopsiloscine G	*K. singapurensis* stem bark and leaf	23 and 48
100	Kopsiloscine H	*K. singapurensis* stem bark	23
101	Kopsiloscine I	*K. hainanensis* stem and leaf, *K. singapurensis* stem bark	7 and 23
102	Kopsiloscine J	*K. singapurensis* leaf	23
103	Kopsimaline A	*K. singapurensis* leaf	23
104	Kopsimaline B	*K. singapurensis* leaf	23
105	Kopsimaline C	*K. singapurensis* leaf	23
106	Kopsimaline D	*K. singapurensis* leaf	23
107	Kopsimaline E	*K. singapurensis* leaf	23
108	Kopsimaline F	*K. singapurensis* leaf	48

Table 1 (*Contd.*)

No.	Compounds	Species	References
109	Kopsinarine	*K. dasyrachis* stem, *K. hainanensis* twig	12 and 18
110	Kopsine	*K. dasyrachis* stem, *K. fruticosa* leaf	18, 20, 38, 39, 41 and 67
111	Kopsinganol	*K. singapurensis* stem bark, *K. teoi* stem, stem bark and leaf	32, 34, 43, 45, 47 and 48
112	Kopsingine	*K. singapurensis* leaf and stem bark, *K. teoi* stem, stem bark and leaf	32–34, 44, 45 and 48
113	Kopsinginine	*K. teoi* stem and stem bark	34, 43–45 and 47
114	Kopsinginol	*K. teoi* stem and stem bark	34, 45 and 47
115	Kopsinidine A	*K. arborea* stem bark	10
116	Kopsinidine B	*K. arborea* stem bark	10
117	Kopsininic acid (kopsinic acid)	*K. hainanensis* stem bark, *K. jasminiflora* stem bark, *K. officinalis* stem, twig and leaf, *K. singapurensis* bark and leaf	11, 13, 16, 24, 29 and 36
118	Kopsinicine	*K. singapurensis* leaf	23
119	Kopsinidine A	*K. arborea* stem bark, *K. officinalis* leaf	10 and 25
120	Kopsinidine B	*K. arborea* stem bark, *K. officinalis* leaf	10 and 25
121	Kopsinidine C	*K. officinalis* leaf and twig	16
122	Kopsinidine D	*K. officinalis* leaf and twig	16
123	Kopsinidine E	*K. officinalis* leaf and twig	16
124	Kopsinilam	*K. hainanensis* stem bark and twig, *K. jasminiflora* stem bark, *K. officinalis* stem, twig, leaf and fruit	11, 12, 14, 16, 24 and 29
125	Kopisininate	*K. hainanensis* stem and leaf	7
126	Kopsinine	*K. arborea* twig and stem bark, *K. dasyrachis* stem, *K. fruticosa* stem bark, *K. jasminiflora* stem bark, *K. grandifolia* stem bark, *K. griffithii* leaf and stem bark, *K. hainanensis* leaf, stem, stem bark and twig, *K. larutensis* stem, stem bark and leaf, *K. officinalis* root, stem, twig, leaf and fruit, *K. singapurensis* stem bark and leaf, *K. pauciflora* stem, stem bark and leaf, *K. teoi* stem bark	7, 9–11, 13–19, 21–25, 28, 29, 32, 36, 42, 43, 48, 50, 51, 64–66 and 68–72
127	Kopsinine-*N*(4)-oxide	*K. dasyrachis* stem, *K. griffithii* stem bark, *K. hainanensis* stem and leaf, *K. officinalis* fruit and leaf, *K. pauciflora* stem, *K. singapurensis* bark	7, 13, 15, 18, 25 and 36
128	Kopsinine methochloride	*K. officinalis* leaf and twig	16
129	Kopsinine B	*K. officinalis* leaf and twig	16
130	Kopsinine F	*K. hainanensis* stem and leaf	7
131	Kopsinitarine A	*K. singapurensis* leaf, *K. teoi* leaf	34, 48, 73 and 74
132	Kopsinitarine B	*K. singapurensis* leaf, *K. teoi* leaf	34, 48, 73 and 74
133	Kopsinitarine C	*K. teoi* leaf	34, 73 and 74
134	Kopsinitarine D	*K. teoi* leaf	34 and 74
135	Kopsinitarine E	*K. teoi* stem bark	43
136	Kopsinol	*K. teoi* stem and stem bark	34, 45 and 47
137	(−)-Kopsinoline	*K. hainanensis* stem bark, *K. officinalis* stem, twig and leaf	11, 16 and 29
138	Kopsiofficine A	*K. officinalis* stem	11
139	Kopsiofficine B	*K. officinalis* stem	11
140	Kopsiofficine C	*K. officinalis* stem	11
141	Kopsiofficine D	*K. officinalis* stem	11
142	Kopsiofficine E	*K. officinalis* stem	11
143	Kopsiofficine F	*K. officinalis* stem	11
144	Kopsiofficine L	*K. officinalis* stem	75
145	Kopsofinone	*K. singapurensis* leaf	23
146	Kopsonoline	*K. teoi* stem bark	43
147	Kopsorinine	*K. fruticosa* leaf and stem bark	31
148	Lahadinine A	*K. pauciflora* leaf	76
149	Lahadinine B	*K. pauciflora* leaf	76
150	Mersingine A	*K. singapurensis* leaf, *K. teoi* leaf	34, 49 and 74
151	Mersingine B	*K. teoi* leaf	34 and 74
152	*N*(1)-Methoxycarbonyl-11,12-dimethoxykopsinaline	*K. arborea* stem bark, *K. pauciflora* stem	10, 19 and 51
153	*N*(1)-Methoxycarbonyl-11,12-methoxylenedioxykopsinaline	*K. officinalis* leaf, twig, stem and root, *K. pauciflora* stem and leaf	11, 16, 42, 51, 69 and 76
154	*N*(1)-Methoxycarbonyl-11,12-methylenedioxy-$\Delta^{16,17}$-kopsinine	*K. profunda* stem	4
155	*N*(1)-Methoxycarbonyl-12-methoxy-$\Delta^{16,17}$-kopsinine	*K. griffithii* leaf, *K. pauciflora* stem, *K. profunda* stem and leaf, *K. teoi* stem bark	4, 17, 19, 43, 51 and 77
156	*N*(1)-Methoxycarbonyl-12-methoxykopsinaline	*K. officinalis* root, stem, twig, leaf and fruit, *K. pauciflora* stem	11, 16, 25, 51 and 69

Table 1 (*Contd.*)

No.	Compounds	Species	References
157	*N*(1)-Methoxycarbonyl-11,12-methylenedioxy-$\Delta^{16,17}$-kopsinine *N*(4) oxide	*K. profunda* stem and leaf	77
158	*N*(1)-Methoxycarbonyl-12-hydroxy-$\Delta^{16,17}$-kopsinine	*K. pauciflora* stem, *K. profunda* stem and leaf	19 and 77
159	*N*(1)-Methoxycarbonyl-12-methoxy-$\Delta^{16,17}$-kopsinine *N*(4) oxide	*K. profunda* stem and leaf	77
160	11-Methoxykopsingine	*K. teoi* leaf	34
161	11-Methoxykopsilongine	*K. dasyrachis* stem, *K. officinalis* stem and leaf	11, 13 and 18
162	11-Methoxykopsilongine *N*(4)-oxide	*K. dasyrachis* stem	18
163	11-Methoxy-12-hydroxy-kopsinol	*K. teoi* leaf	34
164	12-Methoxykopsidasinine	*K. griffithii* leaf	17
165	(−)-12-Methoxykopsinaline	*K. officinalis* leaf and twig	13, 16, 42 and 69
166	12-Methoxykopsine	*K. arborea* leaf, *K. jasminiflora* stem bark, *K. officinalis* root and stem, *K. pauciflora* leaf	11, 22, 24 and 78
167	12-Methoxy-10-demethoxykopsidasinine	*K. griffithii* leaf, *K. pauciflora* stem	15, 51
168	12-Methoxypleiocarpine	*K. dasyrachis* stem and leaf, *K. hainanensis* stem and leaf, *K. griffithii* leaf, *K. pauciflora* stem	7, 15, 17–19 and 30
169	(−)-Methylenedioxy-11,12-kopsinaline	*K. arborea* twig	7
170	*N*(4)-Methylkopsininate	*K. officinalis* leaf and twig	16
171	11,12-Methylenedioxykopsaporine	*K. singapurensis* bark, *K. teoi* stem, stem bark and leaf	33, 34 and 79
172	(−)-11,12-Methylenedioxykopsinaline	*K. dasyrachis* stem, *K. officinalis* root, stem, leaf, twig and fruit	11, 16, 18, 25 and 69
173	11,12-Methylenedioxykopsinaline *N*(4)-oxide	*K. griffithii* stem bark, *K. officinalis* stem, twig and leaf	11, 15 and 16
174	11,12-Methylenedioxykopsine	*K. arborea* stem bark, *K. dasyrachis* stem, *K. officinalis* stem, *K. pauciflora* stem bark	10, 11, 18 and 22
175	Nitaphylline	*K. teoi* leaf	34, 46 and 80
176	5-Oxokopsinic acid	*K. jasminiflora* stem bark, *K. officinalis* twig and leaf	16 and 24
177	Paucidactine A	*K. pauciflora* stem bark	19
178	Paucidactine B	*K. arborea* stem bark, *K. pauciflora* stem bark	10 and 19
179	Paucidactine C	*K. arborea* stem bark, *K. pauciflora* stem bark	10 and 19
180	Paucidactine D	*K. pauciflora* stem bark	19
181	Paucidactine E	*K. pauciflora* stem bark	19
182	Paucidactinine	*K. pauciflora* stem bark	19
183	Paucidisine	*K. pauciflora* stem bark	19
184	Paucidirinine	*K. pauciflora* stem bark	19
185	Paucidirisine	*K. pauciflora* stem bark	19
186	Pauciduridine	*K. officinalis* stem, *K. pauciflora* stem bark	11 and 19
187	Paucifinine	*K. pauciflora* leaf and stem bark	22 and 76
188	Paucifinine-*N*-oxide	*K. pauciflora* leaf	76
189	Pleiocarpine	*K. arborea* stem bark, *K. dasyrachis* stem and leaf, *K. griffithii* leaf, *K. officinalis* fruit, *K. pauciflora* stem,	10, 14, 15, 17–19, 25 and 30
190	Pleiocarpine *N*-oxide	*K. pauciflora* stem	19
191	Pseudokopsinine	*K. pauciflora* leaf and stem bark	22
192	5,6-Secokopsinine	*K. jasminiflora* stem bark	24
193	Singaporentine A	*K. singapurensis* leaf	36
194	Singapurensine A	*K. singapurensis* bark	79
195	Singapurensine B	*K. singapurensis* bark	79
196	Singapurensine C	*K. singapurensis* bark	79
197	Singapurensine D	*K. singapurensis* bark	79
198	Venacarpine A	*K. fruticosa* leaf, *K. singapurensis* bark	31 and 36
199	Venacarpine B	*K. fruticosa* leaf	31
200	Venalstonidine	*K. arborea* stem bark	10
201	(−)-Venalstonine	*K. arborea* stem bark, *K. fruticosa* stem bark, *K. lapidilecta* stem and bark, *K. singapurensis* bark	10, 31, 36 and 81
202	Yunnanoffine A	*K. officinalis* leaf	25
203	Yunnanoffine B	*K. officinalis* leaf	25
204	Yunnanoffine D	*K. officinalis* leaf	25
	Chanofruticosinates		
205	Chanofruticosinic acid	*K. officinalis* leaf and twig	16
206	N_1-Decarbomethoxy chanofruticosinic acid	*K. hainanensis* stem and leaf	7
207	11,12-Dimethoxydanuphylline	*K. fruticosa* aerial part	3
208	Flavisiamine A (prunifoline D)	*K. arborea* leaf, *K. flavida* leaf	82–84
209	Flavisiamine B	*K. flavida* leaf	83

Table 1 (*Contd.*)

No.	Compounds	Species	References
210	Flavisiamine C	*K. arborea* leaf, *K. flavida* leaf	83 and 84
211	Flavisiamine D (prunifoline E)	*K. arborea* leaf and stem bark, *K. flavida* leaf	10 and 82–84
212	Flavisiamine E	*K. flavida* leaf	41
213	Flavisiamine F	*K. flavida* leaf	41
214	12-Hydroxylprunifoline A	*K. lancibracteolata* stem	85
215	12-Hydroxylprunifoline C	*K. lancibracteolata* stem	85
216	Kopreasin A	*K. arborea* leaf	84
217	Kopsia A (methyl chanofruticosinate)	*K. dasyrachis* leaf, *K. hainanensis* stem and leaf, *K. officinalis* leaf, twig, and stem, *K. pauciflora* leaf	7, 13, 16, 22, 25, 30, 75 and 86
218	Kopsia B (des-*N*-(methoxycarbonyl) chanofruticosin-methyleste)	*K. officinalis* leaf	86
219	Kopsia C (6,7-methylendioxychanofruticosin-methylester or methyl 11,12-methylenedioxychanofruticosinate)	*K. arborea* leaf and stem bark, *K. dasyrachis* leaf, *K. officinalis* stem and leaf, twig and leaf, *K. pauciflora* stem bark and leaf	10, 16, 22, 30, 75, 84, 86 and 87
220	Kopsihainanine A	*K. hainanensis* leaf and stem	6
221	Kopsihainanine B	*K. hainanensis* leaf and stem	6
222	12-Methoxychanofruticosinic acid	*K. officinalis* leaf and twig	16
223	Methyl chanofruticosinate *N*(4)-oxide	*K. hainanensis* stem and leaf	7
224	Methyl 11,12-dimethoxychanofruticosinate	*K. arborea* leaf, *K. flavida* leaf, *K. officinalis* leaf	13, 22, 25, 82, 88 and 89
225	Methyl N_1-decarbomethoxychanofruticosinate	*K. arborea* leaf and stem bark, *K. dasyrachis* leaf, *K. flavida* leaf, *K. fruticosa* leaf, *K. hainanensis* stem and leaf, *K. officinalis* twig, leaf and stem, *K. pauciflora* leaf	7, 10, 16, 25, 30, 41, 42, 65, 75, 82–84 and 87
226	Methyl N_1-decarbomethoxy chanofruticosinate *N*(4)-oxide	*K. hainanensis* stem and leaf	7
227	Methyl 12-methoxy-N_1-decarbomethoxychanofruticosinate	*K. arborea* leaf, *K. flavida* leaf	83, 84, 88 and 89
228	Methyl 12-methoxychanofruticosinate	*K. arborea* leaf and stem bark, *K. flavida* leaf, *K. officinalis* stem, twig and leaf, *K. pauciflora* leaf	10, 16, 22, 75, 82, 84, 88 and 89
229	Methyl 11,12-methylenedioxy-N_1-decarbomethoxychanofruticosinate	*K. arborea* stem bark and leaf, *K. dasyrachis* leaf, *K. flavida* leaf, *K. officinalis* leaf, twig and stem, *K. pauciflora* leaf and stem bark	10, 16, 22, 25, 30, 42, 75, 82–84 and 87–89
230	Methyl 11,12-methylenedioxy-N_1-decarbomethoxy-$\Delta^{14,15}$-chanofruticosinate	*K. arborea* stem bark and leaf, *K. flavida* leaf, *K. hainanensis* stem and leaf	7, 10, 82–84 and 87
231	Methyl (2β,11β,12β,19α)-6,7-didehydro-8,21-dioxo-11,21-cycloaspidospermidine-2-carboxylate	*K. officinalis* leaf	13
232	Methyl 3-oxo-12-methoxy-N_1-decarbomethoxy-14,15-didehydrochanofruticosinate	*K. flavida* leaf	89
233	Methyl 3-oxo-11,12-methylenedioxy-N_1-decarbomethoxy-14,15-didehydrochanofruticosinate	*K. flavida* leaf	89
234	$\Delta^{1,2}$-Methyldemethoxycarbonylchanofruticosinate	*K. officinalis* leaf	25
235	11,12-Methylenedioxychanofruticosinic acid	*K. officinalis* leaf and twig	16
236	3-Oxo-11,12-dimethoxy-N^1-decarbomethoxy-14,15-didehydrochanofruticosinate	*K. fruticosa* aerial part	3
237	*N*(4)-Oxide prunifoline D	*K. lancibracteolata* stem	85
238	Prunifoline A	*K. arborea* leaf	82
239	Prunifoline B	*K. arborea* leaf	82 and 84
240	Prunifoline C	*K. arborea* leaf, *K. fruticosa* leaf	41 and 82
241	Prunifoline F	*K. arborea* leaf	82
	Aspidospermines		
242	Aspidospermine	*K. pauciflora* leaf	22
243	(+)-1,2-Dehydroaspidospermine	*K. pauciflora* leaf	22
244	Eburenine	*K. arborea* aerial part	90
245	Kopsiofficine G	*K. officinalis* stem	11
246	Kopsiyunnanine G	*K. arborea* aerial part	90
247	Vincadifformine	*K. arborea* twig and stem bark, *K. officinalis* stem and fruit	10, 11, 14 and 21
248	Vincadifformine *N*(4)-oxide	*K. officinalis* stem	11
	Danuphyllines		
249	Danuphylline	*K. dasyrachis* leaf	30 and 91
250	Danuphylline B	*K. arborea* leaf	78
251	11,12-De(methylenedioxy)danuphylline	*K. officinalis* leaf	13

Table 1 (*Contd.*)

No. Compounds	Species	References
252 Kopsihainin A	*K. hainanensis* stem	65
Eburnamines		
253 (−)-Demethylnorpleiomutine	*K. dasyrachis* stem, *K. pauciflora* stem	18 and 19
254 (+)-Eburnamenine	*K. pauciflora* stem and stem bark	19 and 22
255 (−)-Eburnamenine	*K. arborea* aerial part, *K. hainanensis* twig, stem bark and leaf, *K. larutensis* bark, *K. officinalis* fruit	9, 14, 29, 90 and 70
256 (+)-Eburnamine	*K. hainanensis* stem bark	29
257 (−)-Eburnamine	*K. arborea* aerial part, *K. griffithii* stem bark, *K. hainanensis* twig and leaf, *K. larutensis* leaf, stem and stem bark, *K. officinalis* root and stem, *K. pauciflora* stem and stem bark, *K. singapurensis* stem bark, *K. terengganensis* bark	5, 9, 15, 19, 22, 23, 50, 51, 66, 68, 70, 90 and 92
258 (−)-Eburnaminol	*K. larutensis* stem bark, *K. terengganensis* bark	68 and 92
259 (+)-Eburnamonine	*K. arborea* aerial part, *K. dasyrachis* stem, *K. griffithii* leaf, *K. larutensis* leaf and stem bark, *K. officinalis* leaf and twig, *K. pauciflora* stem	5, 13, 15, 17–19, 42, 51, 68, 70, 90 and 93
260 (+)-Eburnamonine *N*(4)-oxide	*K. larutensis* leaf and stem	5 and 70
261 (−)-Eburnamonine	*K. jasminiflora* stem bark	24
262 (−)-*O*-Ethyleburnamine	*K. arborea* aerial part, *K. larutensis* stem	70 and 90
263 (+)-Ethylisoeburnamine	*K. arborea* aerial part	90
264 16α-Hydroxy-19-oxoeburnamine	*K. officinalis* leaf	25
265 16β-Hydroxy-19-oxoeburnamine	*K. officinalis* leaf	25
266 (+)-19(*R*)-Hydroxyeburnamine	*K. dasyrachis* stem	18 and 93
267 19-Hydroxy-(−)-eburnamonine	*K. arborea* twig, *K. larutensis* leaf, *K. officinalis* twig	5, 7 and 42
268 (−)-19(*R*)-Hydroxyisoeburnamine	*K. dasyrachis* stem, *K. pauciflora* stem and stem bark	19, 22 and 93
269 (+)-(19*R*)-19-Hydroxyeburnamine	*K. officinalis* leaf, *K. pauciflora* stem and stem bark	13, 19 and 22
270 (−)-19(*R*)-Hydroxyeburnamenine	*K. pauciflora* stem	19
271 (−)-(19*R*)-19-Hydroxyisoeburnamine	*K. dasyrachis* stem, *K. officinalis* leaf	13 and 18
272 (−)-19(*R*)-Hydroxy-*O*-ethylisoeburnamine	*K. pauciflora* stem	19
273 19(*S*)-Hydroxy-Δ^{14}-vicamone	*K. jasminiflora* stem bark	24
274 (+)-Isoeburnamine	*K. arborea* aerial part, *K. dasyrachis* stem, *K. hainanensis* stem bark, *K. larutensis* leaf, stem and stem bark, *K. teoi* stem bark and leaf, *K. officinalis* leaf, *K. pauciflora* stem and stem bark, *K. terengganensis* bark	5, 13, 18, 19, 22, 33, 29, 51, 68, 70, 90, 92 and 93
275 (−)-Isoeburnamine	*K. officinalis* root	28 and 69
276 16-Isoeburnamine ((+)-methylisoeburnamine)	*K. arborea* aerial part, *K. officinalis* stem	75 and 90
277 (+)-Kopsoffine	*K. hainanensis*, *K. officinalis* root	28 and 29
278 Kopsiofficine H	*K. officinalis* stem	75
279 Kopsiofficine I	*K. officinalis* stem	75
280 Kopsiofficine J	*K. officinalis* stem	75
281 Kopsiofficine K	*K. officinalis* stem	75
282 Kopsoffinol	*K. dasyrachis* stem, *K. pauciflora* stem	19 and 93
283 (+)-Larutensine	*K. larutensis* stem bark	68
284 Larutenine	*K. larutensis* leaf and stem, *K. officinalis* leaf, *K. pauciflora* leaf, *K. terengganensis* bark	5, 13, 22, 70 and 92
285 Larutenine A	*K. pauciflora* stem, stem bark and leaf	19 and 22
286 Larutenine B	*K. pauciflora* stem and stem bark	19 and 22
287 Melohenine B	*K. hainanensis* twig and leaf	9
288 (−)-Methyleburnamine	*K. arborea* aerial part	90
289 (−)-Norpleiomutine	*K. dasyrachis* stem, *K. macrophylla* bark, *K. pauciflora* stem and stem bark	18, 19, 22, 27 and 51
290 (+)-*O*-Methyleburnamine	*K. officinalis* stem	75
291 (−)-*O*-Methylisoeburnamine (*O*-methylvincanol)	*K. hainanensis* twig and leaf, *K. officinalis* stem	9 and 75
292 (+)-19-Oxoeburnamine	*K. pauciflora* stem and stem bark	19, 22 and 51
293 19-Oxo-(−)-eburnamonine	*K. jasminiflora* stem bark, *K. officinalis* twig	24 and 42
294 (−)-19-Oxoisoeburnamine	*K. pauciflora* stem	19
295 *O*-Methyl-16-*epi*-vincanol	*K. hainanensis* twig and leaf	9
296 20-Oxo-eburnamenine	*K. officinalis* root, leaf and stem	25, 50 and 75
297 Phutdonginin	*K. arborea* twig	21
298 Terengganensine A	*K. terengganensis* bark	92
299 Terengganensine B	*K. terengganensis* bark	92
300 Δ^{14}-Vicamone	*K. jasminiflora* stem bark	24
301 Yunnanoffine C	*K. officinalis* leaf	25

Table 1 (*Contd.*)

