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## REVIEW

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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.<sup>1</sup> 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.<sup>2</sup> This genus, containing about 30 species, is widely distributed in Southeast Asia, China, Australia, and some islands of the Western Pacific.<sup>3,4</sup> *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.<sup>4</sup> In Malaysia, the roots of

# 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 antimicrobial. anti-inflammatory, anti-allergic. anti-diabetic. anti-manic. anti-nociceptive acetylcholinesterase (AChE) inhibitory, cardiovascular, and vasorelaxant activities, especially cytotoxicity.

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.<sup>2,5</sup> *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.<sup>6,7</sup>

Recently, the search for bioactive molecules from the genus *Kopsia* has drawn lots of interest to natural product chemists and pharmacists.<sup>8-13</sup> 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- $\beta$ -carboline 465, and and ranginine 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 5,22dioxokopsane (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.<sup>5-7,9-11,13-19,21-25,28,29,32,36,42,43,48,51,65,66,68-72</sup>

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,<sup>9-11</sup> but aspidofractinine-1,3-dicarboxylic acid (4) was only detected in K. officinalis stem.<sup>11</sup> (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 Ncarbomethoxy-11-hydroxy-12-methoxykopsinaline (5) and Ncarbomethoxy-11-methoxy-12-hydroxykopsinaline (6) were two new metabolites in nature.<sup>14-16</sup> 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 decarbomethoxyisokopsine (12), decarbomethoxykop-(11), sifine (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.<sup>22,30</sup> 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 15a and 17a-hydroxylation of kopsinine, respectively (Fig. 1). In the meantime, the structure of the new metabolite 35 is closely related to kopsinine by 17a-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

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

No.	Compounds	Species	References
Asp	idofractinines		
1	Arbolodinine A	<i>K. arborea</i> stem bark	8
2	Aspidofractinine	K. arborea stem bark, K. hainanensis twig and leaf, K. officinalis stem	9-11
3	$(2\beta,5\beta)$ -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-bydroxy-12-	<i>K griffithii</i> leaf <i>K officinalis</i> twig leaf and fruit	14-16
3	methowskongingling	K. grijjiniti Rai, K. ojjitinitis twig, Rai and fruit	14 10
6	N Carbomathows 11 mathows 12	V officinalis fruit	14
0	N-Carboniethoxy-11-methoxy-12-	K. Officinaiis II alt	14
_			
7	N(1)-Carbomethoxy-11, 12-dimethoxykopsinaline	K. griffithii leat, K. officinalis truit	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	K. fruticosa leaf, K. officinalis leaf and twig	16 and 20
	(demethoxycarbonylkopsin)		
12	Decarbomethoxyisokopsine	K. fruticosa leaf	20
13	Decarbomethoxykopsifine	K. arborea twig, K. dasyrachis stem, K. officinalis stem, K. pauciflora	11, 18, 19, 21 and 22
	5 1	stem and stem bark	, , , ,
14	N(1)-Decarbomethoxykonsamine	<i>K</i> arhorea stem bark <i>K</i> hainanensis stem and leaf <i>K</i> nauciflora leaf	7 10 22 and 23
11	III) Decarboniculoxykopsannic	K. and real, K. putting losf	7, 10, 22 and 25
15	N. Downeth companyl 10 weath combined	K. singupurensis icai	16 04 and 05
15	N <sub>a</sub> -Demetnoxycarbonyi-12-metnoxykopsine	K. jasminifiora 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	11, 12, 14, 16, 19 and
		root, stem, twig and fruit, <i>K. pauciflora</i> stem bark	27-29
18	11,12-Dimethoxykopsamine	K. dasyrachis leaf	30
19	11,12-Dimethoxykopsinaline	<i>K. pauciflora</i> stem bark	22
20	16 <i>-epi-</i> Kopsinine	K. fruticosa stem bark, K. officinalis stem, K. singapurensis leaf	11, 31 and 32
21	16- <i>epi</i> -Kopsinilam	<i>K. jasminiflora</i> stem bark	24
22	16- <i>epi</i> -17 $\alpha$ -Hydroxy- $\Delta^{14,15}$ -kopsinine	K. teoi stem bark and leaf	33
23	14.15-β-Epoxykopsingine	K. teoi leaf	34
24	N(1)-Formylkonsininic acid	K. singanurensis root	35 and 36
25	N(1)-Formylkonsininic acid- $N(4)$ -oxide	K singapurensis root	35 and 36
25	Fruticocomine	K. Singupurchass 1000	20 and 27-41
20	Emitionsiamine A	K. fruitosa Rai, K. jasminijora Rai	20 and 57 41
27	Protice size	K. jruulosu leal	41 20 am J 27 42
28		K. jusminijioru leai, K. jruitosu leai, K. ojjitinuiis twig	20 and 37-42
29	11-Hydroxykopsilongine	<i>k. officinalis</i> 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.	10, 31 and 36
		<i>singapurensis</i> bark	
34	17α-Hydroxykopsinine	K. teoi stem bark	43
35	$17\alpha$ -Hydroxy- $\Delta^{14,15}$ -kopsinine	K. singapurensis stem bark and leaf; K. teoi stem and stem bark	23, 32, 34 and 44-48
36	Iasminiflorine	K. jasminiflora leaf	40
37	Kopsamidine A	<i>K. arborea</i> stem bark	10
38	Kopsamidine B	<i>K</i> arborea stem bark	10
30	Kopsamine	K arborea twig and stem hark K dasurachis stem and leaf K	10 13-15 17-10 21
33	Ropsamme	<i>K. unbolcu</i> twig and stein bark, <i>K. uusyruuns</i> stein and ical, <i>K.</i>	10, 10, 10, 10, 10, 10, 21, 10, 20, 10, 10, 10, 10, 10, 10, 10, 10, 10, 1
		officiality stem, root, leaf and mult, K. griffiant leaf, K. pulcytora	25, 50, 50, 45, 49 and
	T	stem and stem bark, K. singapurensis leaf and root, K. teoi stem bark	50
40	Kopsamine <i>N</i> -oxide	<i>K. arborea</i> stem bark; <i>K. dasyrachis</i> stem and