No. Compounds	Species	References
Akuammilines		
302 Akuammidine	*K. arborea* stem bark, *K. singapurensis* root, stem bark and leaf	10, 23, 32, 48 and 49
303 Akuammiline	*K. macrophylla* bark, *K. teoi* stem and stem bark	27, 34, 43, 45 and 47
304 Akuammiline *N*(4)-oxide	*K. griffithii* stem bark	15
305 ψ-Akuammigine	*K. fruticosa* stem bark	31
306 Deacetylakuammiline (rhazimol)	*K. deverrei* stem bark, *K. griffithii* leaf and stem bark, *K. macrophylla* bark, *K. singapurensis* stem bark, *K. teoi* stem and stem bark	15, 17, 23, 27, 34, 45, 47 and 94
307 Dregamine	*K. macrophylla* bark	27
308 16-*epi*-akuammiline	*K. singapurensis* leaf, stem bark and root, *K. teoi* stem bark	23, 32, 36, 43 and 48
309 16-*epi*-deacetylakuammiline	*K. deverrei* stem bark, *K. griffithii* stem bark, *K. fruticosa* stem bark, *K. singapurensis* bark, stem bark and leaf, *K. teoi* stem and stem bark	15, 23, 31, 32, 34, 36, 43, 48 and 94
310 16-*epi*-deacetylakuammiline-*N*(4)-oxide	*K. griffithii* stem bark, *K. singapurensis* bark	15 and 36
311 16-Hydroxymethyl-pleiocarpamine	*K. deverrei* stem bark, *K. fruticosa* stem bark, *K. singapurensis* stem bark and bark, *K. teoi* stem bark	23, 31, 43, 36 and 94
312 *N*-Methylpleiocarpamine	*K. singapurensis* root	36
313 5-Methoxystrictamine	*K. hainanensis* twig and leaf	9
314 Rhazimal	*K. arborea* stem bark	10
315 Rhazinaline *N*(4)-oxide	*K. griffithii* stem bark	15
316 Rhazinoline	*K. arborea* stem bark	10
317 Picralinal	*K. hainanensis* twig and leaf	9
318 Picramicine	*K. fruticosa* stem bark, *K. singapurensis* stem bark	23 and 31
319 Pleiocarpamine	*K. dasyrachis* stem, *K. deverrei* stem bark, *K. fruticosa* stem bark, *K. singapurensis* bark, *K. teoi* stem bark	18, 31, 36, 43 and 94
320 Pleiocarpamine methochloride	*K. officinalis* leaf and twig	16
321 Pleiomalicine	*K. hainanensis* twig and leaf	9
322 Singaporentinidine	*K. singapurensis* root	35 and 36
Sarpagines		
323 10-Hydroxy-vincadiffine	*K. hainanensis* twig and leaf	9
324 Perivine	*K. officinalis* root and stem	50
325 Tabernaemontanine	*K. macrophylla* bark	27
326 Vincadiffine	*K. hainanensis* twig and leaf	9
Aspidophyllines		
327 Aspidodasycarpine	*K. singapurensis* root and stem bark, *K. teoi* stem and stem bark	23, 32, 34, 36, 43, 48 and 49
328 Aspidophylline A	*K. singapurensis* stem bark	32
329 Aspidophylline B	*K. singapurensis* stem bark	48
330 Lonicerine	*K. fruticosa* stem bark, *K. singapurensis* bark and stem bark, *K. teoi* stem, stem bark and leaf	23, 31–34, 36, 43 and 48
331 Vincophylline	*K. singapurensis* leaf	32
Strychnoses		
332 Akuammicine	*K. pauciflora* leaf	22
333 Arbolodinine B	*K. arborea* stem bark	8
334 Arbolodinine C	*K. arborea* stem bark	8
335 (*E*)-Condylocarpine	*K. arborea* aerial part, *K. pauciflora* leaf	22 and 95
336 (*E*)-Condylocarpine *N*-oxide	*K. arborea* aerial part	95
337 14α-Hydroxycondylocarpine	*K. deverri* stem bark, *K. singapurensis* stem bark	23 and 94
338 14α-Hydroxy-*N*(4)-methylcondylocarpine	*K. singapurensis* root	35 and 36
339 14(*S*)-Hydroxy-19(*R*)-methoxytubotaiwine	*K. jasminiflora* stem bark	24
340 Isocondylocarpine	*K. arborea* aerial part	95
341 Isocondylocarpine *N*-oxide	*K. arborea* aerial part	95
342 Kopsiyunnanine A	*K. arborea* aerial part, *K. officinalis* aerial part	96 and 97
343 Kopsiyunnanine I	*K. arborea* aerial part	98 and 99
344 Kopsiyunnanine J1	*K. arborea* aerial part	99 and 100
345 Kopsiyunnanine J2	*K. arborea* aerial part	99 and 100
346 Kopsiyunnanine L	*K. arborea* aerial part	101 and 102
347 Kopsiyunnanine M	*K. arborea* aerial part	101 and 102
348 Kopsiyunnanine F1	*K. arborea* aerial part	95
349 Kopsiyunnanine F2	*K. arborea* aerial part	95
350 Kopsiyunnanine F3	*K. arborea* aerial part	95

Table 1 (*Contd.*)

No. Compounds	Species	References
351 Leuconicine B	*K. arborea* aerial part	98
352 19(*R*)-Methoxytubotaiwine	*K. arborea* aerial part and stem bark, *K. jasminiflora* stem bark	10, 24 and 95
353 19(*S*)-Methoxytubotaiwine	*K. arborea* aerial part and stem bark, *K. hainanensis* twig	10, 12 and 95
354 Mossambine	*K. singapurensis* stem bark	23
355 Precondylocarpine	*K. pauciflora* leaf	22
356 Tubotaiwine	*K. arborea* aerial part, *K. hainanensis* stem and stem bark	29, 64 and 95
Stemmadenine		
357 Stemmadenine	*K. pauciflora* leaf	22
Mersinines		
358 Mersidasine A	*K. singapurensis* leaf	103
359 Mersidasine B	*K. singapurensis* leaf	103
360 Mersidasine C	*K. singapurensis* leaf	103
361 Mersidasine D	*K. singapurensis* leaf	103
362 Mersidasine E	*K. singapurensis* leaf	103
363 Mersidasine F	*K. singapurensis* leaf	103
364 Mersidasine G	*K. singapurensis* leaf	103
365 Mersifoline A	*K. singapurensis* leaf	103
366 Mersifoline B	*K. singapurensis* leaf	103
367 Mersifoline C	*K. singapurensis* leaf	103
368 Mersilongine	*K. singapurensis* leaf	23 and 104
369 Mersiloscine	*K. singapurensis* leaf	103 and 105
370 Mersiloscine A	*K. singapurensis* leaf	103
371 Mersiloscine B	*K. singapurensis* leaf	103
372 Mersinaline	*K. singapurensis* leaf	23 and 106
373 Mersinine A	*K. fruticosa* leaf, *K. singapurensis* leaf	103 and 105, 107
374 Mersinine B	*K. singapurensis* leaf	103 and 105
375 Mersinine C	*K. singapurensis* leaf	103
376 Mersiphyllines A	*K. singapurensis* leaf	108
377 Mersiphyllines B	*K. singapurensis* leaf	108
378 Mersirachine	*K. singapurensis* leaf	23 and 106
Pauciflorines		
379 11,12-Demethoxy-16-deoxypauciflorine	*K. officinalis* stem and leaf	109
380 20-Deoxykopsijasminilam	*K. jasminiflora* leaf	40
381 Kopsiarborines C	*K. arborea* aerial part	56
382 Kopsijasminilam	*K. jasminiflora* leaf	40
383 Δ^{14}-Kopsijasminilam	*K. jasminiflora* leaf	40
384 Kopsioffine A	*K. officinalis* stem and leaf	109
385 Kopsioffine B	*K. officinalis* stem and leaf	109
386 Kopsioffine C	*K. officinalis* stem and leaf	109
387 Pauciflorine A	*K. pauciflora* leaf	110
388 Pauciflorine B	*K. pauciflora* leaf	110
389 Pauciflorine C	*K. pauciflora* leaf	22
390 Paucifoline	*K. pauciflora* leaf	22
Skytanthines		
391 Kinabalurine A (kinabalurine)	*K. pauciflora* leaf	111 and 112
392 Kinabalurine B	*K. pauciflora* leaf	112
393 Kinabalurine C	*K. pauciflora* leaf	112
394 Kinabalurine D	*K. pauciflora* leaf	112
395 Kinabalurine E	*K. pauciflora* leaf	112
396 Kinabalurine F	*K. pauciflora* leaf	112
397 Kinabalurine G	*K. dasyrachis* leaf	30
398 Kopsilactone	*K. macrophylla* bark	27
399 Kopsirachine	*K. dasyrachis* leaf	30 and 113
400 Kopsone	*K. macrophylla* bark	27
Rhazinilams		
401 5,21-Dihydrorhazinilam	*K. arborea* stem bark, *K. singapurensis* stem bark and leaf	10, 23 and 48
402 Kopsiyunnanine C1	*K. arborea* aerial part, *K. officinalis* aerial part	96 and 114
403 Kopsiyunnanine C2	*K. arborea* aerial part, *K. officinalis* aerial part	96 and 114

Table 1 (*Contd.*)

No. Compounds	Species	References
404 Kopsiyunnanine C3	*K. arborea* aerial part, *K. officinalis* aerial part	96 and 114
405 Leuconolam	*K. griffithii* leaf and stem bark, *K. hainanensis* twigs, stems and leaves, *K. officinalis* leaf, *K. pauciflora* leaf, *K. singapurensis* stem bark	7, 9, 12, 15, 17, 22, 23, 25 and 32
406 *O*-Methylleuconolam	*K. arborea* stem bark, *K. hainanensis* twig, *K. officinalis* stem	10, 12 and 87
407 Rhazinal	*K. dasyrachis* stem	32
408 Rhazinicine	*K. arborea* stem bark, *K. dasyrachis* stem, *K. singapurensis* root	10, 18, 49 and 60
409 Rhazinilam	*K. arborea* aerial part and stem bark, *K. officinalis* leaves and twigs, *K. pauciflora* leaves and stem bark, *K. singapurensis* leaf, bark and stem bark, *K. teoi* stem, stem bark and leaf	16, 13, 22, 23, 25, 32–34, 36, 45, 47, 48 and 114
Lundurines		
410 Epilapidilectinol	*K. lapidilecta* stem and bark	81
411 Grandilodine A	*K. grandifolia* stem bark	72
412 Grandilodine B	*K. grandifolia* stem bark	72
413 Grandilodine C	*K. grandifolia* leaf	72
414 Isolapidilectine A	*K. grandifolia* leaf, *K. lapidilecta* stem and bark	72 and 81
415 Lapidilectam	*K. grandifolia* stem bark, *K. lapidilecta* stem and bark	72 and 81
416 Lapidilectine A	*K. grandifolia* stem bark, *K. lapidilecta* bark, stem and leaf	72 and 115
417 Lapidilectine B	*K. grandifolia* stem bark, *K. lapidilecta* bark, stem and leaf	72 and 115
418 Lapidilectinol	*K. lapidilecta* stem and bark	81
419 Lundurine A	*K. tenuis* leaf	71
420 Lundurine B	*K. tenuis* leaf	71
421 Lundurine C	*K. tenuis* leaf	71
422 Lundurine D	*K. tenuis* leaf	71
423 Tenuisine A	*K. tenuis* leaf	116 and 117
424 Tenuisine B	*K. tenuis* leaf	71, 116 and 117
425 Tenuisine C	*K. tenuis* leaf	71, 116 and 117
426 Tenuiphylline	*K. tenuis* leaf	71 and 117
Aspidospermas		
427 Buchtienine	*K. griffithii* leaf and stem bark	15 and 17
428 Corynantheol	*K. hainanensis* twig and leaf	9
429 19,20-Dihydroisositsirikine	*K. officinalis* stem	75
430 Dihydrocorynantheol	*K. hainanensis* twig and leaf	9
431 16(*R*)-19,20-*E*-Isositsirikine	*K. griffithii* leaf, *K. pauciflora* leaf	15, 17 and 22
Catharinensines		
432 Catharinensine	*K. pauciflora* leaf	22
433 Kopsirensine A	*K. pauciflora* leaf	22
434 Kopsirensine B	*K. pauciflora* leaf	22
435 Kopsirensine C	*K. pauciflora* leaf	22
436 Kopsiyunnanine B	*K. arborea* aerial part, *K. officinalis* aerial part	96 and 97
Leuconoxines		
437 Arboloscine	*K. arborea* stem bark	10 and 118
438 Arboloscine A	*K. pauciflora* leaf	22
439 Leuconodine D	*K. officinalis* stem	75
440 Leuconodine F (6-oxoleuconoxine)	*K. griffithii* leaf, *K. pauciflora* leaf	22 and 43
441 Leuconoxine	*K. arborea* stem bark, *K. griffithii* leaf and stem bark, *K. pauciflora* stem, stem bark and leaf, *K. singapurensis* stem bark, *K. teoi* stem bark	15, 17, 19, 22, 23 and 43
442 Melodinine E	*K. arborea* twig	21
Pericines		
443 Pericidine	*K. arborea* stem bark	10 and 118
444 Pericine	*K. arborea* stem bark	10
445 Pericine *N*-oxide	*K. arborea* stem bark	10
446 Valparicine	*K. arborea* stem bark	119 and 120
Alstonines		
447 Oxayohimban-16-carboxy acid	*K. officinalis* stem	75
448 (−)-Tetrahydroalstonine	*K. arborea* stem bark, *K. dasyrachis* stem, *K. griffithii* leaf, *K. officinalis* root, twigs and leaves, *K. larutensis* stem bark and leaf, *K.*	10, 15, 17–19, 23, 25, 32, 42, 43, 66 and 69

Table 1 (*Contd.*)

No. Compounds	Species	References
	pauciflora stem, stem bark and leaf, *K. singapurensis* stem bark; *K. teoi* stem bark	
449 Tetrahydroalstonine pseudoindoxyl	*K. pauciflora* leaf	22
Quebrachamines		
450 Kopsiyunnanine D	*K. arborea* aerial part	114
451 Kopsiyunnanine H	*K. arborea* aerial part	90
452 (−)-Quebrachamine	*K. arborea* aerial part, *K. hainanensis* twig and leaf, *K. officinalis* root, *K. pauciflora* leaf	9, 22, 69 and 114
Arbophyllinines		
453 Arbophyllinine A	*K. arborea* bark	59
454 Arbophyllinine B	*K. arborea* bark	59
Arboflorines		
455 Arboflorine	*K. arborea* stem bark	10
456 Kopsiyunnanine E	*K. arborea* aerial part, *K. officinalis* aerial part	96, 99 and 121
Andrasinines		
457 Andransinine	*K. pauciflora* leaf	22
458 Andransinine A	*K. pauciflora* leaf	22
Corynantheines		
459 Arboricine	*K. arborea* leaf and stem bark	10 and 120
460 Arboricinine	*K. arborea* leaf and stem bark	10 and 120
Carbolines		
461 Harmane	*K. griffithii* leaf and stem	15 and 17
462 Harmicine	*K. griffithii* leaf	15 and 17
Arbophyllidine		
463 Arbophyllidine	*K. arborea* stem bark	59
Mersicarpine		
464 Mersicarpine	*K. arborea* stem bark, *K. pauciflora* leaf, *K. singapurensis* stem bark	10, 22 and 23
Azepane-fused tetrahydro-β-carboline		
465 Kopsiyunnanine K	*K. arborea* aerial part	102
Andranginine		
466 Andranginine	*K. arborea* aerial part	102
Triterpenoids and sterols		
467 β-Amyrin	*K. singapurensis* leaf and bark	122
468 β-Amyrin acetate	*K. singapurensis* leaf and bark	122
469 β-Amyrone	*K. singapurensis* leaf and bark	122
470 Lupeol	*K. singapurensis* leaf and bark	122
471 Lupeol acetate	*K. singapurensis* leaf and bark	122
472 Stigmasterol	*K. singapurensis* leaf and bark	122

kopsamidines A–B (**37–38**) were separated from the acidic EtOH extract of *K. arborea* stem bark.[10,40]

To search for bioactive metabolites from *Kopsia* plants, Long *et al.* (2018) isolated five new aspidofractinines kopsiafrutines A–E (**43–47**) from the 80% EtOH extract of *K. fruticosa* aerial part.[52] Eleven new analogs, kopsiahainanins A–F (**48–53**) and kopsiahainins A–E (**54–58**) were among the new compounds found in the 80% EtOH extract of *K. hainanensis* twigs and leaves.[53,54] In another approach, chromatographic separation of the 95% EtOH extract of *K. officinalis* aerial part can lead to the isolation of three new metabolites (**59–61**), which named kopsiaofficines A–C.[55] From *K. arborea* aerial part, the new compound kopsiarborines A (**62**) was isolated.[56] Three new metabolites, kopsidasine (**64**), kopsidasine-*N*-oxide (**65**), and kopsidasinine (**66**) were separated from *K. dasyrachis* leaves and structurally confirmed by the NMR analysis and Hofmann reaction.[57] Thirteen previously undescribed metabolites kopsidines A–D (**67–69** and **71**), kopsinitarines B–D (**132–134**), mersingines A–B (**150–151**), 11-methoxykopsingine (**160**), 11-methoxy-12-hydroxy-kopsinol (**163**), 11,12-

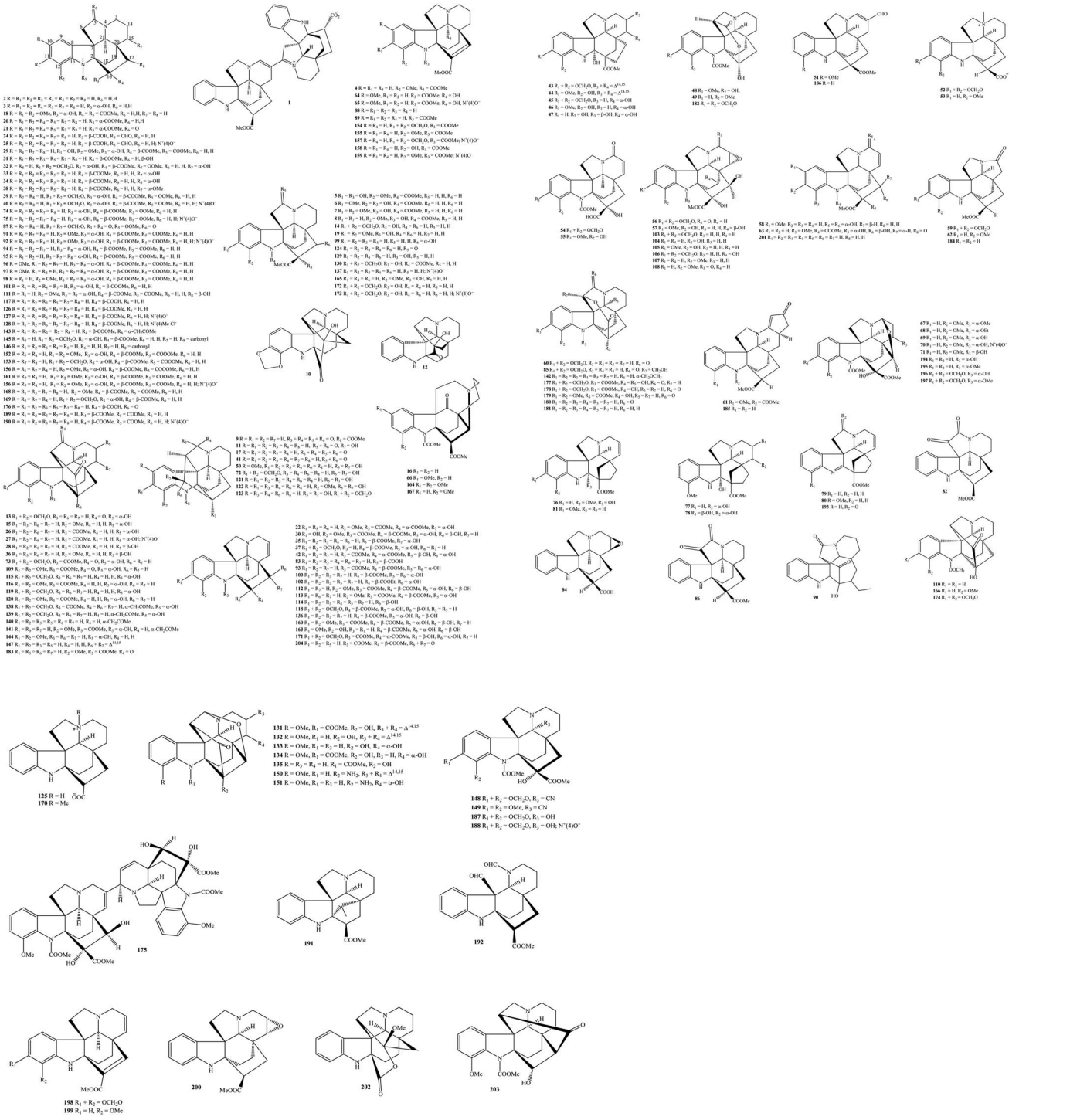

Fig. 1 Aspidofractinines from genus *Kopsia*.

methylenedioxykopsaporine (**171**), and nitaphylline (**175**) have further been observed in *K. teoi* leaf, while its stem bark also contained seven other new compounds kopsinganol (**111**), kopsinginine (**113**), kopsinginol (**114**), kopsinol (**136**), kopsinitarine E (**135**), kopsinol (**136**), and kopsonoline (**146**).[33,34,43–45,73,74,80] Kopsidarine (**63**), kopsidine C *N*-oxide (**70**), and singaporentine A (**193**) were three new compounds existed in *K. singapurensis* leaf, whereas its bark encompassed four new others singapurensines A–D (**194–197**)[36,48,58,79] In two years 2007 and 2008, primarily based on CC approach, Subramaniam *et al.* successfully isolated nineteen new aspidofractinines, including kopsilongine-*N*-oxide (**92**), kopsiloscines A–J (**93–102**), kopsinalines A–F (**103–108**), kopsinicine (**118**), and kopsofinone (**145**) from *K. singapurensis* leaf or stem bark (Table 1 and Fig. 1).[23,32,48] Kopsiflorine (**74**) is now available in the genus *Kopsia*, but its *N*(4)-oxide (**75**) and kopsinarine (**109**) were new in

nature and were found in *K. dasyrachis* stem.[18] Six indole alkaloidal constituents kopsifolines A–F (**76–81**) with unprecedented hexacyclic carbon skeleton were detected in the acidic EtOH extract of *K. fruticosa* leaves.[62,63] Kopsifoline G (**82**) and kopsihainins B–F (**83–87**) were purified as new alkaloids from the stem or twig extracts of *K. hainanensis*.[12,64,65] Among the isolated compounds, kopsijasminine (**88**) and kopsilarutensinine (**90**) were also identified to be two new aspidofractinines derived from the stem bark of *K. teoi* and *K. larutensis*, respectively.[43,66] The earliest report by Guggisberg *et al.* (1963) identified that kopsine (**110**) was a new and major component of *K. fruticosa* leaves, and it was then isolated frequently.[18,20,38,39,41,67] In a phytochemical research on the acidic EtOH extract of *K. arborea* stem bark, five new aspidofractinines, kopsinidines A–B (**115–116**), kopsinidines A–B (**119–120**), and paucidactine C (**179**) were isolated.[10]

Phytochemical analysis aided by NMR structural elucidation on the $CHCl_3$ and *n*-BuOH extracts of *K. officinalis* leaf and twig has resulted in the isolation of eight new compounds kopsinidines C–E (**121–123**), *N*(1)-methoxycarbonyl-11,12-methoxylenedioxykopsinaline (**153**), *N*(1)-methoxycarbonyl-12-methoxykopsinaline (**156**), *N*(4)-methylkopsininate (**170**), (−)-11,12-methylenedioxykopsinaline (**172**), and 5-oxokopsinic acid (**176**), in addition to seven known compounds kopsinilam (**124**), kopsinine (**126**), kopsinine methochloride (**128**), kopsinine B (**129**), (−)-kopsinoline (**137**), (−)-12-methoxykopsinaline (**165**), and 11,12-methylenedioxykopsinaline *N*(4)-oxide (**173**).[16] Among the isolates from *K. hainanensis* stem and leaves, the new compound kopisininate (**125**) itself displayed an interesting feature since it contained a carboxylate group (δ_C 181.6 ppm in CD_3OD).[7] Besides known compounds, the application of NMR and MS tools would take a good advance in the natural product chemistry field, by which the chemical structures of seven new aspidofractinines kopsiofficines A–F and L (**138–144**) from *K. officinalis* stem and three new analogs yunnanoffines A–C (**202–204**) from *K. officinalis* leaf have been determined.[11,25,75] Aspidofractinines were further observed in other *Kopsia* plants. For instance, apart from known compounds, five new derivatives *N*(1)-methoxycarbonyl-11,12-methylenedioxy-$\Delta^{16,17}$-kopsinine (**154**), *N*(1)-methoxycarbonyl-12-methoxy-$\Delta^{16,17}$-kopsinine (**155**), *N*(1)-methoxycarbonyl-11,12-methylenedioxy-$\Delta^{16,17}$-kopsinine *N*(4) oxide (**157**), *N*(1)-methoxycarbonyl-12-hydroxy-$\Delta^{16,17}$-kopsinine (**158**), and *N*(1)-methoxycarbonyl-12-methoxy-$\Delta^{16,17}$-kopsinine *N*(4) oxide (**159**) were characteristics of *K. profunda*,[4,77] or lahadinines A–B (**145–146**), 12-methoxy-10-demethoxykopsidasinine (**167**), paucidactines D–E (**180–181**), paucidactinine (**182**), paucidisine (**183**), paucidirinine (**184**), paucidirisine (**185**), pauciduridine (**186**), paucifinine (**187**), and paucifinine-*N*-oxide (**188**) were new metabolites isolated from the parts of *K. pauciflora*.[19,51,76]

2.2. Chanofruticosinates, aspidospermines, and danuphyllines

In general, *Kopsia* chanofruticosinate derivatives **205–241** have established a similarity in the chemical structural skeleton with aspidofractinines (Table 1 and Fig. 2). However, fragment C-2–C-16–C-17–C-20 in aspidofractinines was replaced by a carbon bridge between C-6 and C-20 in chanofruticosinates. To date, these phytochemicals occurred in *K. arborea*, *K. dasyrachis*, *K. fruticosa*, *K. flavida*, *K. hainanensis*, *K. lancibracteolata*, *K. officinalis*, and *K. pauciflora*.[3,6,7,10,13,16,22,25,30,41,42,65,75,82–89] From Table 1, kopsia A (**217**), kopsia C (**219**), methyl 11,12-dimethoxychanofruticosinate (**224**), methyl N_1-decarbomethoxychanofruticosinate (**225**), methyl 12-methoxychanofruticosinate (**228**), methyl 11,12-methylenedioxy-N_1-decarbomethoxychanofruticosinate (**229**), and methyl 11,12-methylenedioxy-N_1-decarbomethoxy-$\Delta^{14,15}$-chanofruticosinate (**230**) were major components in the group of *Kopsia* chanofruticosinates. Analyzing chemical composition further, the rich alkaloid fraction of *K. officinalis* leaf and twig have also contained five new derivatives, chanofruticosinic acid (**205**), kopsias A–C (**217–219**), 12-methoxychanofruticosinic acid (**222**), and methyl (2β,11β,12β,19α)-6,7-didehydro-8,21-dioxo-11,21-cycloaspidospermidine-2-carboxylate (**231**).[13,16,86] According to the phytochemical report of Chen and partners, N_1-decarbomethoxy chanofruticosinic acid (**206**), kopsihainanines A–B (**220–221**), methyl chanofruticosinate *N*(4)-oxide (**223**), and methyl N_1-decarbomethoxy chanofruticosinate *N*(4)-oxide (**226**) were previously unrecorded compounds and found in *K. hainanensis* stem and leaf for the first time.[6,7] The application of HPLC chromatographic procedure to the 70% EtOH extract of *K. fruticosa* aerial part has resulted in the isolation of two new substances, 11,12-dimethoxydanuphylline (**207**) and 3-oxo-11,12-dimethoxy-N^1-decarbomethoxy-14,15-didehydrochanofruticosinate (**236**).[3] The MeOH extract of *K. flavida* leaf consisted of serial new alkaloids type chanofruticosinates flavisiamines A–F (**208–213**).[41,83] Besides known compounds, the chromatographic isolation of the alcoholic extracts of *K. arborea* leaves has allowed to identify the appearance of seven new methyl chanofruticosinate alkaloids, kopreasin A (**216**), and prunifolines A–F (**208**, **211**, and **238–241**).[82,84] Finally, three new derivatives 12-hydroxylprunifoline A (**214**), 12-hydroxylprunifoline A (**215**), and *N*(4)-oxide prunifoline D (**3**) were purified from the 70% EtOH extract of *K. lancibracteolata* stem.[85]

Regarding aspidospermines, the acidic EtOH extract of *K. pauciflora* leaf contained aspidospermine (**242**), and its (+)-1,2-dehydro derivatives (**243**).[22] A phytochemical report conducted by Wu *et al.* (2010) revealed that the MeOH extract of *K. arborea* aerial part was characterized by the presence of the new aspidospermine kopsiyunnanine G (**246**), and known compound eburenine (**244**).[90] Similarly, new compound kopsiofficine G (**245**), together with two known ones, vincadifformine (**247**) and vincadifformine *N*(4)-oxide (**248**) represented for *K. officinalis* stem.[11]

Only four indole alkaloids danuphyllines **249–252** were found in *Kopsia* plants, in which danuphylline (**249**), danuphylline B (**250**), 11,12-de(methylenedioxy)danuphylline (**251**), and kopsihainin A (**252**) were separated from *K. dasyrachis* leaf, *K. arborea* leaf, *K. officinalis* leaf, and *K. hainanensis* stem, respectively (Table 1 and Fig. 2).[13,30,65,78,91] All these isolates were new in nature. Similar to aspidofractinine derivatives, chanofruticosinates, aspidospermines, and danuphyllines were

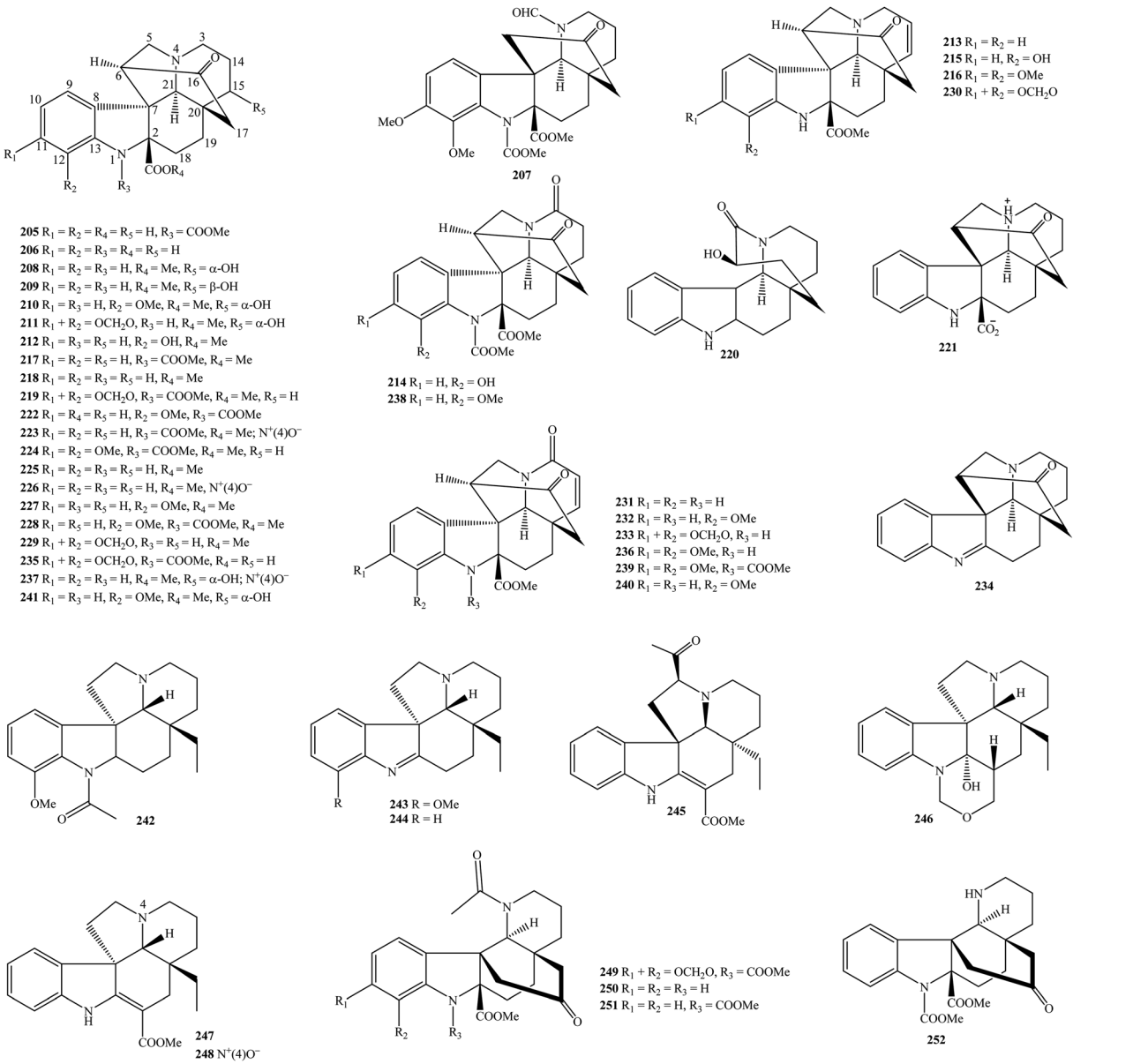

Fig. 2 Chanofruticosinates, aspidospermines and danuphyllines from genus *Kopsia*.

unique chemical classes found in the family Apocynaceae. Especially, danuphylline derivatives were only detected in *Kopsia*, thereby they can be used as chemical markers to recognize this genus.

2.3. Eburnamines

As can be seen from Table 1 and Fig. 3, eburnamines are also a crucial phytochemical class of the genus *Kopsia*. Forty-nine compounds **253–301** were isolated to date, and they were mainly derived from *K. arborea*, *K. dasyrachis*, *K. griffithii*, *K. hainanensis*, *K. hainanensis*, *K. jasminiflora*, *K. larutensis*, *K. macrophylla*, *K. officinalis*, *K. pauciflora*, *K. singapurensis*, *K. teoi*, and *K. terengganensis*.[5,9,13–15,17–19,21–25,27–29,33,42,50,51,66,68–70,75,90,92,93] *Kopsia* eburnamines appeared in both monomer and dimer forms, but not to have connected with sugar units. (−)-Eburnamenine (**255**), (−)-eburnamine (**257**), (+)-eburnamonine (**259**), (+)-isoeburnamine (**274**), and larutenine (**284**) were isolated frequently, *e.g.*, compound **274** was detected in *K. arborea* aerial part, *K. dasyrachis* stem, *K. hainanensis* stem bark, *K. larutensis* leaf, stem and stem bark, *K. teoi* stem bark and leaf, *K. officinalis* leaf, *K. pauciflora* stem and stem bark, and *K. terengganensis* bark.[5,13,18,19,22,29,33,51,68,70,90,92,93]

(−)-Demethylnorpleiomutine (**253**), (−)-eburnaminol (**258**), (−)-*O*-ethyleburnamine (**262**), 19-hydroxy-(−)-eburnamonine (**267**), (−)-19(*R*)-hydroxyisoeburnamine (**268**), (+)-(19*R*)-19-hydroxyeburnamine (**269**), (−)-(19*R*)-19-hydroxyisoeburnamine (**271**), (+)-kopsoffine (**277**), kopsoffinol (**282**), (−)-norpleiomutine (**289**), (−)-*O*-methylisoeburnamine (**291**), and 19-oxo-(−)-eburnamonine (**293**) were found in two or three *Kopsia* plants (Table 1). (+)-Eburnamenine (**254**), (+)-eburnamine (**256**),

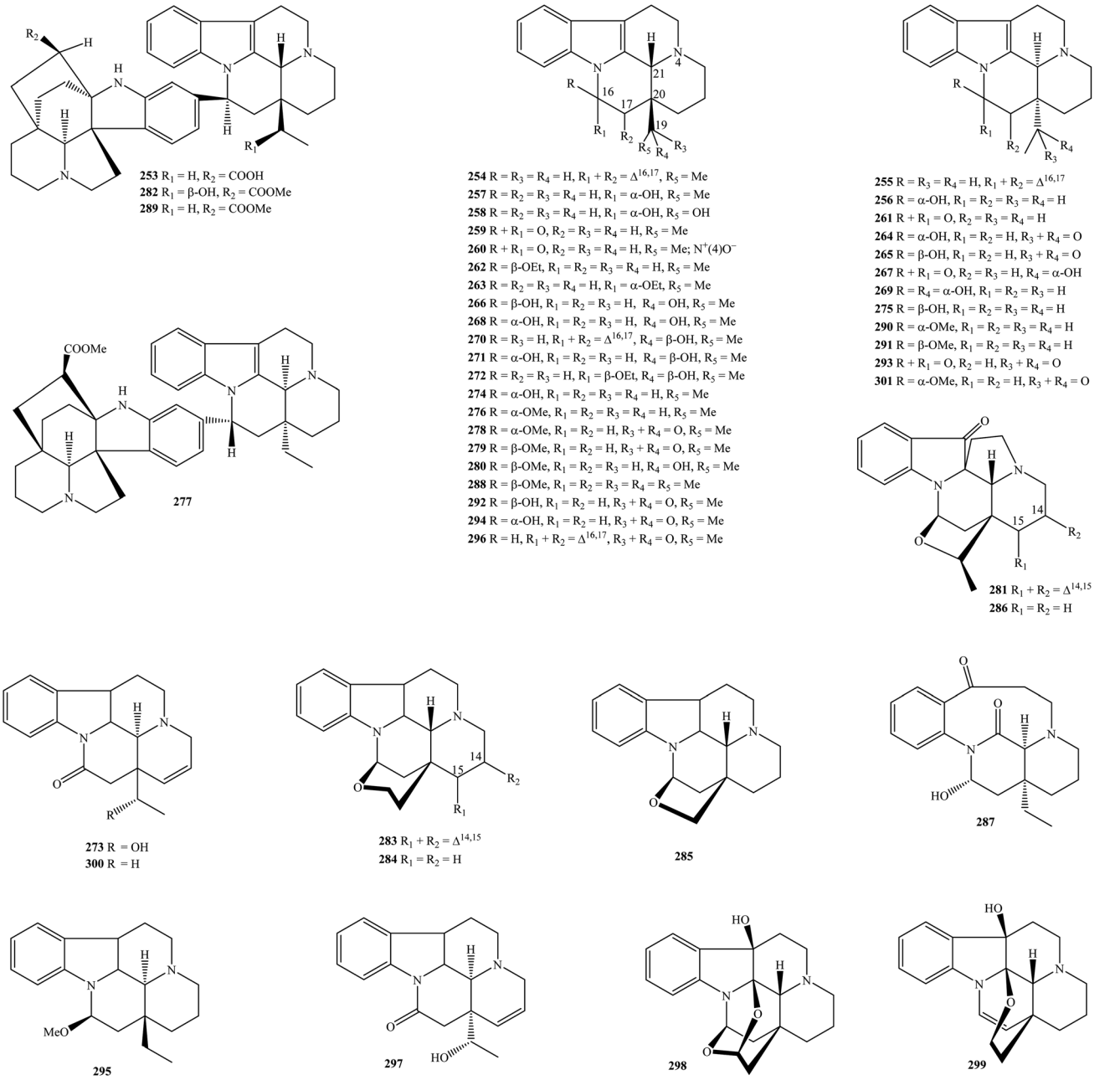

Fig. 3 Eburnamines from genus *Kopsia*.

(−)-eburnamonine (**261**), (+)-ethylisoeburnamine (**263**), 16α-hydroxy-19-oxoeburnamine (**264**), 16β-hydroxy-19-oxoeburnamine (**265**), melohenine B (**287**), (−)-methyleburnamine (**288**), (+)-*O*-methyleburnamine (**290**), and *O*-methyl-16-*epi*-vincanol (**295**), and Δ^{14}-vicamone (**300**) have never been observed in genus *Kopsia* before. Especially, (−)-eburnaminol (**258**), (+)-eburnamonine *N*(4)-oxide (**260**), (+)-19(*R*)-hydroxyeburnamine (**266**), (−)-19(*R*)-hydroxyisoeburnamine (**268**), (−)-19(*R*)-hydroxyeburnamenine (**270**), (−)-(19*R*)-19-hydroxyisoeburnamine (**271**), (−)-19(*R*)-hydroxy-*O*-ethylisoeburnamine (**272**), (−)-isoeburnamine (**275**), kopsiofficines H–K (**278–281**), (+)-larutensine (**283**), larutenine (**284**), larutenines A–B (**285–286**), (−)-norpleiomutine (**289**), (+)-19-oxoeburnamine (**292**), (−)-19-oxoisoeburnamine (**294**), 20-oxo-eburnamenine (**296**), phutdonginin (**297**), terengganensines A–B (**298–299**), and yunnanoffine C (**301**) were new in literature and isolated from genus *Kopsia* for the first time. Eburnamines is now abundant in genus *Kopsia*, but this chemical class was only found in the family Apocynaceae.

2.4. Akuammilines, sarpagines, and aspidophyllines

A total of twenty-one akuammilines **302–322** have been outlined in Table 1 and Fig. 4. *K. arborea*, *K. dasyrachis*, *K. deverrei*, *K. fruticosa*, *K. griffithii*, *K. hainanensis*, *K. macrophylla*, *K.*

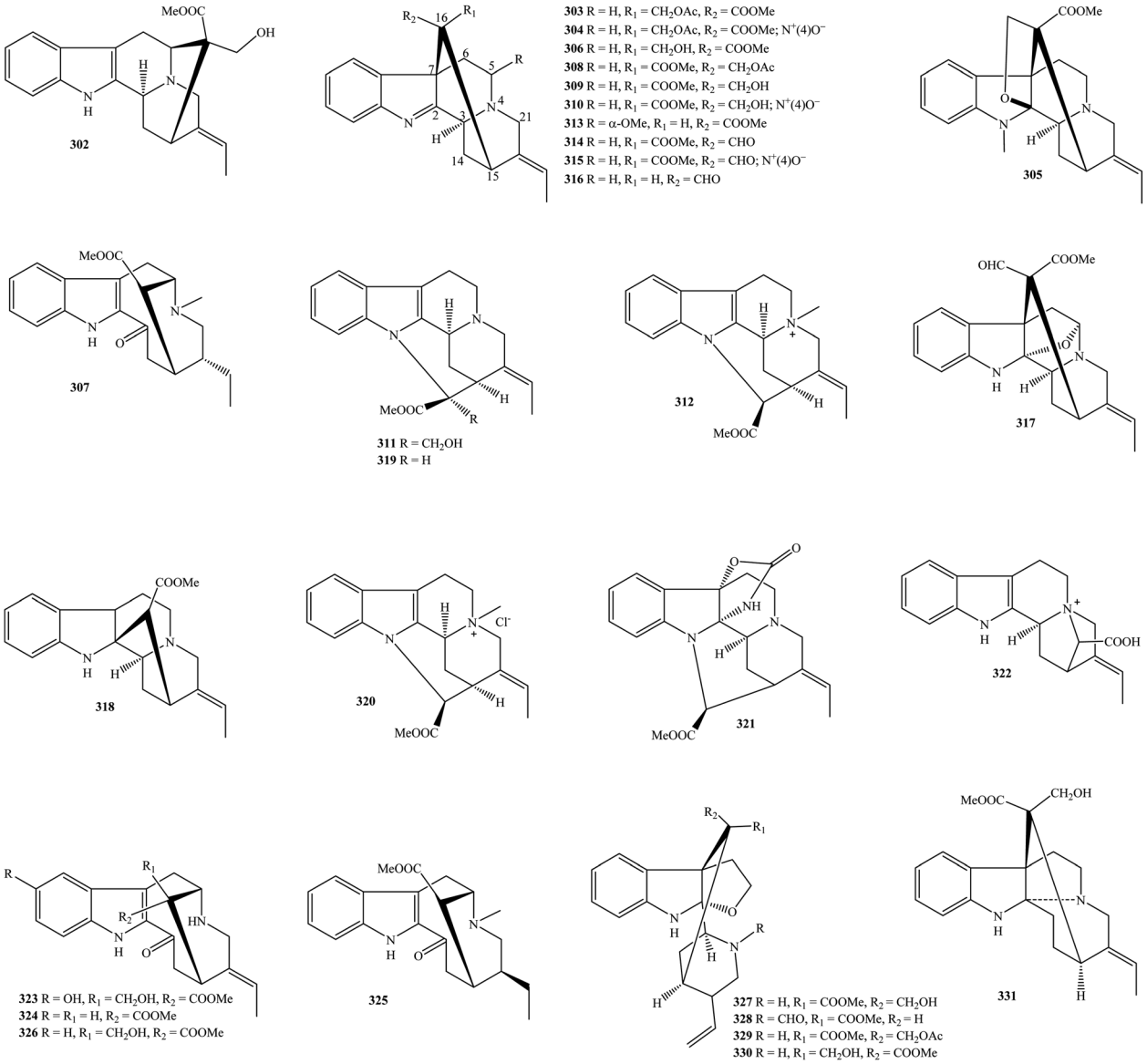

Fig. 4 Akuammilines, sarpagines and aspidophyllines from genus *Kopsia*.

officinalis, *K. singapurensis*, and *K. teoi* were main resource of these phyto-constituents.[9,10,15–17,23,27,31,32,34–36,43,45,47–49,94] Previous studies revealed that deacetylakuammiline (**306**), 16-*epi*-deacetylakuammiline (**309**), 16-hydroxymethyl-pleiocarpamine (**311**), and pleiocarpamine (**319**) were likely to be major akuammilines in genus *Kopsia*.

The first compound akuammidine (**302**) was originated from *K. arborea* stem bark, *K. singapurensis* root, stem bark, and leaves, while akuammiline (**303**) presented in the aerial part of *K. macrophylla* and *K. teoi*.[10,23,27,32,34,43,45,47–49] Akuammiline *N*(4)-oxide (**304**) and 16-*epi*-deacetylakuammiline-*N*(4)-oxide (**310**) were reported to be two new derivatives, which were separated from the rich alkaloidal fraction of *K. griffithii* stem bark.[15] ψ-Akuammigine (**305**), dregamine (**307**), *N*-methylpleiocarpamine (**312**), 5-methoxystrictamine (**313**), rhazimal (**314**), rhazinaline *N*(4)-oxide (**315**), picralinal (**317**), pleiocarpamine methochloride (**320**), and pleiomalicine (**321**) were isolated from genus *Kopsia* for the first time.[9,10,15,16,27,31,36] Lastly, two new metabolites, rhazinoline (**316**) and singaporentinidine (**322**), were purified from the extracts of *K. arborea* stem bark, *K. singapurensis* root, respectively.[10,35]

A list of four alkaloidal sarpagines **323–326** has been updated in Table 1 and Fig. 4.[9,27,50] Vincadiffine (**326**) was a well-known metabolite, but its 10-hydroxy derivative (**323**) was a new compound in the literature, and both of them were isolated from the MeOH extract of *K. hainanensis*.[9] Perivine (**324**) and tabernaemontanine (**325**) were two known sarpagines derived from *K. officinalis* root and stem and *K. macrophylla* bark, respectively.[27,50]

Resemble sarpagines, aspidophylline derivatives are not available in genus *Kopsia*. A total of five isolates **327–331** were summarized in Table 1 and Fig. 4.[23,31–34,36,43,48,49]

Aspidodasycarpine (**327**) was recorded by various authors and was detected in *K. singapurensis* root and stem bark, *K. teoi* stem, and stem bark.[23,32,34,36,43,48,49] Two new phyto constituents aspidophyllines A–B (**328–329**), were determined to exist in *K. singapurensis* stem bark, while the new analog vincophylline (**331**) was found in its leaves.[32,48] It can be concluded that lonicerine (**330**) was a major component in the group of aspidophyllines because it has occurred in various *Kopsia* plants such as *K. fruticosa* stem bark, *K. singapurensis* bark and stem bark, and *K. teoi* stem, stem bark and leaf.[23,31–34,36,43,48]

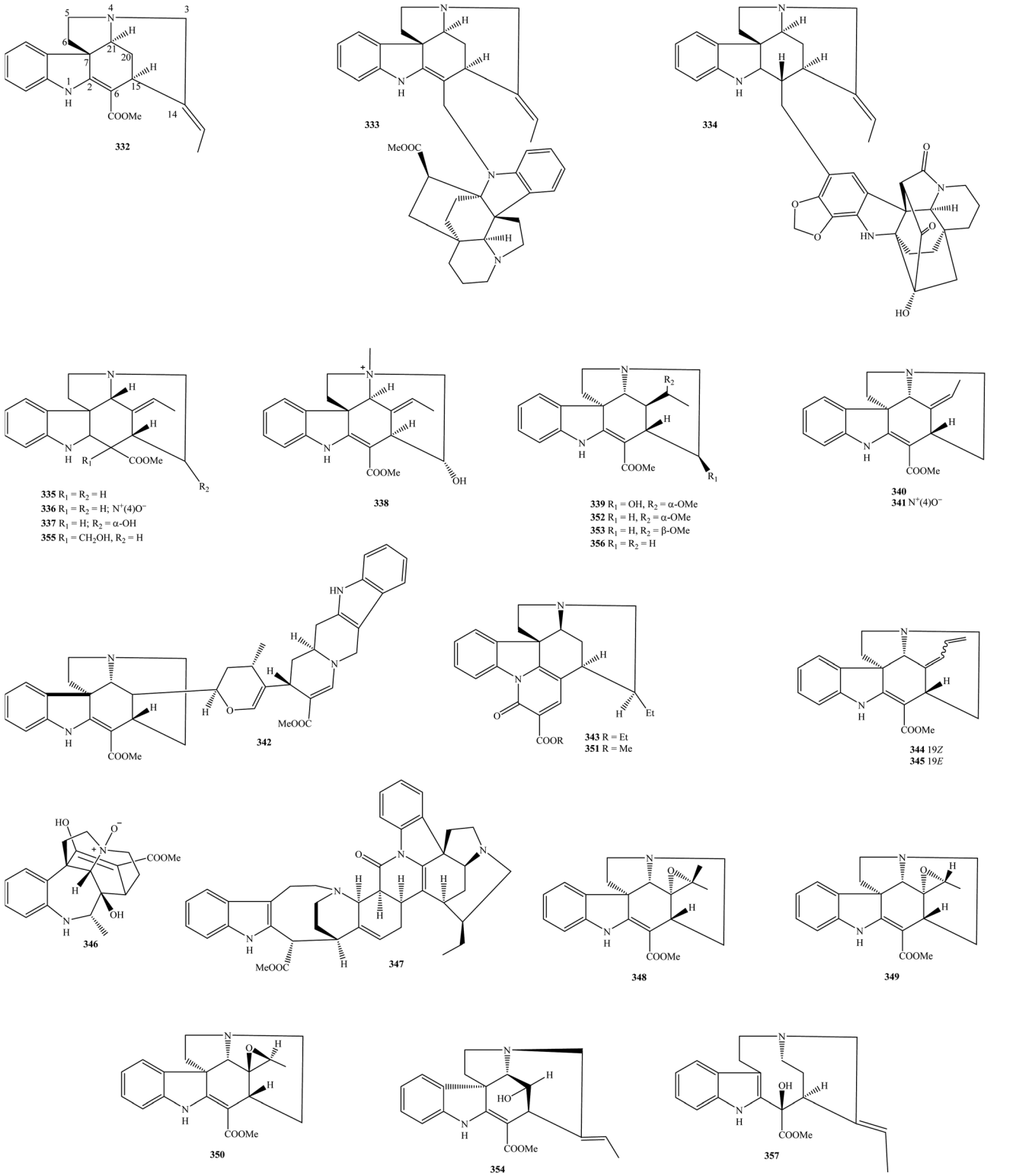

Fig. 5 Strychnoses and stemmadenine from genus *Kopsia*.

2.5. Strychnoses

Compounds **332–357** have been fallen into the group of alkaloidal strychnos derivatives (Table 1 and Fig. 5). Similar to aspidofractinines and eburnamines, *Kopsia* strychnoses were presented in both mono-or dimer forms, and they were mainly sourced from *K. deverri*, *K. hainanensis*, *K. jasminiflora*, *K. officinalis*, *K. pauciflora*, *K. singapurensis*, especially *K. arborea*.[8,10,12,22–24,29,35,36,64,94–102] Significantly, except for akuammicine (**332**), (*E*)-condylocarpine (**335**), (*E*)-condylocarpine *N*-oxide (**336**), leuconicine B (**351**), precondylocarpine (**355**), and tubotaiwine (**356**), the remaining compounds were new in nature.

By the analysis of NMR, MS, and CD data, two isolated dimeric compounds, arbolodinines B–C (**333–334**), were elucidated as bulk novel strychnoses, which were derived from *K. arborea* stem bark.[8] Compound **335** is a known compound,[22,95] but its 14α-hydroxy and 14(*S*)-hydroxy-19(*R*)-methoxy derivatives **337–338** were new in the literature and first were isolated from *K. deverri* stem bark and *K. singapurensis* root, respectively.[35,94] Mossambine (**354**) was another new *strychnos* found in *K. singapurensis* stem bark.[23] *K. arborea* aerial part has so far distributed thirteen new compounds, isocondylocarpine (**340**), isocondylocarpine *N*-oxide (**341**), kopsiyunnanines A, I, J1–J2, L, M, and F1–F3 (**342–350**), 19(*R*)-methoxytubotaiwine (**352**), and 19(*S*)-methoxytubotaiwine (**353**).[10,95–98,100,101] The well-known compound tubotaiwine (**356**) was characteristic of *K. arborea* aerial part, *K. hainanensis* stem and stem bark, but its 14(*S*)-hydroxy-19(*R*)-methoxy derivative **339** isolated from the MeOH extract of *K. jasminiflora* stem bark has been determined as a new metabolite.[24,29,64,95] Stemmadenine (**357**) from *K. pauciflora* leaves was the only stemmadenine detected in the genus *Kopsia*.[22]

2.6. Mersinines and pauciflorines

Mersinines with tetracyclic quinolinic skeleton are a new subclass of monoterpenoid indole alkaloids, which were only found in the plants genus *Kopsia*. *Kopsia* mersinines **358–378** were only detected in *K. singapurensis* leaves and occasionally in *K. fruticosa* leaves (Table 1 and Fig. 6).[23,103–108] Of particular interest, all these isolates were novel compounds in literature. Searching for cytotoxic agents from plants, sixteen novel mersinines, comprising of mersidasines A–G (**358–364**), mersifolines A–C (**365–367**), mersiloscine (**369**), mersiloscines A–B (**370–371**), and mersinines A–C (**373–375**) were isolated from the acidic EtOH extract of *K. singapurensis* leaf.[103] Their stereochemistry was confirmed by NMR, IR, UV, and X-ray analysis. *K. singapurensis* leaf has further been shown to contain five novel congeners, mersilongine (**368**), mersinaline (**372**), mersiphyllines A–B (**376–377**), and mersirachine (**378**).[23,106,108]

It is similar to mersinines, *Kopsia* pauciflorines **379–390** have induced interest since all isolates were novel in the literature, except for 11,12-demethoxy-16-deoxypauciflorine (**379**). *K. arborea*, *K. jasminiflora*, *K. officinalis*, and *K. pauciflora* might be a reservoir of this chemical class.[22,40,56,109,110]

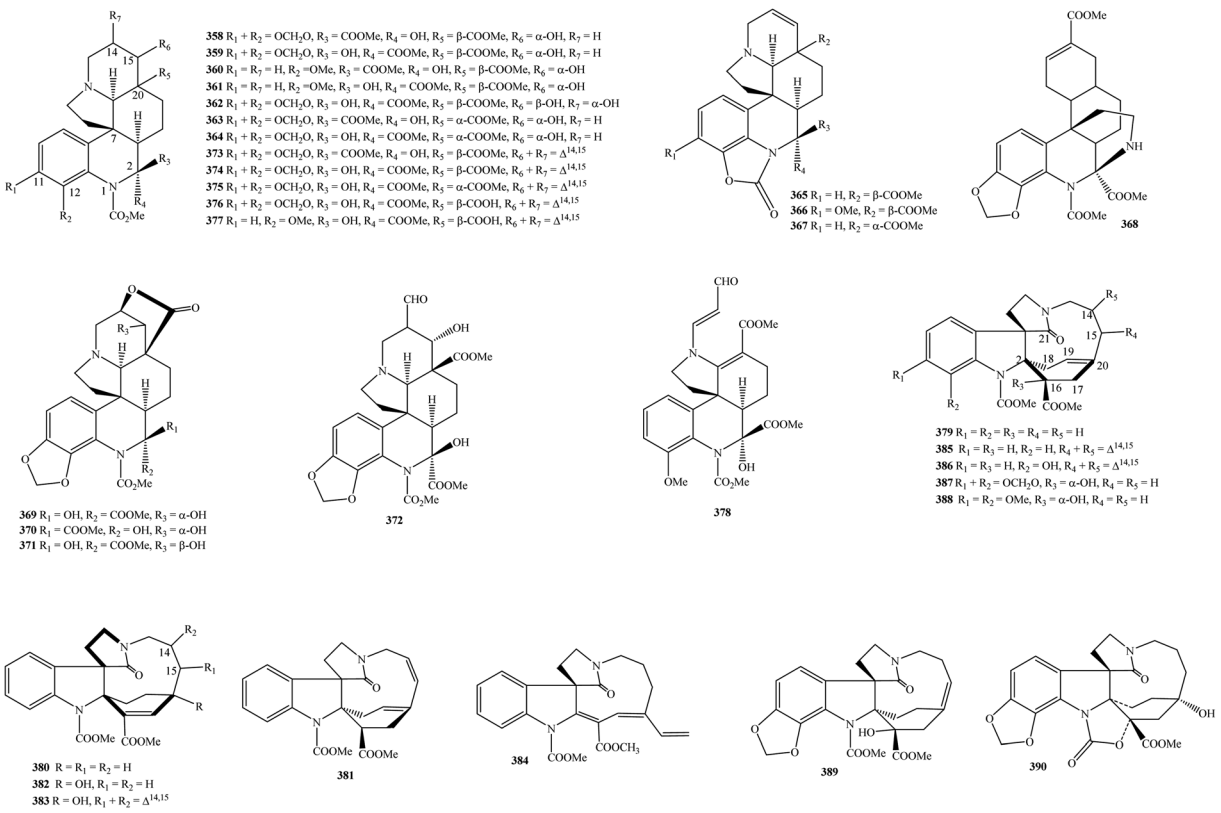

Fig. 6 Mersinines and pauciflorines from genus *Kopsia*.

Besides aspidofractinines, the MeOH extract of *K. jasminiflora* leaf has associated with the presence of three novel pauciflorines 20-deoxykopsijasminilam (**380**), kopsijasminilam (**382**), and Δ^{14}-kopsijasminilam (**383**).[40] In addition to known compound **379**, three novel derivatives, kopsioffines A–C (**384–386**) were arisen from the 95% EtOH extract of *K. officinalis* dried stem and leaves.[109] Pauciflorines A–B (**387–388**) reached 0.22 and 0.03 g kg^{-1} in *K. pauciflora* leaf.[110] In the meantime, two other novel compounds, pauciflorine C (**389**) and paucifoline (**390**), were minor components in the acidic EtOH extract of *K. pauciflora* leaves.[22] It is possible to conclude that mersinines and pauciflorines could be used as chemical indicators to distinguish the genus *Kopsia* and other genera of the family Apocynaceae.

2.7. Skytanthines, rhazinilams, and lundurines

It is recognized that the unique chemical class of skytanthines can be arranged as a new group of alkaloids. These phytochemicals were isolated from Apocynaceae *Skytanthus acutus* for the first time in 1960.[123] From Table 1 and Fig. 7, ten new skytanthines **391–400** have been summarized. The extracts of *K. dasyrachis* and *K. macrophylla*, especially *K. pauciflora*, are accompanied by the presence of this type.[27,30,112,113] Two publications in 1996 and 1997 by Kam and partners successfully reported the structures of serial new skytanthines kinabalurines

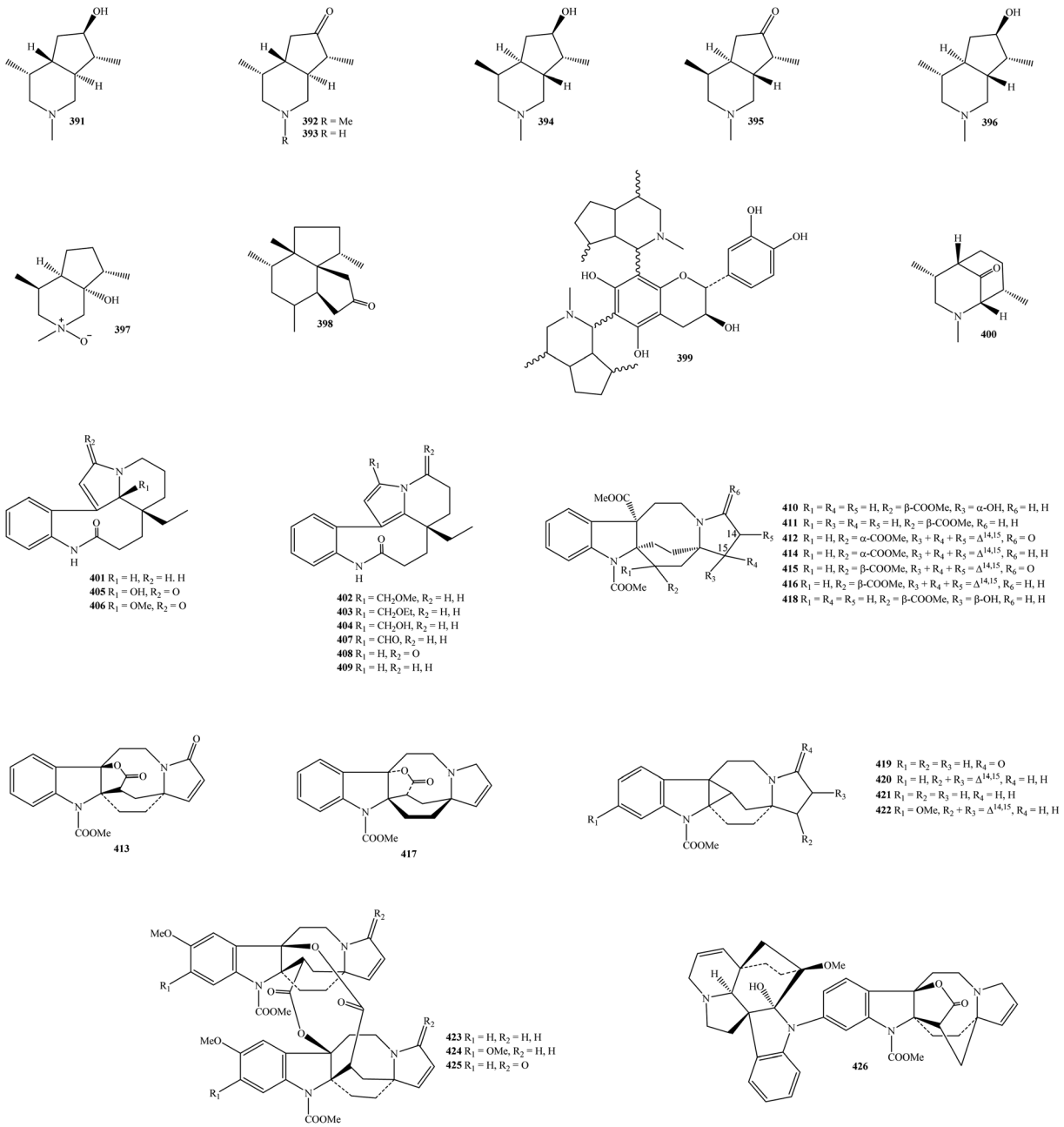

Fig. 7 Skytanthines, rhazinilams and lundurines from genus *Kopsia*.

A–F (**391–396**) from *K. pauciflora* leaves.[111,112] while their following congener kinabalurine G (**397**) was derived from *K. dasyrachis* leaf.[30] Significantly, the novel alkaloidal kopsirachine (**399**) isolated from *K. dasyrachis* leaves was determined to be a hybrid compound by the combination of catechin and skytanthine.[113] After being run Sephadex LH-20 and silica gel CC, a new monoterpene alkaloids containing a lactone ring, kopsilactone (**398**), and other new monoterpene alkaloids possessing 2-azabicyclo[3.3.1] backbone, kopsone (**400**), were isolated from the MeOH extract of *K. macrophylla* bark.[27] Based on these findings, skytanthines can be seen as chemical evidence to determine the close relationship among Apocynaceae plants, especially between genera *Skytanthus* and *Kopsia*.

Rhazinilam (**409**) is an alkaloid discovered in the Apocynaceae plant *Melodinus australis* in 1965.[124] It was then isolated from the shrub of the other Apocynaceae plant *Rhazya stricta* as well as other organisms.[125] This compound was established as a main component in the group of *Kopsia* rhazinilams since it was found in *K. arborea* aerial parts and stem bark, *K. officinalis* leaf and twig, *K. pauciflora* leaf and stem bark, *K. singapurensis* leaf, bark and stem bark, and *K. teoi* stem, stem bark and leaf.[13,16,22,23,25,32–34,36,45,47,48,114] Leuconolam (**405**) can be also seen as another main component because of its occurrence in *K.*

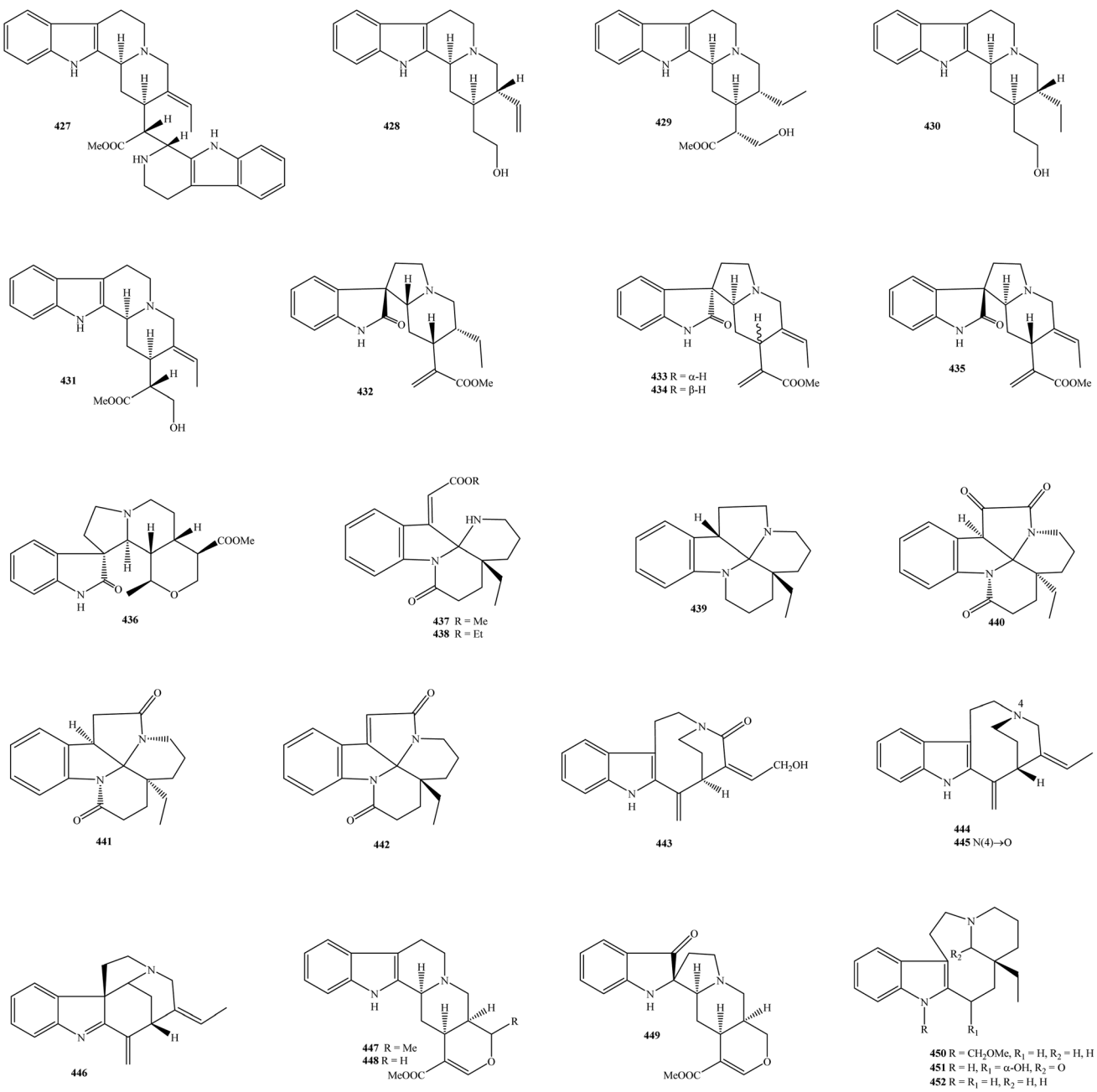

Fig. 8 Aspidospermas, catharinensines, leuconoxines, pericines, alstonines and quebrachamines from genus *Kopsia*.

griffithii leaves and stem bark, *K. hainanensis* twig, stem and leaf, *K. officinalis* leaf, *K. pauciflora* leaves, and *K. singapurensis* stem bark.[7,9,12,15,17,22,23,25,32] As shown in Table 1, known compound 5,21-dihydrorhazinilam (**401**) existed in *K. arborea* stem bark and *K. singapurensis* stem bark and leaves.[10,23,48] From Fig. 7, three new compounds, kopsiyunnanines C1–C3 (**402–404**), which were isolated from the aerial part of *K. arborea* and *K. officinalis*, established the same backbone with rhazinilam (**409**).[96,114] *O*-Methylleuconolam (**406**) and rhazinal (**407**) were two well-known compounds, but their congener rhazinicine (**408**) separated from *K. arborea* stem bark, *K. dasyrachis* stem, and *K. singapurensis* root was a new derivative.[10,12,18,32,49,60,87] To the best of our knowledge, rhazinilams were only observed in the family Apocynaceae, as well as the plants of three genus *Melodinus*, *Rhazya*, and *Kopsia* being the main resources.

Kopsia lundurines **410–426** have generally been formed by the combination of an indole ring and a lactam ring through an eight-ring member (Fig. 7). Notably, all of these seventeen compounds were novel in nature, and the three plants, *K. lapidilecta*, *K. grandifolia*, and *K. tenuis*, are the main reservoirs (Table 1).

Awang and partners also isolated and identified six novel pauciflorines, epilapidilectinol (**410**), isolapidilectine A (**414**), lapidilectam (**415**), lapidilectines A–B (**416–417**), and lapidilectinol (**418**) from aerial part of *K. lapidilecta*.[81,115] Three novel indole alkaloids, grandilodines A–C (**411–413**) were extracted from the EtOH extract of *K. grandifolia* stem bark or leaves with the yield ranging from 0.07 to 3.18%, and their chemical structures were proved by NMR, MS, and X-ray spectral data.[72] The eight remainders, including lundurines A–B (**419–422**), tenuisine A–C (**423–425**), and tenuiphylline (**426**), were novel lundurines presented in the *K. tenuis* leaf.[71,116,117] In which compounds **423–425** were unprecedented dimers, while compound **426** is unique due to the incorporation between aspidofractinine and lundurine units. As of a consequence, *Kopsia* lundurines, especially compounds **423–426**, could be seen as significant chemotaxonomic agents.

2.8. Aspidospermas, catharinensines, leuconoxines, pericines, alstonines, and quebrachamines

Alkaloid type aspidospermas were named following the name of the genus *Aspidospermas* (family Apocynaceae). With regard to genus *Kopsia*, five known isolates **427–431** were summarized in Table 1 and Fig. 8. It turns out that buchtienine (**427**) was presented in either the leaf or stem of *K. griffithii*.[15,17] The MeOH extract of *K. hainanensis* twig and leaf consisted of two aspidospermas, corynantheol (**428**) and dihydrocorynantheol (**430**).[9] Only *K. officinalis* stem was found to contain 19,20-dihydroisositsirikine (**429**), while its congener 16(*R*)-19,20-*E*-isositsirikine (**431**) has been observed in the leaf of both *K. griffithii* and *K. pauciflora*.[15,17,22] Therefore, alkaloidal aspidospermas are usefully chemotaxonomic agents to confirm the close relationship between the genus *Kopsia* and other genera in the family Apocynaceae.

Catharinensines, which belong to the group of oxindole alkaloids, can be found in several higher plants, such as *Peschiera catharinensis*.[126] In *Kopsia* plants, five catharinensines **432–436** were detected (Table 1 and Fig. 8). Phytochemical research conducted by Gan and partners revealed that the use of mobile phase $CHCl_3$–MeOH is appropriate to isolate alkaloidal catharinensines.[22] By this approach, three new compounds, kopsirensines A–C (**433–435**), together with known analog catharinensine (**432**), have been successfully purified from the acidic EtOH extract of *K. pauciflora* leaves.[22] New catharinensine kopsiyunnanine B (**436**) was first collected as a light yellow solid from the alcoholic extract of *K. officinalis* aerial part, and then was detected in the *K. arborea* aerial part.[96,97]

Phytochemical studies on *Kopsia* plants have also led to the isolation of alkaloid leuconoxines **437–442**, and their structures were compiled in Fig. 8. Leuconoxine (**441**) was described as a major component since it occurred in *K. arborea* stem bark, *K. griffithii* leaf and stem bark, *K. pauciflora* stem, stem bark and leaf, *K. singapurensis* stem bark, *K. teoi* stem bark.[15,17,19,22,23,43] Arboloscine (**437**) was one of the new compounds in *K. arborea* stem bark, while melodinine E (**442**) was a known metabolite extracted from its twigs.[10,21,118] New compound arboloscine A (**438**) isolated from *K. pauciflora* leaf has a similarity in structural feature with compound **437**, but the methyl group of **437** was replaced by the ethyl group in **438**.[22] In the genus *Kopsia*, leuconodine D (**439**) was only detected in *K. officinalis* stems, whereas leuconodine F (**440**) was characteristic of *K. griffithii* leaves and *K. pauciflora* leaves.[22,43,75]

To find bioactive molecules from medicinal plants, four alkaloids type pericines, including two new compounds pericidine (**443**) and pericine *N*-oxide (**445**) and two known analogs pericine (**444**) and valparicine (**446**) were isolated (Table 1 and Fig. 8). All of these isolates originated from *K. arborea* stem bark.[10,118,119]

To the best of our knowledge, only three compounds **447–449** were classified as alkaloid alstonines (Table 1 and Fig. 8). Oxayohimban-16-carboxy acid (**447**) derived from *K. officinalis* stem has never been isolated from the genus *Kopsia* before.[75] The major component (−)-tetrahydroalstonine (**448**) appeared in *K. arborea* stem bark, *K. dasyrachis* stem, *K. griffithii* leaf, *K. officinalis* root, twig and leaf, *K. larutensis* stem bark and leaf, *K. pauciflora* stem, stem bark and leaf, *K. singapurensis* stem bark; *K. teoi* stem bark.[10,15,17–19,22,23,25,32,42,43,66] Compound **449**, a pseudoindoxyl derivative of compound **448**, was identified to be a new constituent from the acidic EtOH extract of *K. pauciflora* leaves.[22]

In the same manner, there are only three quebrachamines from the genus *Kopsia* till now (Table 1 and Fig. 8). (−)-Quebrachamine (**452**) is now abundant in nature and can be found in *K. arborea* aerial parts, *K. hainanensis* twigs and leaves, *K. officinalis* roots, and *K. pauciflora* leaves.[9,22,69,114] However, kopsiyunnanines D and H (**450–451**) from *K. arborea* aerial part were confirmed to be two new analogs.[90,114]

2.9. Others indole alkaloids and non-alkaloids

Phytochemical studies on *Kopsia* plants also recorded the appearance of other alkaloidal types (Table 1 and Fig. 9). Chromatographic procedure on the acidic MeOH extract of *K. arborea*

bark has resulted in the isolation of three new metabolites, arbophyllinines A–B (**453–454**) and arbophyllidine (**463**).[59] Arboflorine (**455**) from *K. arborea* stem bark was a known alkaloid type arboflorine, but its new analog kopsiyunnanine E (**456**) was detected in the aerial part of *K. arborea* and *K. officinalis*.[10,96,99,121] Besides the main constituents, the EtOH extract of *K. pauciflora* leaves has composed of a new component, andransinine A (**458**), along with a known one andransinine (**457**).[22] New corynantheines arboricine (**459**) and arboricine (**460**) were found in both the leaves and stem of *K. arborea*.[10,120] The new carboline harmane (**461**) was presented in both leaves and stem of *K. griffithii*, but the new congener harmicine (**462**) was only detected in its leaves.[15,17] To find bioactive compounds from plants, mersicarpine (**464**) was first isolated from *K. arborea* stem bark.[10] It was then further found in *K. pauciflora* leaves and *K. singapurensis* stem bark.[22,23] Two final alkaloids, a new alkaloid type, azepane-fused tetrahydro-β-carboline kopsiyunnanine K (**465**) and a known alkaloid type andranginine (**466**), were constituents of *K. arborea* aerial part.[102]

To date, there have not been many results on the separation of non-alkaloidal constituents from the plants of the genus *Kopsia*. A phytochemical report from Shan and partner (2017) identified that the *n*-hexane extract of *K. singapurensis* dried leaf and bark has accompanied with the existence of five triterpenoids β-amyrin (**467**), β-amyrin acetate (**468**), β-amyrone (**469**), lupeol (**470**), lupeol acetate (**471**), and one sterol stigmasterol (**472**) (Table 1 and Fig. 10).[122] This is the first time to observe these compounds in the genus *Kopsia*.

Taken together, despite the fact that there have been preliminary chemotaxonomic and synthetic reviews.[127,128] This is the first time that we provide fully information on phytochemical separation, a detailed list of almost isolated compounds, chemical classification, botanical resource, and the great value of *Kopisa* monoterpene alkaloids in botanical and chemical relationship.

3. Pharmacological activities

Cytotoxic, antimicrobial, anti-inflammatory, anti-diabetic, cardiovascular, vasorelaxant, and other positive properties have been studied utilizing *Kopsia* secondary metabolites and extracts in pharmacological research. In Table 2, a summary of prior pharmacological appraisals on *Kopsia* plant materials is presented in detail.

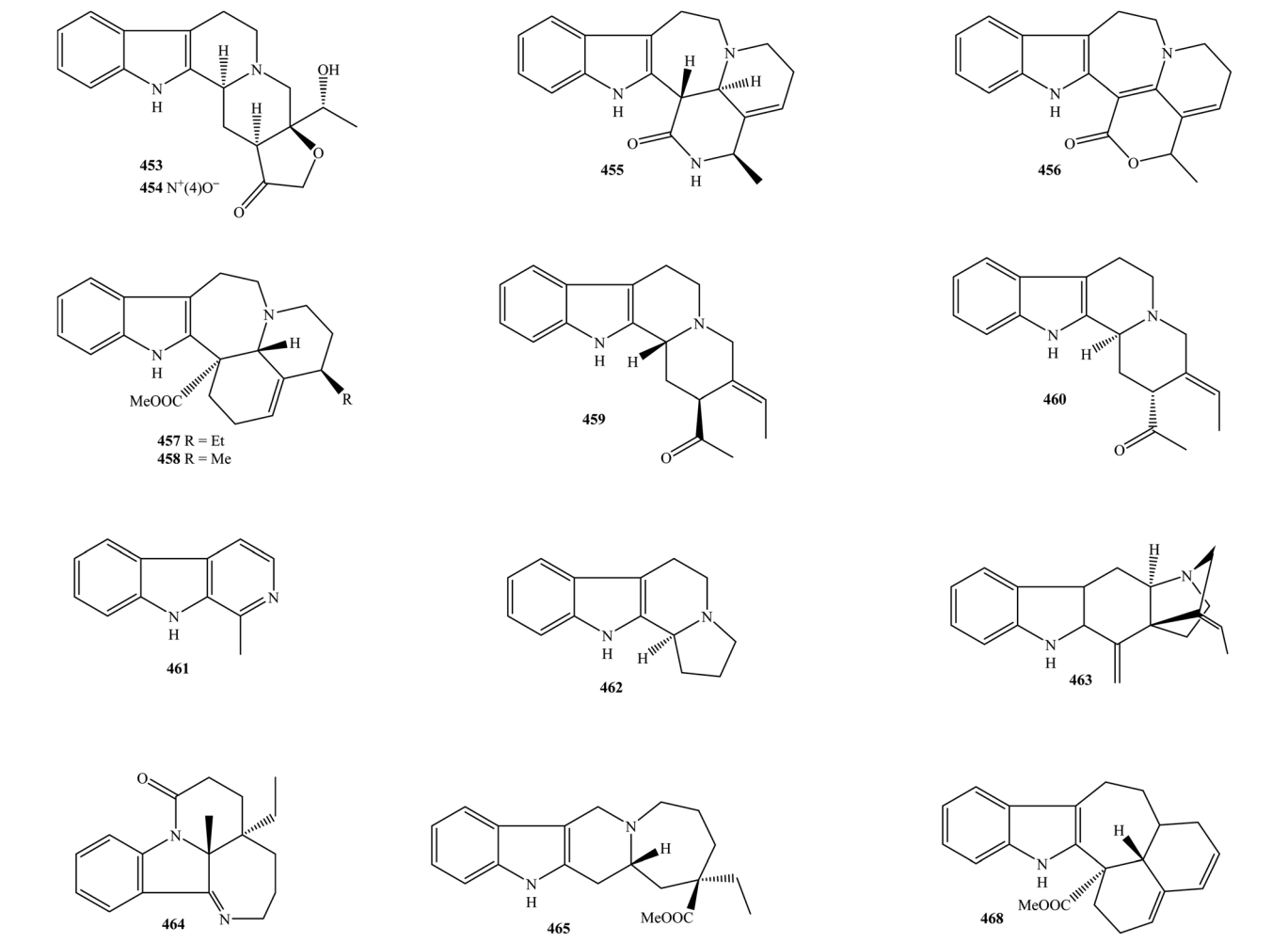

Fig. 9 Others type indole alkaloids from genus *Kopsia*.

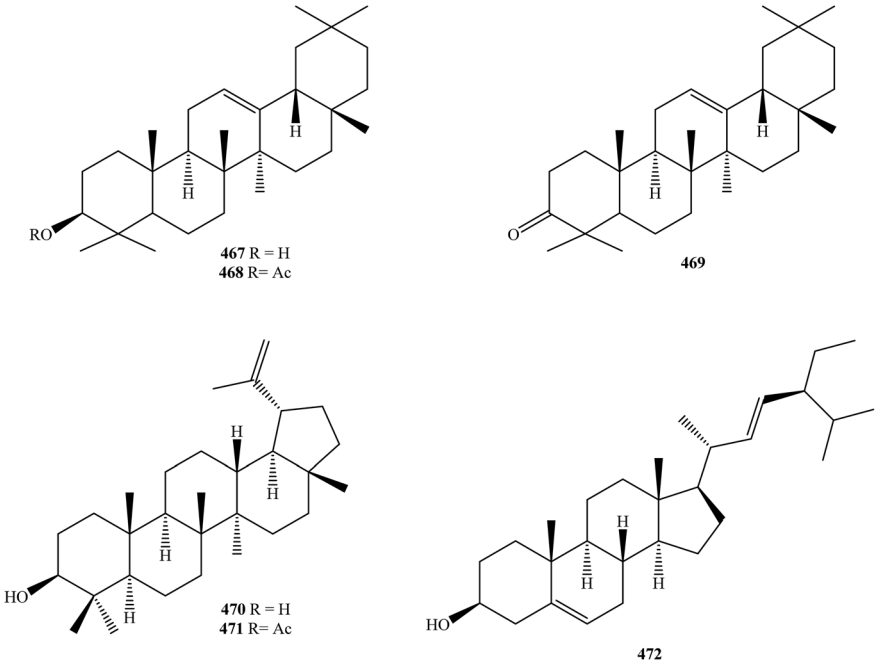

Fig. 10 Triterpenoids and sterol from genus *Kopsia*.

3.1. Cytotoxic activity

It is obvious to the view that monoterpene alkaloids are the major phytochemicals in *Kopsia* plants so that cytotoxic experiments using *Kopsia* constituents may be thought of as a big content in pharmacological development. Six alkaloidal constituents **39–40**, **73**, **302**, **327**, and **408** from *K. singapurensis* root were submitted to cytotoxic assay against NIH/3T3, HL-60, and HeLa cells.[49] Among them, kopsifine (**73**) induced the lowest CD_{50} value of 0.9 μg mL^{-1} against HL-60 cells in referencing with the positive control vincristine (CD_{50} 1.8 μg mL^{-1}).[49]

Kopsiafrutine E (**47**) possessing hydroxyl groups at carbons C-14 and C-15 demonstrated as the most bioactive compound against HS-1, HS-4, SCL-1, A-431, BGC-823, MCF-7, and W-480 with the IC_{50} values of 7.3–9.5 μM.[52] Meanwhile, its congeners kopsiafrutines C–D (**45–46**) containing a hydroxyl group at carbon C-15 have shown to associate with the respective IC_{50} values of 10.3–12.5 and 11.8–13.8 μM, but kopsiafrutines A–B (**43–44**) and kopsifoline A (**76**) did not inhibit cancer cell growth (IC_{50} > 20 μM).[52] In the same way, the following new aspidofractinines kopsiahainanins A–B (**48–49**) with a lactone bridge have induced the respective IC_{50} values of 9.4–11.7 and 12.2–15.9 μM against A-549, BGC-823, HepG-2, HL-60, MCF-7, SMMC-7721, and W-480 cells.[53] However, four new analogous kopsiahainanins C–F (**50–53**) accompanied by the IC_{50} values of >20 μM.[53]

From Table 2, new aspidofractines kopsiahainins A–E (**54–58**) were also further examined by cytotoxic test towards BGC-823, HepG-2, MCF-7, SGC-7901, SK-MEL-2, and SK-OV-3 cancer cells. It evidenced that compounds **56–57** demonstrated strong activity with IC_{50} values of ≤10 μM.[54] Similarly, in the N(4)-oxide group, new alkaloid **237** possessed the IC_{50} values from 7.2 to 8.9 μM to inhibit BGC-823, HepG-2, MCF-7, SGC-7901, and SK-MEL-2 cells, but new metabolites **214–215** was inactive (IC_{50} > 20 μM).[85]

The new metabolite kopsiaofficines C (**61**) showed the IC_{50} values of <10 μM towards cancer cell lines 95-D, A-549, ATCC, H-446, H-460, H-292, and SPCA-1, and was better than its analogs **59** (10 < IC_{50} ≤ 20 μM) and **60** (IC_{50} > 20 μM).[55] The bulk dimeric molecule arbolodinine B (**333**) successfully controlled the growth of HT-29, MCF-7, PC-3, KB (VJ300), MDA-MB-231, HCT-116, and A-549 with the IC_{50} values ranging from 1.3 to 9.6 μg mL^{-1}, while arbolodinines A and C (**1** and **334**) failed to do so.[8]

Rhazinilam (**409**) itself displayed the potential application in cancer treatments because its strong inhibitory capacity to A-549 and HT-29 cells (IC_{50} 0.35 μM), kopsiyunnanines A–C (**402–404**) indicated moderate activities (IC_{50} 4.67–8.89 μM), but both kopsiyunnanine D (**450**) and (−)-quebrachamine (**452**) were inactive (>30 μM).[114] Novel alkaloidal arbophyllidine (**463**) suppressed HT-29 cell growth with the IC_{50} value of 6.2 μM, but the novel metabolite arbophyllinine A (**453**) failed to inhibit.[59] Six non-alkaloidal constituents **467–472** were also subjected to cytotoxic assay, in which their IC_{50} values ranged from 14.5 to 22.5 μg mL^{-1}.[122]

Vincristine, a renowned chemotherapy medication, is usually used in combining with other drugs to treat many types of cancers.[132] In this scenario, experiments using a combination of *Kopsia* alkaloids and vincristine for anticancer treatments also bring out significant results. In VJ300 cells, kopsiflorine **74** (10 μg mL^{-1}) showed reversal of multiple drug resistance (MRD) by suppressing the bound of [3*H*]azidopine to *P*-glycoprotein.[61] Alkaloidal compounds **88**, **102–107**, **411**, **413**, **417**, **434**, and **438** exhibited no appreciable cytotoxic activity against KB (VJ300) cells.[22,23,43,72] However, they possessed IC_{50} values of 0.39–38.7

Table 2 Pharmacological activities of isolated compounds and plant extracts from the genus *Kopsia*

Compounds	Models	Effect	Positive control	Effect	References
Anti-cancer activity					
39	*In vitro*	CD_{50} > 60 μg mL^{-1}/NIH/3T3 and HeLa cells CD_{50} = 6.9 μg mL^{-1}/HL-60 cells	Vincristine	CD_{50} > 60 μg mL^{-1}/NIH/3T3 cells CD_{50} = 1.8 μg mL^{-1}/HL-60 cells CD_{50} = 0.4 μg mL^{-1}/HeLa cells	49
40	*In vitro*	CD_{50} > 60 μg mL^{-1}/NIH/3T3, HL-60 and HeLa cells	Vincristine	CD_{50} > 60 μg mL^{-1}/NIH/3T3 cells CD_{50} = 1.8 μg mL^{-1}/HL-60 cells CD_{50} = 0.4 μg mL^{-1}/HeLa cells	49
43	*In vitro*	IC_{50} = 33.7 μM/HS-1 cells IC_{50} = 28.4 μM/HS-4 cells IC_{50} = 32.4 μM/SCL-1 cells IC_{50} = 29.7 μM/A-431 cells IC_{50} = 30.9 μM/BGC-823 cells IC_{50} = 27.1 μM/MCF-7 cells IC_{50} = 31.2 μM/W-480 cells	Adiamycin	IC_{50} = 17.8 μM/HS-1 cells IC_{50} = 24.7 μM/HS-4 cells IC_{50} = 21.8 μM/SCL-1 cells IC_{50} = 33.7 μM/A-431 cells IC_{50} = 28.4 μM/BGC-823 cells IC_{50} = 37.6 μM/MCF-7 cells IC_{50} = 14.1 μM/W-480 cells	52
44	*In vitro*	IC_{50} = 34.9 μM/HS-1 cells IC_{50} = 29.9 μM/HS-4 cells IC_{50} = 33.1 μM/SCL-1 cells IC_{50} = 30.1 μM/A-431 cells IC_{50} = 35.5 μM/BGC-823 cells IC_{50} = 31.2 μM/MCF-7 cells IC_{50} = 32.6 μM/W-480 cells	Adiamycin	IC_{50} = 17.8 μM/HS-1 cells IC_{50} = 24.7 μM/HS-4 cells IC_{50} = 21.8 μM/SCL-1 cells IC_{50} = 33.7 μM/A-431 cells IC_{50} = 28.4 μM/BGC-823 cells IC_{50} = 37.6 μM/MCF-7 cells IC_{50} = 14.1 μM/W-480 cells	52
45	*In vitro*	IC_{50} = 12.4 μM/HS-1 cells IC_{50} = 12.3 μM/HS-4 and BGC-823 cells IC_{50} = 12.9 μM/SCL-1 cells IC_{50} = 11.8 μM/A-431 cells IC_{50} = 12.6 μM/MCF-7 cells IC_{50} = 13.8 μM/W-480 cells	Adiamycin	IC_{50} = 17.8 μM/HS-1 cells IC_{50} = 24.7 μM/HS-4 cells IC_{50} = 21.8 μM/SCL-1 cells IC_{50} = 33.7 μM/A-431 cells IC_{50} = 28.4 μM/BGC-823 cells IC_{50} = 37.6 μM/MCF-7 cells IC_{50} = 14.1 μM/W-480 cells	52
46	*In vitro*	IC_{50} = 11.6 μM/HS-1 cells IC_{50} = 11.4 μM/HS-4 cells IC_{50} = 12.1 μM/SCL-1 cells IC_{50} = 10.3 μM/A-431 cells IC_{50} = 11.7 μM/BGC-823 cells IC_{50} = 10.4 μM/MCF7 cells IC_{50} = 12.5 μM/W-480 cells	Adiamycin	IC_{50} = 17.8 μM/HS-1 cells IC_{50} = 24.7 μM/HS-4 cells IC_{50} = 21.8 μM/SCL-1 cells IC_{50} = 33.7 μM/A-431 cells IC_{50} = 28.4 μM/BGC-823 cells IC_{50} = 37.6 μM/MCF-7 cells IC_{50} = 14.1 μM/W-480 cells	52
47	*In vitro*	IC_{50} = 7.3 μM/HS-1 cells IC_{50} = 8.6 μM/HS-4 and MCF-7 cells IC_{50} = 8.2 μM/SCL-1 cells IC_{50} = 9.5 μM/A431 cells IC_{50} = 8.9 μM/BGC-823 cells IC_{50} = 9.2 μM/W-480 cells	Adiamycin	IC_{50} = 17.8 μM/HS-1 cells IC_{50} = 24.7 μM/HS-4 cells IC_{50} = 21.8 μM/SCL-1 cells IC_{50} = 33.7 μM/A-431 cells IC_{50} = 28.4 μM/BGC-823 cells IC_{50} = 37.6 μM/MCF-7 cells IC_{50} = 14.1 μM/W-480 cells	52
48	*In vitro*	IC_{50} = 11.3 μM/A-549 cells IC_{50} = 9.4 μM/BGC-823 cells IC_{50} = 10.1 μM/HepG-2 cells IC_{50} = 11.1 μM/HL-60 cells IC_{50} = 10.4 μM/MCF-7 cells IC_{50} = 9.7 μM/SMMC-7721 cells IC_{50} = 11.7 μM/W-480 cells	Doxorubicin	IC_{50} = 0.02 μM/A-549, HepG-2 and W-480 cells IC_{50} = 0.01 μM/BGC-823 cells IC_{50} = 0.03 μM/HL-60 cells IC_{50} = 0.04 μM/SMMC-7721 cells	53
49	*In vitro*	IC_{50} = 12.7 μM/A-549 cells IC_{50} = 12.2 μM/BGC-823 cells IC_{50} = 12.8 μM/HepG-2 cells IC_{50} = 13.8 μM/HL-60 cells IC_{50} = 14.3 μM/MCF-7 and SMMC-7721 cells IC_{50} = 15.9 μM/W-480 cells	Doxorubicin	IC_{50} = 0.02 μM/A-549, HepG-2 and W-480 cells IC_{50} = 0.01 μM/BGC-823 cells IC_{50} = 0.03 μM/HL-60 cells IC_{50} = 0.04 μM/SMMC-7721 cells	53
50	*In vitro*	IC_{50} = 31.9 μM/A-549 cells IC_{50} = 31.2 μM/BGC-823 cells IC_{50} = 30.7 μM/HepG-2 cells IC_{50} = 32.2 μM/HL-60 cells IC_{50} = 28.1 μM/MCF-7 cells	Doxorubicin	IC_{50} = 0.02 μM/A-549, HepG-2 and W-480 cells IC_{50} = 0.01 μM/BGC-823 cells IC_{50} = 0.03 μM/HL-60 cells IC_{50} = 0.04 μM/SMMC-7721 cells	53

Table 2 (*Contd.*)

Compounds	Models	Effect	Positive control	Effect	References
		IC_{50} = 29.9 μM/SMMC-7721 cells			
		IC_{50} = 27.6 μM/W-480 cells			
51	*In vitro*	IC_{50} = 29.7 μM/A-549 cells	Doxorubicin	IC_{50} = 0.02 μM/A-549, HepG-2 and W-480 cells	53
		IC_{50} = 29.6 μM/BGC-823 cells		IC_{50} = 0.01 μM/BGC-823 cells	
		IC_{50} = 29.4 μM/HepG-2 and HL-60 cells		IC_{50} = 0.03 μM/HL-60 cells	
		IC_{50} = 27.1 μM/MCF-7 cells		IC_{50} = 0.04 μM/SMMC-7721 cells	
		IC_{50} = 30.1 μM/SMMC-7721 cells			
		IC_{50} = 24.9 μM/W-480 cells			
52	*In vitro*	IC_{50} = 76.3 μM/A-549 cells	Doxorubicin	IC_{50} = 0.02 μM/A-549, HepG-2 and W-480 cells	53
		IC_{50} = 68.7 μM/BGC-823 cells		IC_{50} = 0.01 μM/BGC-823 cells	
		IC_{50} = 66.8 μM/HepG-2 cells		IC_{50} = 0.03 μM/HL-60 cells	
		IC_{50} = 72.3 μM/HL-60 cells		IC_{50} = 0.04 μM/SMMC-7721 cells	
		IC_{50} = 76.2 μM/MCF-7 cells			
		IC_{50} = 70.8 μM/SMMC-7721 cells			
		IC_{50} = 69.4 μM/W-480 cells			
53	*In vitro*	IC_{50} = 80.2 μM/A-549 cells	Doxorubicin	IC_{50} = 0.02 μM/A-549, HepG-2 and W-480 cells	53
		IC_{50} = 78.8 μM/BGC-823 cells		IC_{50} = 0.01 μM/BGC-823 cells	
		IC_{50} = 79.4 μM/HepG-2 cells		IC_{50} = 0.03 μM/HL-60 cells	
		IC_{50} = 80.3 μM/HL-60 cells		IC_{50} = 0.04 μM/SMMC-7721 cells	
		IC_{50} = 80.5 μM/MCF-7 cells			
		IC_{50} = 81.6 μM/SMMC-7721 cells			
		IC_{50} = 81.8 μM/W-480 cells			
54	*In vitro*	IC_{50} = 15.8 μM/BGC-823 cells	Doxorubicin	IC_{50} = 0.02 μM/BGC-823 cells	54
		IC_{50} = 16.8 μM/HepG-2 cells		IC_{50} = 0.01 μM/HepG-2 and SK-OV-3 cells	
		IC_{50} = 16.5 μM/MCF-7 cells		IC_{50} = 0.06 μM/MCF-7 cells	
		IC_{50} = 18.7 μM/SGC-7901 cells		IC_{50} = 0.05 μM/SGC-7901 cells	
		IC_{50} = 19.7 μM/SK-MEL-2 cells		IC_{50} = 0.03 μM/SK-MEL-2 cells	
		IC_{50} = 17.6 μM/SK-OV-3 cells			
55	*In vitro*	IC_{50} = 13.8 μM/BGC-823 cells	Doxorubicin	IC_{50} = 0.02 μM/BGC-823 cells	54
		IC_{50} = 12.4 μM/HepG-2 cells		IC_{50} = 0.01 μM/HepG-2 and SK-OV-3 cells	
		IC_{50} = 14.8 μM/MCF-7 cells		IC_{50} = 0.06 μM/MCF-7 cells	
		IC_{50} = 13.9 μM/SGC-7901 and SK-OV-3 cells		IC_{50} = 0.05 μM/SGC-7901 cells	
		IC_{50} = 12.6 μM/SK-MEL-2 cells		IC_{50} = 0.03 μM/SK-MEL-2 cells	
56	*In vitro*	IC_{50} = 7.3 μM/BGC-823 cells	Doxorubicin	IC_{50} = 0.02 μM/BGC-823 cells	54
		IC_{50} = 8.6 μM/HepG-2 cells		IC_{50} = 0.01 μM/HepG-2 and SK-OV-3 cells	
		IC_{50} = 8.2 μM/MCF-7 cells		IC_{50} = 0.06 μM/MCF-7 cells	
		IC_{50} = 9.5 μM/SGC-7901 cells		IC_{50} = 0.05 μM/SGC-7901 cells	
		IC_{50} = 8.9 μM/SK-MEL-2 cells		IC_{50} = 0.03 μM/SK-MEL-2 cells	
		IC_{50} = 8.6 μM/SK-OV-3 cells			
57	*In vitro*	IC_{50} = 9.5 μM/BGC-823 cells	Doxorubicin	IC_{50} = 0.02 μM/BGC-823 cells	54
		IC_{50} = 10.6 μM/HepG-2 cells		IC_{50} = 0.01 μM/HepG-2 and SK-OV-3 cells	
		IC_{50} = 9.3 μM/MCF-7 cells		IC_{50} = 0.06 μM/MCF-7 cells	
		IC_{50} = 10.4 μM/SGC-7901 cells		IC_{50} = 0.05 μM/SGC-7901 cells	
		IC_{50} = 9.2 μM/SK-MEL-2 cells		IC_{50} = 0.03 μM/SK-MEL-2 cells	
		IC_{50} = 10.3 μM/SK-OV-3 cells			
58	*In vitro*	IC_{50} = 33.1 μM/BGC-823 cells	Doxorubicin	IC_{50} = 0.02 μM/BGC-823 cells	54
		IC_{50} = 32.4 μM/HepG-2 cells		IC_{50} = 0.01 μM/HepG-2 and SK-OV-3 cells	
		IC_{50} = 29.7 μM/MCF-7 cells		IC_{50} = 0.06 μM/MCF-7 cells	
		IC_{50} = 30.9 μM/SGC-7901 cells		IC_{50} = 0.05 μM/SGC-7901 cells	
		IC_{50} = 27.1 μM/SK-MEL-2 cells		IC_{50} = 0.03 μM/SK-MEL-2 cells	
		IC_{50} = 30.1 μM/SK-OV-3 cells			
59	*In vitro*	IC_{50} = 12.9 μM/95-D cells	Doxorubicin	IC_{50} = 24.7 μM/95-D cells	55
		IC_{50} = 12.4 μM/A-549 cells		IC_{50} = 21.8 μM/A-549 cells	
		IC_{50} = 13.8 μM/ATCC cells		IC_{50} = 33.7 μM/ATCC cells	
		IC_{50} = 14.8 μM/H-446 cells		IC_{50} = 22.3 μM/H-446 cells	

Table 2 (*Contd.*)

Compounds	Models	Effect	Positive control	Effect	References
		IC_{50} = 13.3 μM/H-460 cells		IC_{50} = 14.1 μM/H-460 cells	
		IC_{50} = 12.6 μM/H-292 cells		IC_{50} = 13.7 μM/H-292 cells	
		IC_{50} = 13.9 μM/SPCA-1 cells		IC_{50} = 14.1 μM/SPCA-1 cells	
60	*In vitro*	IC_{50} = 46.8 μM/95-D cells	Doxorubicin	IC_{50} = 24.7 μM/95-D cells	55
		IC_{50} = 47.1 μM/ATCC cells		IC_{50} = 33.7 μM/ATCC cells	
		IC_{50} = 46.6 μM/H-446 cells		IC_{50} = 22.3 μM/H-446 cells	
		IC_{50} = 45.9 μM/H-292 cells		IC_{50} = 13.7 μM/H-292 cells	
61	*In vitro*	IC_{50} = 9.5 μM/95-D cells	Doxorubicin	IC_{50} = 24.7 μM/95-D cells	55
		IC_{50} = 8.6 μM/A-549 cells		IC_{50} = 21.8 μM/A-549 cells	
		IC_{50} = 9.3 μM/ATCC and H-292 cells		IC_{50} = 33.7 μM/ATCC cells	
		IC_{50} = 9.4 μM/H-446 cells		IC_{50} = 22.3 μM/H-446 cells	
		IC_{50} = 9.2 μM/H-460 cells		IC_{50} = 14.1 μM/H-460 cells	
		IC_{50} = 9.7 μM/SPCA-1 cells		IC_{50} = 13.7 μM/H-292 cells	
				IC_{50} = 14.1 μM/SPCA-1 cells	
73	*In vitro*	CD_{50} = 20.7 μg mL^{-1}/NIH/3T3 cells	Vincristine	CD_{50} > 60 μg mL^{-1}/NIH/3T3 cells	49
		CD_{50} = 0.9 μg mL^{-1}/HL-60 cells		CD_{50} = 1.8 μg mL^{-1}/HL-60 cells	
		CD_{50} = 36.5 μg mL^{-1}/HeLa cells		CD_{50} = 0.4 μg mL^{-1}/HeLa cells	
74	*In vitro*	To suppress the bound of [3H]azidopine to *P*-glycoprotein			61
76	*In vitro*	IC_{50} = 67.3 μM/HS-4 cells	Adiamycin	IC_{50} = 24.7 μM/HS-4 cells	52
		IC_{50} = 74.2 μM/A-431 cells		IC_{50} = 33.7 μM/A-431 cells	
		IC_{50} = 66.2 μM/W-480 cells		IC_{50} = 14.1 μM/W-480 cells	
88	*In vitro*	IC_{50} = 38.7 μg mL^{-1}/KB (VJ300) + 0.1 μg mL^{-1} vincristine	Vincristine	IC_{50} = 1.0 μg mL^{-1}/KB (VJ300)	43
93	*In vitro*	IC_{50} = 19.5 μg mL^{-1}/KB cells	Vincristine	IC_{50} = 1.0 μg mL^{-1}/KB (VJ300)	32
		IC_{50} = 18.0 μg mL^{-1}/KB (VJ300) cells			
		IC_{50} = 3.80 μg mL^{-1}/KB (VJ300) + 0.1 μg mL^{-1} vincristine			
102	*In vitro*	IC_{50} = 15.0 μg mL^{-1}/KB (VJ300) + 0.1 μg mL^{-1} vincristine	Vincristine	IC_{50} = 1.0 μg mL^{-1}/KB (VJ300)	23
103	*In vitro*	IC_{50} = 3.9 μg mL^{-1}/KB (VJ300) + 0.1 μg mL^{-1} vincristine	Vincristine	IC_{50} = 1.0 μg mL^{-1}/KB (VJ300)	23
104	*In vitro*	IC_{50} = 13.0 μg mL^{-1}/KB (VJ300) + 0.1 μg mL^{-1} vincristine	Vincristine	IC_{50} = 1.0 μg mL^{-1}/KB (VJ300)	23
105	*In vitro*	IC_{50} = 18.2 μg mL^{-1}/KB (VJ300) + 0.1 μg mL^{-1} vincristine	Vincristine	IC_{50} = 1.0 μg mL^{-1}/KB (VJ300)	23
106	*In vitro*	IC_{50} = 9.2 μg mL^{-1}/KB (VJ300) + 0.1 μg mL^{-1} vincristine	Vincristine	IC_{50} = 1.0 μg mL^{-1}/KB (VJ300)	23
107	*In vitro*	IC_{50} = 18.0 μg mL^{-1}/KB (VJ300) + 0.1 μg mL^{-1} vincristine	Vincristine	IC_{50} = 1.0 μg mL^{-1}/KB (VJ300)	23
214	*In vitro*	IC_{50} = 29.7 μM/BGC-823 cells	Doxorubicin	IC_{50} = 29.7 μM/BGC-823 cells	85
		IC_{50} = 37.6 μM/HepG-2 cells		IC_{50} = 37.6 μM/HepG-2 cells	
		IC_{50} = 35.8 μM/MCF-7 cells		IC_{50} = 35.8 μM/MCF-7 cells	
		IC_{50} = 36.8 μM/SGC-7901 cells		IC_{50} = 36.8 μM/SGC-7901 cells	
		IC_{50} = 36.5 μM/SK-MEL-2 cells		IC_{50} = 36.5 μM/SK-MEL-2 cells	
215	*In vitro*	IC_{50} = 32.1 μM/BGC-823 cells	Doxorubicin	IC_{50} = 29.7 μM/BGC-823 cells	85
		IC_{50} = 29.8 μM/HepG-2 cells		IC_{50} = 37.6 μM/HepG-2 cells	
		IC_{50} = 31.9 μM/MCF-7 cells		IC_{50} = 35.8 μM/MCF-7 cells	
		IC_{50} = 27.9 μM/SGC-7901 cells		IC_{50} = 36.8 μM/SGC-7901 cells	
		IC_{50} = 33.3 μM/SK-MEL-2 cells		IC_{50} = 36.5 μM/SK-MEL-2 cells	
237	*In vitro*	IC_{50} = 8.6 μM/BGC-823 cells	Doxorubicin	IC_{50} = 29.7 μM/BGC-823 cells	85
		IC_{50} = 7.2 μM/HepG-2 cells		IC_{50} = 37.6 μM/HepG-2 cells	
		IC_{50} = 8.3 μM/MCF-7 cells		IC_{50} = 35.8 μM/MCF-7 cells	
		IC_{50} = 8.2 μM/SGC-7901 cells		IC_{50} = 36.8 μM/SGC-7901 cells	
		IC_{50} = 8.9 μM/SK-MEL-2 cells		IC_{50} = 36.5 μM/SK-MEL-2 cells	
282	*In vitro*	IC_{50} = 9.7 μg mL^{-1}/PC-3 cells	Cisplatin	IC_{50} = 1.5 μg mL^{-1}/PC-3 cells	19
		IC_{50} = 15.9 μg mL^{-1}/HCT-116 cells		IC_{50} = 3.2 μg mL^{-1}/HCT-116 cells	
		IC_{50} = 14.1 μg mL^{-1}/MCF-7 cells		IC_{50} = 4.2 μg mL^{-1}/MCF-7 cells	
		IC_{50} > 25 μg mL^{-1}/A-549 and KB (VJ300) cells		IC_{50} = 4.3 μg mL^{-1}/A-549 cells	
		IC_{50} = 8.6 μg mL^{-1}/KB (VJ300) + 0.1 μg mL^{-1} vincristine	Verapamil	IC_{50} = 4.7 μg mL^{-1}/KB (VJ300) + 0.1 μg mL^{-1} vincristine	
289	*In vitro*	IC_{50} = 7.1 μg mL^{-1}/PC-3 cells	Cisplatin	IC_{50} = 1.5 μg mL^{-1}/PC-3 cells	19
		IC_{50} = 7.6 μg mL^{-1}/HCT-116 cells		IC_{50} = 3.2 μg mL^{-1}/HCT-116 cells	

Table 2 (*Contd.*)

Compounds	Models	Effect	Positive control	Effect	References
		IC_{50} = 9.7 μg mL^{-1}/MCF-7 cells IC_{50} = 20.4 μg mL^{-1}/A-549 cells IC_{50} = 23 μg mL^{-1}/KB (VJ300) cells IC_{50} = 4.80 μg mL^{-1}/KB (VJ300) + 0.1 μg mL^{-1} vincristine		IC_{50} = 4.2 μg mL^{-1}/MCF-7 cells IC_{50} = 4.3 μg mL^{-1}/A-549 cells IC_{50} = 4.7 μg mL^{-1}/KB (VJ300) + 0.1 μg mL^{-1} vincristine	
302	*In vitro*	CD_{50} > 60 μg mL^{-1}/NIH/3T3 cells CD_{50} = 30.2 μg mL^{-1}/HL-60 cells CD_{50} = 2.8 μg mL^{-1}/HeLa cells	Vincristine	CD_{50} > 60 μg mL^{-1}/NIH/3T3 cells CD_{50} = 1.8 μg mL^{-1}/HL-60 cells CD_{50} = 0.4 μg mL^{-1}/HeLa cells	49
327	*In vitro*	CD_{50} = 6.4 μg mL^{-1}/NIH/3T3 cells CD_{50} > 60 μg mL^{-1}/HL-60 cells CD_{50} = 7.5 μg mL^{-1}/HeLa cells	Vincristine	CD_{50} > 60 μg mL^{-1}/NIH/3T3 cells CD_{50} = 1.8 μg mL^{-1}/HL-60 cells CD_{50} = 0.4 μg mL^{-1}/HeLa cells	49
333	*In vitro*	IC_{50} = 1.3 μg mL^{-1}/HT-29 cells IC_{50} = 4.9 μg mL^{-1}/MCF-7 cells IC_{50} = 4.7 μg mL^{-1}/PC-3 cells IC_{50} = 7.0 μg mL^{-1}/MDA-MB -231 cells IC_{50} = 7.3 μg mL^{-1}/HCT-116 cells IC_{50} = 9.6 μg mL^{-1}/A-549 cells IC_{50} = 3.0 μg mL^{-1}/KB (VJ300) cells	Cisplatin Vincristine	IC_{50} = 8.8 μg mL^{-1}/HT-29 cells IC_{50} = 6.6 μg mL^{-1}/MCF-7 cells IC_{50} = 4.2 μg mL^{-1}/PC-3 cells IC_{50} = 2.1 μg mL^{-1}/MDA-MB -231 cells IC_{50} = 4.6 μg mL^{-1}/HCT-116 cells IC_{50} = 5.4 μg mL^{-1}/A-549 cells IC_{50} = 0.8 μg mL^{-1}/KB (VJ300) cells	8
366	*In vitro*	IC_{50} = 3.70 μg mL^{-1}/KB (VJ300) + 0.1 μg mL^{-1} vincristine	Vincristine	IC_{50} = 1.0 μg mL^{-1}/KB (VJ300)	103
367	*In vitro*	IC_{50} = 7.0 μg mL^{-1}/KB (VJ300) + 0.1 μg mL^{-1} vincristine	Vincristine	IC_{50} = 1.0 μg mL^{-1}/KB (VJ300)	103
373	*In vitro*	IC_{50} = 4.1 μg mL^{-1}/KB (VJ300) + 0.1 μg mL^{-1} vincristine	Vincristine	IC_{50} = 1.0 μg mL^{-1}/KB (VJ300)	103
374	*In vitro*	IC_{50} = 3.2 μg mL^{-1}/KB (VJ300) + 0.1 μg mL^{-1} vincristine	Vincristine	IC_{50} = 1.0 μg mL^{-1}/KB (VJ300)	103
375	*In vitro*	IC_{50} = 11.2 μg mL^{-1}/KB (VJ300) + 0.1 μg mL^{-1} vincristine	Vincristine	IC_{50} = 1.0 μg mL^{-1}/KB (VJ300)	103
402	*In vitro*	IC_{50} = 5.38 μM/A-549 cells IC_{50} = 4.67 μM/HT-29 cells	Docetaxel	IC_{50} = 4.95 × 10^{-4} μM/A-549 cells IC_{50} = 3.34 × 10^{-4} μM/HT-29 cells	114
403	*In vitro*	IC_{50} = 7.44 μM/A-549 cells IC_{50} = 6.39 μM/HT-29 cells	Docetaxel	IC_{50} = 4.95 × 10^{-4} μM/A-549 cells IC_{50} = 3.34 × 10^{-4} μM/HT-29 cells	114
404	*In vitro*	IC_{50} = 8.21 μM/A-549 cells IC_{50} = 8.89 μM/HT-29 cells	Docetaxel	IC_{50} = 4.95 × 10^{-4} μM/A-549 cells IC_{50} = 3.34 × 10^{-4} μM/HT-29 cells	114
407	*In vitro*	IC_{50} = 0.24 μg mL^{-1}/KB cells IC_{50} = 0.25 μg mL^{-1}/KB (VJ300) cells IC_{50} = 0.30 μg mL^{-1}/KB (VJ300) + 0.1 μg mL^{-1} vincristine	Vincristine	IC_{50} = 1.0 μg mL^{-1}/KB (VJ300)	32
408	*In vitro*	CD_{50} = 20.8 μg mL^{-1}/NIH/3T3 cells CD_{50} > 60 μg mL^{-1}/HL-60 cells CD_{50} = 2.9 μg mL^{-1}/HeLa cells IC_{50} = 0.19 μg mL^{-1}/KB cells IC_{50} = 0.25 μg mL^{-1}/KB (VJ300) cells IC_{50} = 0.34 μg mL^{-1}/KB (VJ300) + 0.1 μg mL^{-1} vincristine	Vincristine Vincristine	CD_{50} > 60 μg mL^{-1}/NIH/3T3 cells CD_{50} = 1.8 μg mL^{-1}/HL-60 cells CD_{50} = 0.4 μg mL^{-1}/HeLa cells IC_{50} = 1.0 μg mL^{-1}/KB (VJ300)	49 32
409	*In vitro*	IC_{50} = 0.35 μM/A-549 and HT-29 cells IC_{50} = 1.25 μg mL^{-1}/KB cells IC_{50} = 2.50 μg mL^{-1}/KB (VJ300) cells IC_{50} = 1.85 μg mL^{-1}/KB (VJ300) + 0.1 μg mL^{-1} vincristine	Docetaxel Vincristine	IC_{50} = 4.95 × 10^{-4} μM/A-549 cells IC_{50} = 3.34 × 10^{-4} μM/HT-29 cells IC_{50} = 1.0 μg mL^{-1}/KB (VJ300)	114 32
411	*In vitro*	IC_{50} = 4.35 μg mL^{-1}/KB (VJ300) + 0.1 μg mL^{-1} vincristine	Vincristine	IC_{50} = 1.0 μg mL^{-1}/KB (VJ300)	72
413	*In vitro*	IC_{50} = 4.11 μg mL^{-1}/KB (VJ300) + 0.1 μg mL^{-1} vincristine	Vincristine	IC_{50} = 1.0 μg mL^{-1}/KB (VJ300)	72
417	*In vitro*	IC_{50} = 0.39 μg mL^{-1}/KB (VJ300) + 0.1 μg mL^{-1} vincristine	Vincristine	IC_{50} = 1.0 μg mL^{-1}/KB (VJ300)	72
434	*In vitro*	IC_{50} = 21.8 μg mL^{-1}/KB (VJ300) + 0.1 μg mL^{-1} vincristine	Vincristine	IC_{50} = 1.0 μg mL^{-1}/KB (VJ300)	22
437	*In vitro*	IC_{50} = 15.0 μg mL^{-1}/KB cells IC_{50} = 11.0 μg mL^{-1}/KB (VJ300) cells IC_{50} = 3.8 μg mL^{-1}/KB (VJ300) + 0.1 μg mL^{-1} vincristine	Vincadifformine	IC_{50} = 10.2 μg mL^{-1}/KB cells IC_{50} = 6.3 μg mL^{-1}/KB (VJ300) cells IC_{50} = 4.5 μg mL^{-1}/KB (VJ300) + 0.1 μg mL^{-1} vincristine	10

Table 2 (*Contd.*)

Compounds	Models	Effect	Positive control	Effect	References
438	*In vitro*	IC_{50} = 6.4 μg mL^{-1}/KB (VJ300) + 0.1 μg mL^{-1} vincristine	Vincristine	IC_{50} = 1.0 μg mL^{-1}/KB (VJ300)	22
446	*In vitro*	IC_{50} = 0.25 μg mL^{-1}/Jurkat cells IC_{50} = 3.6 μg mL^{-1}/KB cells IC_{50} = 0.75 μg mL^{-1}/KB (VJ300) cells IC_{50} = 0.46 μg mL^{-1}/KB (VJ300) + 0.1 μg mL^{-1} vincristine	Vincadifformine	IC_{50} = 21.8 μg mL^{-1}/Jurkat cells IC_{50} = 10.2 μg mL^{-1}/KB cells IC_{50} = 6.3 μg mL^{-1}/KB (VJ300) cells IC_{50} = 4.5 μg mL^{-1}/KB (VJ300) + 0.1 μg mL^{-1} vincristine	10
450 and **452**	*In vitro*	IC_{50} > 30 μM/A-549 cells IC_{50} = 30 μM/HT-29 cells	Docetaxel	IC_{50} = 4.95 × 10^{-4} μM/A-549 cells IC_{50} = 3.34 × 10^{-4} μM/HT-29 cells	114
463	*In vitro*	IC_{50} = 6.2 μM/HT-29 cells			59
467	*In vitro*	IC_{50} = 15.5 μg mL^{-1}/MCF-7 cells			122
468	*In vitro*	IC_{50} = 22.5 μg mL^{-1}/MCF-7 cells			122
469	*In vitro*	IC_{50} = 21.5 μg mL^{-1}/MCF-7 cells			122
470	*In vitro*	IC_{50} = 17 μg mL^{-1}/MCF-7 cells			122
471	*In vitro*	IC_{50} = 26 μg mL^{-1}/MCF-7 cells			122
472	*In vitro*	IC_{50} = 14.5 μg mL^{-1}/MCF-7 cells			122
Anti-microbial activity					
14	*In vitro*	MIC = 31.3 μg mL^{-1}/*E. coli*, *E. carotovra*, *B. subtilis*, *B. cereus*, and *S. aureus* MIC = 15.5 μg mL^{-1}/*E. carotovra* EC_{50} = 33.3 μg mL^{-1}/*R. solani* EC_{50} = 29.2 μg mL^{-1}/*P. italicum* EC_{50} = 16.3 μg mL^{-1}/*F. oxysporum* f. sp. Cubense EC_{50} = 31.8 μg mL^{-1}/*F. oxysporum* f. sp. Niveum	Ampicillin Mildothane	MIC = 100 μg mL^{-1}/*E. coli* and *E. carotovra* MIC = 12.5 μg mL^{-1}/*B. subtilis* MIC = 25.0 μg mL^{-1}/*B. cereus* and *S. aureus* EC_{50} = 17.0 μg mL^{-1}/*R. solani* EC_{50} = 7.8 μg mL^{-1}/*P. italicum* EC_{50} = 57.0 μg mL^{-1}/*F. oxysporum* f. sp. Cubense EC_{50} = 101.0 μg mL^{-1}/*F. oxysporum* f. sp. Niveum	7
43	*In vitro*	IZ = 11 mm/*K. pneumoniae* IZ = 10 mm/*E. coli*, *S. aureus* and *S. viridans* IZ = 9 mm/*C. glabrata*, *E. cloacae* and *S. mutans* IZ = 8 mm/*S. epidermidis* and *S. dysenteriae* IZ = 7 mm/*C. albicans*, *C. tropicalis* and *P. aeruginosa*	Sanguinarine Netilmicin	IZ = 25 mm/*S. mutans* and *S. viridans* IZ = 21 mm/*S. aureus* IZ = 8 mm/*S. epidermidis* and *K. pneumoniae* IZ = 24 mm/*E. coli* IZ = 22 mm/*E. cloacae* IZ = 23 mm/*P. aeruginosa* and *S. dysenteriae*	52
44	*In vitro*	IZ = 12 mm/*P. aeruginosa* and *S. mutans* IZ = 11 mm/*E. coli* IZ = 10 mm/*C. glabrata* IZ = 9 mm/*E. cloacae*, *S. aureus* and *S. dysenteriae* IZ = 8 mm/*C. albicans*, *K. pneumoniae* and *S. epidermidis* IZ = 7 mm/*C. tropicalis* and *S. viridans*	Sanguinarine Netilmicin	IZ = 25 mm/*S. mutans* and *S. viridans* IZ = 21 mm/*S. aureus* IZ = 8 mm/*S. epidermidis* and *K. pneumoniae* IZ = 24 mm/*E. coli* IZ = 22 mm/*E. cloacae* IZ = 23 mm/*P. aeruginosa* and *S. dysenteriae*	52
45	*In vitro*	IZ = 18 mm and MIC = 0.77 mM/*K. pneumoniae* IZ = 18 mm and MIC = 0.87 mM/*S. viridans* IZ = 17 mm and MIC = 0.89 mM/*E. coli* IZ = 18 mm and MIC = 0.97 mM/*S. aureus* and *S. epidermidis* IZ = 18 mm and MIC = 0.97 mM/*E. cloacae* IZ = 19 mm and MIC = 1.01 mM/*P. aeruginosa* IZ = 18 mm and MIC = 1.13 mM/*S. mutans* IZ = 19 mm and MIC = 1.18 mM/*C. tropicalis* IZ = 18 mm and MIC = 2.68 mM/*S. dysenteriae* IZ = 17 mm and MIC = 2.87 mM/*C. albicans* IZ = 17 mm and MIC = 3.09 mM/*C. glabrata*	Sanguinarine Netilmicin	IZ = 25 mm/*S. mutans* and *S. viridans* IZ = 21 mm/*S. aureus* IZ = 8 mm/*S. epidermidis* and *K. pneumoniae* IZ = 24 mm/*E. coli* IZ = 22 mm/*E. cloacae* IZ = 23 mm/*P. aeruginosa* and *S. dysenteriae*	52
46	*In vitro*	IZ = 20 mm and MIC = 0.72 mM/*E. coli* IZ = 20 mm and MIC = 0.82 mM/*S. mutans*	Sanguinarine	IZ = 25 mm/*S. mutans* and *S. viridans*	52

Table 2 (*Contd.*)

Compounds	Models	Effect	Positive control	Effect	References
		IZ = 20 mm and MIC = 0.91 mM/*S. epidermidis* IZ = 20 mm and MIC = 1.03 mM/*S. dysenteriae* IZ = 20 mm and MIC = 1.11 mM/*S. viridans* IZ = 20 mm and MIC = 1.18 mM/*P. aeruginosa* IZ = 19 mm and MIC = 1.20 mM/*E. cloacae* IZ = 20 mm and MIC = 1.23 mM/*C. tropicalis* and *S. aureus* IZ = 17 mm and MIC = 1.32 mM/*C. glabrata* IZ = 21 mm and MIC = 1.37 mM/*K. pneumoniae* IZ = 17 mm and MIC = 2.87 mM/*C. albicans*	Netilmicin	IZ = 21 mm/*S. aureus* IZ = 8 mm/*S. epidermidis* and *K. pneumoniae* IZ = 24 mm/*E. coli* IZ = 22 mm/*E. cloacae* IZ = 23 mm/*P. aeruginosa* and *S. dysenteriae*	
47	*In vitro*	IZ = 24 mm and MIC = 0.15 mM/*E. coli* IZ = 24 mm and MIC = 0.20 mM/*S. epidermidis* IZ = 23 mm and MIC = 0.22 mM/*C. glabrata* IZ = 23 mm and MIC = 0.30 mM/*C. tropicalis* IZ = 24 mm and MIC = 0.30 mM/*S. dysenteriae* and *C. albicans* IZ = 24 mm and MIC = 0.25 mM/*S. aureus* IZ = 24 mm and MIC = 0.27 mM/*E. cloacae* IZ = 24 mm and MIC = 0.32 mM/*P. aeruginosa* IZ = 23 mm and MIC = 0.37 mM/*K. pneumoniae* IZ = 23 mm and MIC = 0.87 mM/*S. viridans* IZ = 24 mm and MIC = 1.14 mM/*S. mutans*	Sanguinarine Netilmicin	IZ = 25 mm/*S. mutans* and *S. viridans* IZ = 21 mm/*S. aureus* IZ = 8 mm/*S. epidermidis* and *K. pneumoniae* IZ = 24 mm/*E. coli* IZ = 22 mm/*E. cloacae* IZ = 23 mm/*P. aeruginosa* and *S. dysenteriae*	52
48	*In vitro*	IZ = 23 mm and MIC = 0.12 mM/*K. pneumoniae* IZ = 24 mm and MIC = 0.12 mM/*S. dysenteriae* IZ = 24 mm and MIC = 0.13 mM/*P. aeruginosa* IZ = 23 mm and MIC = 0.15 mM/*E. cloacae* IZ = 23 mm and MIC = 0.16 mM/*S. epidermidis* IZ = 24 mm and MIC = 0.18 mM/*S. aureus* IZ = 24 mm and MIC = 0.23 mM/*E. coli*	Netilmicin	IZ = 25 mm and MIC = 0.009 mM/*K. pneumoniae* IZ = 23 mm and MIC = 0.011 mM/*S. dysenteriae* IZ = 23 mm and MIC = 0.015 mM/*P. aeruginosa* IZ = 22 mm and MIC = 0.01 mM/*E. cloacae* IZ = 25 mm and MIC = 0.004 mM/*S. epidermidis* IZ = 21 mm and MIC = 0.005 mM/*S. aureus* IZ = 24 mm and MIC = 0.015 mM/*E. coli*	53
49	*In vitro*	IZ = 24 mm and MIC = 0.14 mM/*K. pneumoniae* IZ = 23 mm and MIC = 0.16 mM/*P. aeruginosa* IZ = 24 mm and MIC = 0.17 mM/*S. aureus* IZ = 22 mm and MIC = 0.18 mM/*S. dysenteriae* IZ = 24 mm and MIC = 0.19 mM/*E. cloacae* IZ = 23 mm and MIC = 0.19 mM/*S. epidermidis* IZ = 24 mm and MIC = 0.26 mM/*E. coli*	Netilmicin	IZ = 25 mm and MIC = 0.009 mM/*K. pneumoniae* IZ = 23 mm and MIC = 0.015 mM/*P. aeruginosa* IZ = 21 mm and MIC = 0.005 mM/*S. aureus* IZ = 22 mm and MIC = 0.01 mM/*E. cloacae* IZ = 25 mm and MIC = 0.004 mM/*S. epidermidis* IZ = 24 mm and MIC = 0.015 mM/*E. coli*	53
50	*In vitro*	IZ = 18 mm and MIC = 0.94 mM/*P. aeruginosa* IZ = 17 mm and MIC = 1.10 mM/*E. cloacae* IZ = 17 mm and MIC = 1.12 mM/*K. pneumoniae* and *S. dysenteriae* IZ = 18 mm and MIC = 1.20 mM/*S. aureus* IZ = 19 mm and MIC = 1.23 mM/*S. epidermidis*	Netilmicin	IZ = 23 mm and MIC = 0.015 mM/*P. aeruginosa* IZ = 22 mm and MIC = 0.01 mM/*E. cloacae* IZ = 25 mm and MIC = 0.009 mM/*K. pneumoniae* IZ = 23 mm and MIC = 0.011 mM/*S. dysenteriae* IZ = 21 mm and MIC = 0.005 mM/*S. aureus*	53

Table 2 (*Contd.*)

Compounds	Models	Effect	Positive control	Effect	References
		IZ = 18 mm and MIC = 1.32 mM/*E. coli*		IZ = 25 mm and MIC = 0.004 mM/*S. epidermidis* IZ = 24 mm and MIC = 0.015 mM/*E. coli*	
51	*In vitro*	IZ = 17 mm and MIC = 0.92 mM/*P. aeruginosa* IZ = 18 mm and MIC = 1.01 mM/*E. cloacae* IZ = 19 mm and MIC = 1.02 mM/*S. dysenteriae* IZ = 18 mm and MIC = 1.09 mM/*K. pneumoniae* IZ = 19 mm and MIC = 1.15 mM/*S. epidermidis* IZ = 20 mm and MIC = 1.18 mM/*S. aureus* IZ = 17 mm and MIC = 1.24 mM/*E. coli*	Netilmicin	IZ = 23 mm and MIC = 0.015 mM/*P. aeruginosa* IZ = 22 mm and MIC = 0.01 mM/*E. cloacae* IZ = 23 mm and MIC = 0.011 mM/*S. dysenteriae* IZ = 25 mm and MIC = 0.009 mM/*K. pneumoniae* IZ = 25 mm and MIC = 0.004 mM/*S. epidermidis* IZ = 21 mm and MIC = 0.005 mM/*S. aureus* IZ = 24 mm and MIC = 0.015 mM/*E. coli*	53
52	*In vitro*	IZ = 17 mm and MIC = 1.19 mM/*K. pneumoniae* IZ = 18 mm and MIC = 1.21 mM/*E. coli* IZ = 17 mm and MIC = 1.21 mM/*P. aeruginosa* IZ = 17 mm and MIC = 1.31 mM/*E. cloacae* IZ = 15 mm and MIC = 1.31 mM/*S. dysenteriae*	Netilmicin	IZ = 25 mm and MIC = 0.009 mM/*K. pneumoniae* IZ = 24 mm and MIC = 0.015 mM/*E. coli* IZ = 23 mm and MIC = 0.015 mM/*P. aeruginosa* IZ = 22 mm and MIC = 0.01 mM/*E. cloacae* IZ = 23 mm and MIC = 0.011 mM/*S. dysenteriae*	53
53	*In vitro*	IZ = 16 mm and MIC = 0.99 mM/*K. pneumoniae* IZ = 18 mm and MIC = 1.01 mM/*S. dysenteriae* IZ = 17 mm and MIC = 1.24 mM/*P. aeruginosa* IZ = 15 mm and MIC = 1.31 mM/*E. coli* IZ = 17 mm and MIC = 1.32 mM/*E. cloacae*	Netilmicin	IZ = 25 mm and MIC = 0.009 mM/*K. pneumoniae* IZ = 23 mm and MIC = 0.011 mM/*S. dysenteriae* IZ = 23 mm and MIC = 0.015 mM/*P. aeruginosa* IZ = 24 mm and MIC = 0.015 mM/*E. coli* IZ = 22 mm and MIC = 0.01 mM/*E. cloacae*	53
74	*In vitro*	IZ = 9.7 mm/*S. aureus*	Kanamycin sulfate	IZ = 24.7 mm/*S. aureus*	12
76	*In vitro*	IZ = 13 mm/*S. aureus* IZ = 12 mm/*S. epidermidis* IZ = 9 mm/ *C. albicans* and *C. glabrata* IZ = 8 mm/*C. tropicalis*, *S. mutans* and *S. dysenteriae* IZ = 7 mm/*E. coli* and *K. pneumoniae*	Kanamycin sulfate	IZ = 24.7 mm/*S. aureus*	12
85	*In vitro*	IZ = 11.2 mm/*S. aureus*	Kanamycin sulfate	IZ = 24.7 mm/*S. aureus*	12
86	*In vitro*	IZ = 9.1 mm/*S. aureus*	Kanamycin sulfate	IZ = 24.7 mm/*S. aureus*	12
87	*In vitro*	IZ = 10.3 mm/*S. aureus*	Kanamycin sulfate	IZ = 24.7 mm/*S. aureus*	12
206	*In vitro*	MIC = 15.5 μg mL^{-1}/*E. coli*, *Erwinia carotovra*, *Bacillus subtilis*, *B. cereus*, and *S. aureus* MIC = 7.8 μg mL^{-1}/*E. carotovra* EC_{50} = 21.9 μg mL^{-1}/*R. solani* EC_{50} = 19.4 μg mL^{-1}/*P. italicum* EC_{50} = 15.2 μg mL^{-1}/*F. oxysporum* f. sp. Cubense EC_{50} = 43.8 μg mL^{-1}/*F. oxysporum* f. sp. Niveum	Ampicillin Mildothane	MIC = 100 μg mL^{-1}/*E. coli* and *E. carotovra* MIC = 12.5 μg mL^{-1}/*B. subtilis* MIC = 25.0 μg mL^{-1}/*B. cereus* and *S. aureus* EC_{50} = 17.0 μg mL^{-1}/*R. solani* EC_{50} = 7.8 μg mL^{-1}/*P. italicum* EC_{50} = 57.0 μg mL^{-1}/*F. oxysporum* f. sp. Cubense EC_{50} = 101.0 μg mL^{-1}/*F. oxysporum* f. sp. Niveum	7

Table 2 (*Contd.*)

Compounds	Models	Effect	Positive control	Effect	References
267 and **297**	*In vitro*	MIC = 32 μg mL^{-1}/*E. coli*			21
Anti-inflammatory activity					
11	*In vitro*	IC_{50} = 25.4 μM/T cell inhibition			16
170	*In vitro*	IC_{50} = 21.6 μM/T cell inhibition			16
222	*In vitro*	IC_{50} = 27.8 μM/T cell inhibition			16
409	*In vitro*	IC_{50} = 1.0 μM/T cell inhibition To arrest the G2/M phase of the T cell cycle To decrease IL-6 and IL-17 levels in T cells			16
219, **225**, **228**, **279–280**, **291**, and **439**	*In vitro*	The inhibitory effects on IL-1β and TNF-α, and PGE2 were comparable with positive control dexamethasone			75
Anti-allergic activity					
90	*In vitro*	IC_{10} = 3.73 μg mL^{-1}/histamine and β-hexosaminidase inhibition in RBL-2H3 cell	Ketotifen fumarate	IC_{10} = 1.37 μg mL^{-1}/histamine and β-hexosaminidase inhibition in RBL-2H3 cell	66
126	*In vitro*	IC_{10} = 7.06 μg mL^{-1}/histamine and β-hexosaminidase inhibition in RBL-2H3 cell	Ketotifen fumarate	IC_{10} = 1.37 μg mL^{-1}/histamine and β-hexosaminidase inhibition in RBL-2H3 cell	66
257	*In vitro*	IC_{10} = 5.51 μg mL^{-1}/histamine and β-hexosaminidase inhibition in RBL-2H3 cell	Ketotifen fumarate	IC_{10} = 1.37 μg mL^{-1}/histamine and β-hexosaminidase inhibition in RBL-2H3 cell	66
448	*In vitro*	IC_{10} = 11.78 μg mL^{-1}/histamine and β-hexosaminidase inhibition in RBL-2H3 cell	Ketotifen fumarate	IC_{10} = 1.37 μg mL^{-1}/histamine and β-hexosaminidase inhibition in RBL-2H3 cell	66
The MeOH extract of *K. larutensis* bark	*In vitro*	IC_{10} = 2.17 μg mL^{-1}/histamine and β-hexosaminidase inhibition in RBL-2H3 cell	Ketotifen fumarate	IC_{10} = 1.37 μg mL^{-1}/histamine and β-hexosaminidase inhibition in RBL-2H3 cell	66
The MeOH extract of *K. arborea* bark	*In vitro*	IC_{10} = 3.82 μg mL^{-1}/histamine and β-hexosaminidase inhibition in RBL-2H3 cell	Ketotifen fumarate	IC_{10} = 1.37 μg mL^{-1}/histamine and β-hexosaminidase inhibition in RBL-2H3 cell	129
The MeOH extract of *K. larutensis* leaf	*In vitro*	IC_{10} = 3.01 μg mL^{-1}/histamine and β-hexosaminidase inhibition in RBL-2H3 cell	Ketotifen fumarate	IC_{10} = 1.37 μg mL^{-1}/histamine and β-hexosaminidase inhibition in RBL-2H3 cell	66
The MeOH extract of *K. arborea* leaf	*In vitro*	IC_{10} = 2.58 μg mL^{-1}/histamine and β-hexosaminidase inhibition in RBL-2H3 cell	Ketotifen fumarate	IC_{10} = 1.37 μg mL^{-1}/histamine and β-hexosaminidase inhibition in RBL-2H3 cell	129
The MeOH extract of *K. larutensis* root	*In vitro*	IC_{10} = 1.61 μg mL^{-1}/histamine and β-hexosaminidase inhibition in RBL-2H3 cell	Ketotifen fumarate	IC_{10} = 1.37 μg mL^{-1}/histamine and β-hexosaminidase inhibition in RBL-2H3 cell	66
The MeOH extract of *K. arborea* root	*In vitro*	IC_{10} = 4.32 μg mL^{-1}/histamine and β-hexosaminidase inhibition in RBL-2H3 cell	Ketotifen fumarate	IC_{10} = 1.37 μg mL^{-1}/histamine and β-hexosaminidase inhibition in RBL-2H3 cell	129
Anti-diabetic activity					
29	*In vitro*	EC_{50} = 24.5 μM/glucose-evoked podocyte injury inhibition	Astragaloside IV	EC_{50} = 15.4 μM/glucose-evoked podocyte injury inhibition	25
126	*In vitro*	EC_{50} = 3.0 μM/glucose-evoked podocyte injury inhibition	Astragaloside IV	EC_{50} = 15.4 μM/glucose-evoked podocyte injury inhibition	25
224	*In vitro*	EC_{50} = 10.2 μM/glucose-evoked podocyte injury inhibition	Astragaloside IV	EC_{50} = 15.4 μM/glucose-evoked podocyte injury inhibition	25
264	*In vitro*	EC_{50} = 12.0 μM/glucose-evoked podocyte injury inhibition	Astragaloside IV	EC_{50} = 15.4 μM/glucose-evoked podocyte injury inhibition	25
405	*In vitro*	EC_{50} = 3.80 μM/glucose-evoked podocyte injury inhibition	Astragaloside IV	EC_{50} = 15.4 μM/glucose-evoked podocyte injury inhibition	25
379 and **384–386**	*In vitro*	IC_{50} > 50 μM/α-glucosidase inhibition			109
AChE inhibitory activity					
39	*In vitro*	MIR = 12.5 μg/AChE inhibition	Galanthamine	MIR = 0.004 μg/AChE inhibition	21
220	*In vitro*	IC_{50} = 12.5 μg/AChE inhibition			6
221	*In vitro*	IC_{50} = 12.5 μg/AChE inhibition			6

Table 2 (*Contd.*)

Compounds	Models	Effect	Positive control	Effect	References
Anti-manic activity					
165	*In vitro*	IC_{50} = 12.5 mg mL^{-1}/anti-manic activity in *Drosophila*			13
Anti-tussive activity					
126	*In vivo*	88% Cough inhibition/citric acid activated Guinea pig cough model Interaction to δ-opioid receptor			65
250	*In vivo*	76% Cough inhibition/citric acid activated Guinea pig cough model			65
Anti-nociceptive activity					
The alkaloidal extract of *K. macrophylla*	*In vivo*	To decrease in the number of contortion and stretching *via* peripheral mechanism			130
Cardiovascular and vasorelaxant activities					
112	*In vivo*	To decrease arterial blood pressure and heart rate			131
208	*In vivo*	13% Relaxation occurred rat aorta ring			84
210	*In vivo*	24% Relaxation occurred rat aorta ring			84
211	*In vivo*	26% Relaxation occurred rat aorta ring			84
216	*In vivo*	28% Relaxation occurred rat aorta ring			84
219	*In vivo*	40% Relaxation occurred rat aorta ring			84
225	*In vivo*	41% Relaxation occurred rat aorta ring			84
227	*In vivo*	15% Relaxation occurred rat aorta ring			84
228	*In vivo*	37% Relaxation occurred rat aorta ring			84
229	*In vivo*	19% Relaxation occurred rat aorta ring			84
230	*In vivo*	19% Relaxation occurred rat aorta ring			84
239	*In vivo*	23% Relaxation occurred rat aorta ring			84

μg mL^{-1} against KB (VJ300) cells in the presence of 0.1 μg mL^{-1} vincristine. Subramaniam *et al.* (2007) reported that kopsiloscine A (**93**), rhazinilam (**409**), especially two alkaloids rhazinal (**407**) and rhazinicine (**408**), showed inhibition to both KB, KB (VJ300), and KB (VJ300) + 0.1 μg mL^{-1} vincristine.[32]

Dimeric alkaloid norpleiomutine (**282**) exhibited cytotoxicity to PC-3, HCT-116, MCF-7, A-549, KB (VJ300), especially in terms of KB (VJ300) + 0.1 μg mL^{-1} vincristine, better than its analogous dimer kopsoffinol (**289**).[19] This can be explained by the functionality of OH group at carbon C-19. Most *Kopsia* mersinines seem not to be anticancer agents. However, novel compounds **366–367** and **373–375** also established the significant cytotoxicity to reserve MDR in drug-resistant KB (VJ300) with the IC_{50} values of 3.2–11.2 μg mL^{-1}.[103] Valparicine (**446**) would be superior to the positive control vincadifformine in a cytotoxic assay against Jurkat cell growth.[10] In addition, this compound and arboloscine (**437**) showed positive signals to resist the growth of KB (VJ300) and KB (VJ300) + 0.1 μg mL^{-1} vincristine (Table 2).[10]

3.2. Anti-microbial activity

Nowadays, microbial resistance to well-known antibiotics has caused major concern about the treatment of infectious diseases. A vast amount of studies has recently been conducted to determine possible answers. Phytochemicals have been shown to exhibit antibacterial activity against sensitive and resistant infections through various approaches. To have a look at the IZ (inhibitory zone) and MIC values of *Kopsia* constituents (Table 2), compounds **43–47**, **48–53**, and **76** are not only potential anticancer molecules but also useful antimicrobial agents.[52,53] Especially, kopsiafrutine E (**47**) with the MIC values of 0.15–1.14 mM established a remarkable antimicrobial effect against twelve pathogenic microorganisms, including two Gram positive bacteria *Staphylococcus aureus* and *S. epidermidis*, five Gram negative bacteria *Escherichia coli*, *Enterobacter cloacae*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Shigella dysenteriae*, three fungi *Candida albicans*, *C. tropicalis*, and *C. glabrata*, and two oral pathogens *Streptococcus mutans* and *S. viridans*.[52] Likewise, compounds **48–49** showed strong antimicrobial activity with MIC values of less than 0.3 mM against seven bacteria *E. cloacae*, *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *S. aureus*, *S. dysenteriae*, and *S. epidermidis*.[53]

In another assessment, kopsiflorine (**74**) and kopsihainins D–F (**85–87**) showed suppression towards the Gram positive bacterium *Staphylococcus aureus* with IZ values ranging from 9.7 to 11.2 mm, but compounds **3**, **17**, **73**, **109**, **124**, **405**, and **406** were inactive.[12] In an antimicrobial assay against *E. coli*, *Erwinia carotovra*, *Bacillus subtilis*, *B. cereus*, and *S. aureus*, two best agents *N*-decarbomethoxykopsamine (**14**) and N_1-decarbomethoxy chanofruticosinic acid (**206**) were associated with the MIC values of 7.8–15.5 and 15.5–31.3 μg mL^{-1}, respectively.[7] These two molecules further showed antifungal activity against

Rhizoctonia solani, *Penicillium italicum*, *Fusarium oxysporum* f. sp. Cubense, and *F. oxysporum* f. sp. Niveum (Table 2).[7] Lastly, two eburnamines 19-hydroxy-(−)-eburnamonine (**267**) and phutdonginin (**297**) showed moderate activity against the growth of *E. coli* with the same MIC value of 32 μg mL^{-1}.[21]

3.3. Anti-inflammatory activity

Inflammation is a part of the complicated biological reaction of living bodies to harmful stimuli such as irradiation, physical injury, metabolic stress, and infection.[133–135] *K. officinalis* constituents are such useful agents to treat autoimmune diseases due to their inhibition of human T cell proliferation and proinflammatory cytokines.[16] Indeed, *K. officinalis* constituents decarbomethoxykopsine (**11**), *N*(4)-methylkopsininate (**170**), 12-methoxychanofruticosinic acid (**222**), and rhazinilam (**409**) inhibited T cell growth with the IC_{50} values of 25.4, 21.6, 27.8, and 1.0 μM, respectively.[16] The best molecule **409** also responded to the arrest in the G2/M phase of the T cell cycle and caused a decrease in IL-6 and IL-17 levels in activated T cells.[16]

The secretion of cytokines IL-1β and TNF-α or PGE2 levels has mainly caused inflammatory reactions. When LPS-stimulated RAW 264.7 cells, at the concentration of 5 μg mL^{-1}, kopsia C (**219**), methyl N_1-decarbomethoxychanofruticosinate (**225**), methyl 12-methoxychanofruticosinate (**228**), kopsiofficines I–J (**279–280**), (+)-*O*-methyleburnamine (**290**), (−)-*O*-methylisoeburnamine (**291**), and leuconodine D (**439**) have remarkable anti-inflammatory effects on IL-1β and TNF-α, and PGE2, and comparable with positive control dexamethasone at the concentration of 10 μg mL^{-1}.[75]

3.4. Anti-allergic and antidiabetic activities

Naturally occurring compounds have been recognized as potential antiallergic agents. In an experiment against histamine and β-hexosaminidase in RBL-2H3 cells, the IC_{10} values of 3.73–11.78 μg mL^{-1} were assigned to four alkaloids kopsilarutensinine (**90**), kopsinine (**126**), (−)-eburnamine (**257**), and (−)-tetrahydroalstonine (**448**).[66] In the same model against histamine and β-hexosaminidase in RBL-2H3 cells, in contrast to the MeOH extract of *K. arborea* leaves, the MeOH extracts of *K. larutensis* bark and root were found better than those of *K. arborea* bark and root (Table 2).[66,129]

For antidiabetic activity, among tested compounds for the high glucose-evoked podocyte injury inhibition, the EC_{50} values were orderly run as kopsinine **126** (3.0 μM) > leuconolam **405** (3.8 μM) > methyl 11,12-dimethoxychanofruticosinate **224** (10.2 μM) > 16α-hydroxy-19-oxoeburnamine **264** (12.0 μM) > reference compound astragaloside IV (15.4 μM) > 11-hydroxykopsilongine **29** (24.5 μM).[25] However, four pauciflorine derivatives 11,12-demethoxy-16-deoxypauciflorine (**379**) and kopsioffines A–C (**384–386**) failed to suppress enzyme α-glucosidase (IC_{50} > 50 μM).[109]

3.5. AChE inhibitory, anti-manic, anti-tussive, and anti-nociceptive activities

In Alzheimer's disease treatment based AChE inhibitory examination, kopsamine (**39**) has the minimum inhibitory requirement (MIR) value of 12.5 μg, as compared with that of the reference compound galanthamine (MIR 0.004 μg).[21] Meanwhile, two novel chanofruticosinates, kopsihainanines A–B (**220–221**), displayed weak AChE inhibitory activity with the respective IC_{50} values of 38.5 and 50.6 μM.[6] (−)-12-Methoxykopsinaline (**165**) with the IC_{50} value of 12.5 mg mL^{-1}, showed anti-manic activity in *Drosophila*.[13]

Kopsinine **126** (70 mg kg^{-1}, i.p.) and methyl N_1-decarbomethoxychanofruticosinate **225** (250 mg kg^{-1}, i.p.) exhibited 88 and 76% cough inhibition in the antitussive assays when citric acid activated guinea pig cough model.[65] In addition, antitussive effect of compound **126** was due to its interaction with δ-opioid receptors.[65]

The alkaloidal extract of *K. macrophylla* (400 mg kg^{-1}, p.o.) was responsible for a decrease in the number of contortions and stretching *via* the peripheral mechanism in anti-nociceptive assays when acetic acid stimulated pain in mice, but it has no effect in anti-pyretic assay.[130]

3.6. Cardiovascular and vasorelaxant activities

Cardiovascular disease (CVD) refers to a group of illnesses affecting the heart and blood arteries. CVD is the largest cause of death worldwide with 17.9 million deaths (32.1%) in 2015.[136] Drug discovery for CVD started from the 18th century at least.[137] To consider *Kopsia* constituents for cardiovascular treatment, at doses of 0.2–10.0 mg kg^{-1} intravenous injection, kopsingine (**112**) caused decreases in arterial blood pressure and heart rate when hypertensive mice were anesthetized.[123] However, kopsaporine (**42**) was reasonable for blood pressure increase, and kopsidine A (**67**) with the deletion of the methoxy group did not alter the responsible hypotension.[123]

Vasodilators can be used for cerebral vasospasm and hypertension treatments, as well as to enhance peripheral circulation.[138,139] Flavisiamines A, C, and D (**208** and **210–211**), kopreasin A (**216**), methyl 11,12-methylenedioxychanofruticosinate (**219**), methyl N_1-decarbomethoxychanofruticosinate (**225**), methyl 12-methoxy-N_1-decarbomethoxychanofruticosinate (**227**), methyl 12-methoxychanofruticosinate (**228**), methyl 11,12-methylenedioxy-N_1-decarbomethoxychanofruticosinate (**229**), methyl 11,12-methylenedioxy-N_1-decarbomethoxy-$\Delta^{14,15}$-chanofruticosinate (**230**), and prunifoline B (**239**) at the concentration of 3×10^{-5} M showed a moderate vasorelaxant effect of 14–41% when phenylephrine (3×10^{-7} M) precontracted rat aortic rings.[84]

4. Conclusion and future perspectives

To a certain extent, our comprehensive review establishes a panel of useful information on phytochemistry and pharmacology of the genus *Kopsia*. Since the 1950s, about nineteen *Kopsia* plants were used in phytochemical investigations, and more than four hundred seventy secondary metabolites have been isolated. Among 472 isolated compounds, monoterpene alkaloids (466 compounds) accounted for 98.73%. *Kopsia* monoterpene alkaloids have been fallen into about 30 structural skeletons, but aspidofractinines (204 compounds),

eburnamines (48 compounds), and chanofruticosinates (37 compounds) predominated over. Various compounds were isolated from *Kopsia* plants for the first time. Many chemical classes of isolated compounds, such as mersinines and pauciflorines, can be seen as newly alkaloidal classes and were useful for chemotaxonomy. Some metabolites, such as kopsamine (**39**), kopsinine (**126**), (−)-eburnamine (**257**), (+)-isoeburnamine (**274**), rhazinilam (**409**), and (−)-tetrahydroalstonine (**448**), are characteristic metabolites of genus *Kopsia*. It also evidenced that *Kopsia* plant extracts and isolated compounds have induced a variety of pharmacological results, *e.g.*, antimicrobial, anti-inflammatory, anti-diabetic, cardiovascular, vasorelaxant activities, especially cytotoxicity. With the great cytotoxic values, monoterpene alkaloids derived from *Kopsia* plants are promising anticancer agents in drug development programmes. However, studies on *in vivo* apoptotic mechanism, bioavailability, and metabolic approaches seem not available. To this end, no research was carried out to determine toxic effects of *Kopsia* plant extracts and their constituents. Therefore, it is necessary to deal with the extensive clinical studies to confirm the effects of *Kopsia* constituents on humans.

This review will be especially useful in offering fundamental insights into the medicinal usefulness of *Kopsia* plants. Furthermore, this evaluation can be used as a reference for clinical medication, long-term development, and plant consumption.

Abbreviations

HPLC	High performance liquid chromatography
MS	Mass spectrum
CC	Column chromatography
IC_{50}	Half-maximal inhibitory concentration
IZ	Inhibitory zone
MDR	Multidrug resistance
MIR	Minimum inhibitory requirement
MIC	Minimum inhibitory concentration
LPS	lipopolysaccharide
AChE	Acetylcholinesterase
NIH/3T3	Normal mouse fibroblast cells
HL-60	Human promyelocytic cells
HeLa	Human cervical cancer cells
HS-1, HS-4, SCL-1, and A-431	Dermatoma cells
BGC-823	Human gastric carcinoma cells
MCF-7	Human breast cancer cells
W-480	Colon cancer cells
HepG-2	Human hepatocellular carcinoma cells; SMMC-7721 cells
SGC-7901	Human gastric adenocarcinoma cells
SK-MEL-2	Human skin cancer cells
SK-OV-3	Ovarian cancer cells
A-549, 95-D, ATCC, H-446, H-460 and H-292, and SPCA-1	Lung cancer cells
HT-29 and HCT-116	Colorectal cancer cells
PC-3	Human prostate cancer cells
Jurkat	Human T lymphocyte cells
KB	Epidermoid carcinoma cells

Conflicts of interest

The authors declare no conflict of interest, financial or otherwise.

References

1 D. A. Williams, W. O. Foye and T. L. Lemke, *Natural products. Foye's principles of medicinal chemistry*, Lippincott Williams Wilkins, Philadelphia, 5th edn, 2002, ch. 1.
2 J. W. Kadereit and V. Bittrich, *Flowering Plants. Eudicots*, Springer, 2018.
3 J. Hu, X. Mao, L. Zhang, N. Jin, S. Yin, T. Peng and J. Shi, *Chem. Nat. Compd.*, 2019, **55**, 502–505.
4 T. S. Kam and O. S. Tan, *Phytochemistry*, 1990, **29**, 2321–2322.
5 T. S. Kam, P. S. Tan and C. H. Chuah, *Phytochemistry*, 1992, **31**, 2936–2938.
6 J. Chen, J. J. Chen, X. Yao and K. Gao, *Org. Biomol. Chem.*, 2011, **9**, 5334–5536.
7 J. Chen, M. L. Yang, J. Zeng and K. Gao, *Phytochem. Lett.*, 2014, **7**, 156–160.
8 S. K. Wong, J. S. Y. Yeap, C. H. Tan, K. S. Sim, S. H. Lim, Y. Y. Low and T. S. Kam, *Tetrahedron*, 2021, **78**, 131802.
9 T. He, Y. D. Wang, F. R. Li, S. Y. He, Q. M. Cui, Y. P. Liu, T. R. Zhao and G. G. Cheng, *Biochem. Syst. Ecol.*, 2020, **93**, 104159.
10 K. H. Lim, O. Hiraku, K. Komiyama, T. M. Koyano, M. Hayashi and T. S. Kam, *J. Nat. Prod.*, 2007, **70**, 1302–1307.
11 T. Z. Xie, Y. L. Zhao, W. G. Ma, Y. F. Wang, H. F. Yu, B. W. Wang, H. Z. Xin, P. F. Zhu, Y. P. Liu and X. D. Luo, *Chin. J. Org. Chem.*, 2020, **40**, 679–687.
12 Y. Yang, W. J. Zuo, Y. X. Zhao, W. H. Dong, W. L. Mei and H. F. Dai, *Planta Med.*, 2012, **78**, 1881–1884.
13 H. Zhou, H. P. He, N. C. Kong, Y. H. Wang, X. D. Liu and X. J. Hao, *Helv. Chim. Acta*, 2006, **89**, 515–519.
14 J. J. Zheng, Y. L. Zhou and Z. H. Huang, *Acta Chim. Sin.*, 1989, **2**, 168–175.
15 T. S. Kam, K. M. Sim, T. Koyano and K. Komiyama, *Phytochemistry*, 1999, **50**, 75–79.
16 T. Zeng, X. Y. Wu, S. X. Yang, W. C. Lai, S. D. Shi, Q. Zou, Y. Liu and L. M. Li, *J. Nat. Prod.*, 2017, **80**, 864–871.
17 T. S. Kam and K. M. Sim, *Phytochemistry*, 1998, **47**, 145–147.
18 T. S. Kam, G. Subramaniam and W. Chen, *Phytochemistry*, 1999, **51**, 159–169.
19 W. S. Yap, C. Y. Gan, K. S. Sim, S. H. Lim, Y. Y. Low and T. S. Kam, *J. Nat. Prod.*, 2016, **79**, 230–239.

20 A. Guggisberg, T. R. Govindachari, K. Nagarajan and H. Schmid, *Helv. Chim. Acta*, 1963, **46**, 679–683.
21 S. Cheenprachaa, A. Raksat, T. Ritthiwigrom and S. Laphookhieo, *Nat. Prod. Commun.*, 2014, **9**, 1441–1443.
22 C. Y. Gan, K. Yoganathan, K. S. Sim, Y. Y. Low, S. H. Lim and T. S. Kam, *Phytochemistry*, 2014, **108**, 234–242.
23 G. Subramaniam, O. Hiraku, M. Hayashi, T. Koyano, K. Komiyama and T. S. Kam, *J. Nat. Prod.*, 2008, **71**, 53–57.
24 M. Kitajima, M. Anbe, N. Kogure, S. Wongseripipatana and H. Takayama, *Tetrahedron*, 2014, **70**, 9099–9106.
25 Z. W. Wang, C. R. Guo, Y. L. Lin, H. J. Yan, Y. Mu, Y. L. Geng, W. Liua and X. Wang, *Fitoterapia*, 2019, **137**, 104258.
26 M. O. Hamburger, G. A. Cordell, K. Likhitwitayawuid and N. Ruangrungsi, *Phytochemistry*, 1988, **27**, 2719–2723.
27 C. Kan-Fan, T. Sevenet, H. A. Hadi, M. Bonin, J. C. Quirion and H. P. Husson, *Nat. Prod. Lett.*, 1995, **7**, 283–290.
28 X. Z. Feng, C. Kan, H. P. Husson, P. Potie, S. K. Kan and M. Lounasmaa, *J. Nat. Prod.*, 1984, **47**, 117–122.
29 J. Zhu, A. Guggisberg and M. Hesse, *Planta Med.*, 1986, **52**, 63–64.
30 T. S. Kam, Y. M. Choo, W. Chen and J. X. Yao, *Phytochemistry*, 1999, **52**, 959–963.
31 T. S. Kam and Y. M. Choo, *Phytochemistry*, 2004, **65**, 2119–2122.
32 G. Subramaniam, O. Hiraku, M. Hayashi, T. Koyano, K. Komiyama and T. S. Kam, *J. Nat. Prod.*, 2007, **70**, 1783–1789.
33 T. Varea, C. Kan, F. Remy, T. Sevene, J. C. Quirion, H. P. Husson and H. A. Hadi, *J. Nat. Prod.*, 1993, **56**, 2166–2169.
34 T. S. Kam, K. Yoganathan and S. L. Mok, *Phytochemistry*, 1997, **45**, 789–792.
35 K. Ahmad, Y. Hirasawa, A. E. Nugroho, A. H. A. Hadi and H. Morita, *Heterocycles*, 2012, **86**, 1611–1619.
36 K. Ahmad, Y. Hirasawa, A. E. Nugroho, A. H. A. Hadi, K. Takeya, N. F. Thomas, K. Awang, H. Morita, T. S. Ping and M. A. Nafiah, *Open Conf. Proc. J.*, 2013, **4**, 75–82.
37 A. R. Battersby, J. C. Byrne, H. Gregory and S. P. Popli, *J. Chem. Soc. C*, 1967, **9**, 813–819.
38 A. R. Battersby and H. Gregor, *J. Am. Chem. Soc.*, 1963, **16**, 22–32.
39 R. P. Glover, K. Yoganathan and M. S. Butler, *Magn. Reson. Chem.*, 2005, **43**, 483–485.
40 N. Ruangrungsi, K. Likhitwitayawuid, V. Jongbunprasert, D. Ponglux, N. Aimi, K. Ogata, M. Yasuoka, J. Haginiwa and S. Sakai, *Tetrahedron Lett.*, 1987, **28**, 3679–3682.
41 M. Sekiguchi, Y. Hirasawa, K. Zaima, T. C. Hoe, K. L. Chan and H. Morita, *Heterocycles*, 2008, **76**, 867–874.
42 C. Q. Yang, Y. F. Ma and Y. G. Chen, *Chem. Nat. Compd.*, 2017, **53**, 595–597.
43 S. H. Lim, K. M. Sim, Z. Abdullah, O. Hiraku, M. Hayashi, K. Komiyama and T. S. Kam, *J. Nat. Prod.*, 2007, **70**, 1380–1383.
44 T. S. Kam, K. Yoganathan, C. H. Chuah and C. Wei, *Phytochemistry*, 1993, **32**, 1343–1346.
45 T. S. Kam, K. Yoganathan and C. H. Chuah, *Tetrahedron Lett.*, 1993, **34**, 1819–1822.
46 T. S. Kam, T. M. Lim, G. Subramaniam, Y. M. Tee and K. Yoganathan, *Phytochemistry*, 1990, **50**, 171–175.
47 T. S. Kam and K. Yoganathan, *Phytochemistry*, 1996, **42**, 539–541.
48 G. Subramaniam and T. S. Kam, *Helv. Chim. Acta*, 2008, **91**, 930–937.
49 Halimatussakdiah, U. Amna, S. P. Tan, K. Awang, A. M. Ali, M. A. Nafiah and K. Ahmad, *Int. J. Pharm. Sci. Rev. Res.*, 2015, **31**, 89–95.
50 Y. L. Zhou, Z. H. Huang, L. Y. Huang, J. P. Zhu, C. M. Li and G. L. Wu, *Acta Chim. Sin.*, 1985, **1**, 82–83.
51 T. S. Kam, L. Arasu and K. Yoganathan, *Phytochemistry*, 1996, **43**, 1385–1387.
52 S. Y. Long, C. L. Li, J. Hu, Q. J. Zhao and D. Chen, *Fitoterapia*, 2018, **129**, 145–149.
53 W. Q. Chia, Y. H. Jianga, J. Hub and J. Pan, *Fitoterapia*, 2018, **130**, 259–264.
54 Y. Wanga, L. Hang, L. Jiaoc, H. Liud and F. Li, *Fitoterapia*, 2017, **121**, 53–57.
55 T. Liu, J. Hu, J. X. Li and M. W. Chen, *J. Asian Nat. Prod. Res.*, 2020, **22**, 724–731.
56 X. D. Chen, J. Hu, J. X. Li and F. S. Chi, *J. Asian Nat. Prod. Res.*, 2020, **22**, 1024–1030.
57 K. Homberger and M. Hesse, *Helv. Chim. Acta*, 1982, **65**, 2548–2557.
58 T. S. Kam, K. Yoganathan and K. H. Chuah, *Phytochemistry*, 1997, **45**, 623–625.
59 S. K. Wong, S. P. Wong, K. S. Sim, S. H. Lim, Y. Y. Low and T. S. Kam, *J. Nat. Prod.*, 2019, **82**, 1902–1907.
60 T. S. Kam and G. Subramaniam, *Nat. Prod. Lett.*, 1998, **11**, 131–136.
61 M. C. Rho, M. Toyoshima, M. Hayashi, T. Koyano, G. Subramaniam, T. S. Kam and K. Komiyama, *Planta Med.*, 1999, **65**, 307–310.
62 T. S. Kam and Y. M. Choo, *Tetrahedron Lett.*, 2003, **44**, 1317–1319.
63 T. S. Kam and Y. M. Choo, *Helv. Chim. Acta*, 2004, **78**, 991–998.
64 J. Chen, X. Li, N. Li, J. Lu, X. Xu, H. Duan and L. Qin, *Chem. Nat. Compd.*, 2012, **48**, 834–835.
65 M. J. Tan, C. Yin, C. P. Tang, C. Q. Ke, G. Lin and Y. Ye, *Planta Med.*, 2011, **77**, 939–944.
66 M. S. Shahari, A. F. Ismail, E. Kumolosasi, N. F. Rajab and K. Husain, *J. Innovations Pharm. Biol. Sci.*, 2017, **4**, 80–86.
67 A. Bhattacharya, A. Chatterjee and P. B. Bose, *J. Am. Chem. Soc.*, 1949, **71**, 3370–3372.
68 K. Awang, M. Pais, T. Sevenet, H. Schaller, A. M. Nasir and A. H. A. Hadi, *Phytochemistry*, 1991, **30**, 3164–3167.
69 X. Z. Feng, C. Kan, P. Potier, S. K. Kan and M. Lounasmaa, *J. Med. Plants Res.*, 1983, **84**, 280–282.
70 T. S. Kam, P. S. Tan and C. Wei, *Phytochemistry*, 1993, **33**, 921–924.
71 T. S. Kam, K. H. Lim, K. Yoganathan, M. Hayashi and K. Komiyama, *Tetrahedron*, 2004, **60**, 10739–10745.
72 W. S. Yap, C. Y. Gan, Y. Y. Low, Y. M. Choo, T. Etoh, M. Hayashi, K. Komiyama and T. S. Kam, *J. Nat. Prod.*, 2011, **74**, 1309–1312.

73 T. S. Kam, K. Yoganathan and C. H. Chuah, *Tetrahedron Lett.*, 1994, **35**, 4457–4460.
74 T. S. Kam, K. Yoganathan and C. Wei, *J. Nat. Prod.*, 1996, **59**, 1109–1112.
75 T. Z. Xie, Y. L. Zhao, J. J. He, L. X. Zhao, X. Wei, Y. P. Liub and X. D. Luo, *Fitoterapia*, 2020, **143**, 104547.
76 T. S. Kam and K. Yoganathan, *Phytochemistry*, 1997, **46**, 785–787.
77 T. S. Kam and P. S. Tan, *Phytochemistry*, 1995, **39**, 469–471.
78 K. H. Lim, Y. Y. Low, G. H. Tan, T. M. Lim and T. S. Kam, *Helv. Chim. Acta*, 2008, **91**, 1559–1566.
79 K. Awang, O. Thoison, A. H. A Hadi, M. Païs and T. Sévenet, *Nat. Prod. Lett.*, 1993, **3**, 283–289.
80 T. S. Kam and K. Yoganathan, *Nat. Prod. Lett.*, 1997, **10**, 69–74.
81 K. Awang, T. Sévenet, M. Païs and A. H. A. Hadi, *J. Nat. Prod.*, 1993, **56**, 1134–1139.
82 K. H. Lim and T. S. Kam, *Phytochemistry*, 2008, **69**, 558–561.
83 M. Sekiguchi, Y. Hirasawa, K. Zaima, T. H. Hoe, K. L. Chan and H. Morita, *Heterocycles*, 2008, **75**, 2283–2288.
84 K. Zaima, Y. Matsuno, Y. Hirasawa, A. Rahman, G. Indrayanto, N. C. Zaini and H. Morita, *Heterocycles*, 2008, **75**, 2535–2540.
85 J. F. Wang, Y. Wang, H. L. Wang, C. B. Xu and H. T. Wang, *J. Asian Nat. Prod. Res.*, 2018, **21**, 227–233.
86 W. S. Chen, S. H. Li, A. Kirfel, G. Win and E. Breitmaier, *Liebigs Ann. Chem.*, 1981, **1981**, 1886–1892.
87 T. S. Kam, P. S. Tan, P. Y. Hoong and C. H. Chuah, *Phytochemistry*, 1993, **32**, 489–491.
88 K. Husain, I. Jantan, N. Kamaruddin, I. M. Said, N. Aimia and H. Takayama, *Phytochemistry*, 2001, **57**, 603–606.
89 K. Husain, I. Jantan, I. M. Said, N. Aimi and H. Takayama, *J. Asian Nat. Prod. Res.*, 2003, **5**, 63–67.
90 Y. Wu, M. Kitajima, N. Kogure, Y. Wang, R. Zhang and H. Takayama, *Chem. Pharm. Bull.*, 2010, **58**, 961–963.
91 T. S. Kam, T. M. Lim, Y. M. Choo and G. Subramaniam, *Tetrahedron Lett.*, 1998, **39**, 5823–5826.
92 S. Uzir, A. M. Mustapha, A. H. A. Hadi, K. Awang, C. Wiart, J. F. Gallard and M. Pais, *Tetrahedron Lett.*, 1997, **38**, 1571–1574.
93 T. S. Kam, G. Subramaniam and C. Wei, *Nat. Prod. Lett.*, 1998, **12**, 293–298.
94 C. Kan, J. R. Deverre, T. Sevenet, J. C. Quirion and H. P. Husson, *Nat. Prod. Lett.*, 1995, **7**, 275–281.
95 Y. Wu, M. Kitajima, N. Kogure, Y. Wang, R. Zhang and H. Takayama, *J. Nat. Med.*, 2009, **63**, 283–289.
96 Y. Wu, M. Suehiro, N. Takahashi, M. Kitajima, N. Kogure, R. Zhang and H. Takayama, *Chem. Nat. Prod.*, 2008, **50**, 47–52.
97 Y. Wu, M. Kitajima, N. Kogure, R. Zhang and H. Takayama, *Tetrahedron Lett.*, 2008, **49**, 5935–5938.
98 N. Kogure, Y. Suzuki, Y. Wu, M. Kitajima, R. Zhang and H. Takayama, *Tetrahedron Lett.*, 2012, **53**, 6523–6526.
99 Y. Murakami, T. Koyama, Y. Suzuki, N. Takahashi, Y. Wu, N. Kogure, R. Zhang, M. Kitajima and H. Takayama, *Chem. Nat. Prod.*, 2018, **56**, 327–332.
100 M. Kitajima, T. Koyama, Y. Wu, N. Kogure, R. Zhan and H. Takayama, *Nat. Prod. Commun.*, 2015, **10**, 49–51.
101 M. Kitajima, M. Nakazawa, Y. Wu, N. Kogure, R. P. Zhang and H. Takayama, *Tetrahedron*, 2016, **72**, 6692–6696.
102 N. Kogure, R. Tokuda, S. Tooriyama, M. Nakazawa, T. Koyama, Y. Okamoto, Y. Mimori, Y. Wu, R. P. Zhang, M. Kitajima and H. Takayama, *Chem. Nat. Prod.*, 2017, **24**, 139–144.
103 G. Subramaniam, Y. M. Choo, O. Hiraku, K. Komiyama and T. S. Kam, *Tetrahedron*, 2008, **64**, 1397–1408.
104 T. S. Kam and G. Subramaniam, *Tetrahedron Lett.*, 2004, **45**, 3521–3524.
105 T. S. Kam, G. Subramaniam and T. M. Lim, *Tetrahedron Lett.*, 2001, **42**, 5977–5980.
106 G. Subramaniam and T. S. Kam, *Tetrahedron Lett.*, 2007, **48**, 6677–6680.
107 G. Subramaniam, T. S. Kam and S. W. Ng, *Acta Crystallogr., Sect. E: Struct. Rep. Online*, 2003, **59**, o555–o557.
108 Y. Y. Low, G. Subramaniam, K. H. Lim, R. C. S. W. Wong, T. Robinson and T. S. Kam, *Tetrahedron*, 2009, **65**, 6873–6876.
109 Z. W. Wang, X. J. Shi, Y. Mu, L. Fang, Y. Y. Chen and L. Lin, *Fitoterapia*, 2017, **119**, 8–11.
110 T. S. Kam, K. Yoganathan, T. Koyano and K. Komiyama, *Tetrahedron Lett.*, 1996, **37**, 5765–5768.
111 T. S. Kam, K. Yoganathan and C. Wei, *Nat. Prod. Lett.*, 1996, **8**, 231–235.
112 T. S. Kam, K. Yoganathan and C. Wei, *J. Nat. Prod.*, 1997, **60**, 673–676.
113 K. Homherger and M. Hesse, *Helv. Chim. Acta*, 1984, **67**, 237–248.
114 Y. Wu, M. Suehiro, M. Kitajima, T. Matsuzaki, S. Hashimoto, M. Nagaoka, R. Zhang and H. Takayama, *J. Nat. Prod.*, 2009, **72**, 204–209.
115 K. Awang, T. Sévenet, A. H. A. Hadi, B. David and M. Païs, *Tetrahedron Lett.*, 1992, **33**, 2493–2496.
116 T. S. Kam, K. Yoganathan and H. Y. Li, *Tetrahedron Lett.*, 1996, **37**, 8811–8814.
117 T. S. Kam, K. Yoganathan, K. H. Y. Li and N. Harada, *Tetrahedron*, 1997, **53**, 12661–12670.
118 K. H. Lim and T. S. Kam, *Helv. Chim. Acta*, 2007, **90**, 31–35.
119 K. H. Lim, Y. Y. Low and T. S. Kam, *Tetrahedron Lett.*, 2006, **47**, 5037–5039.
120 K. H. Lim, K. Komiyama and T. S. Kam, *Tetrahedron Lett.*, 2007, **48**, 1143–1145.
121 M. Kitajima, Y. Murakami, N. Takahashi, Y. Wu, N. Kogure, R. P. Zhang and H. Takayama, *Org. Lett.*, 2014, **16**, 5000–5003.
122 L. Y. Shan, T. C. Thing, T. S. Ping, K. Awang, N. M. Hashim, M. A. Nafiah and K. Ahmad, *J. Chem. Pharm. Res.*, 2014, **6**, 815–822.
123 G. B. Marini-Bettòlo, *Ann. Ist. Super. Sanita*, 1968, **4**, 489–500.
124 J. H. Jiang, W. D. Zhang and Y. G. Chen, *Trop. J. Pharm. Res.*, 2015, **14**, 2325–2344.
125 K. Jewers, D. F. G. Pusey, S. R. Shama and Y. Ahmad, *Planta Med.*, 1980, **38**, 359–362.

126 A. R. Araujo, C. Kascheres, F. Fujiwara and A. J. Marsaioli, *Phytochemistry*, 1984, **23**, 2359–2363.
127 T. Sevenet, L. Allorge, B. David, K. Awang, A. Hamid, C. Kan-Fan, J. C. Quirion, F. Remy, H. Schaller and L. E. Teo, *J. Ethnopharmacol.*, 1994, **41**, 1471–1483.
128 B. Qin, Y. Wang, X. Wang and Y. Jia, *Org. Chem. Front.*, 2021, **8**, 369–383.
129 M. S. Shahari, K. Husain, E. Kumolosasi and N. F. Rajab, *Nat. Prod.: Indian J.*, 2017, **13**, 1–7.
130 W. Reanmongkol, S. Subhadhirasakul, S. Thienmontree, K. Thanyapanit, J. Kalnaowakul and S. Sengsui, *Songklanakarin J. Sci. Technol.*, 2005, **27**, 509–516.
131 S. L. Mok, K. Yoganathan, T. M. Lim and T. S. Kam, *J. Nat. Prod.*, 1998, **61**, 328–332.
132 G. Z. Li, Y. H. Hu, D. Y. Li, Y. Zhang, H. L. Guo, Y. M. Li, F. Chen and J. Xu, *Neurotoxicology*, 2020, **81**, 161–171.
133 N. T. Son, L. T. Anh, D. T. T. Thuy, N. D. Luyen, T. T. Tuyen, H. T. M. Duong and N. M. Ha, *Nat. Prod. Commun.*, 2021, **16**, 1–6.
134 N. T. Son, L. T. Anh, D. T. T. Thuy, N. D. Luyen, T. T. Tuyen and P. T. Hai, *Z. Naturforsch., C: J. Biosci.*, 2022, **77**, 207–218.
135 N. T. T. Linh, N. T. T. Ha, N. T. Tra, L. T. T. Anh, N. V. Tuyen and N. T. Son, *Mini-Rev. Med. Chem.*, 2021, **21**, 273–287.
136 H. Wang, M. Naghavi, C. Allen, R. M. Barber, Z. A. Bhutta, A. Carter, *et al.*, *Lancet*, 2016, **388**, 1459–1544.
137 F. B. Alberti, *Bull. Roy. Coll. Surg. Engl.*, 2013, **95**, 168–169.
138 S. Saponara, M. Durante, O. Spiga, P. Mugnai, G. Sgaragli, T. T Huong, P. N. Khanh, N. T. Son, N. M. Cuong and F. Fusi, *Br. J. Pharmacol.*, 2016, **173**, 292–304.
139 F. Fusi, M. Durante, G. Sgaragli, P. N. Khanh, N. T. Son, T. T. Huong and N. M. Cuong, *Planta Med.*, 2015, **81**, 298–304.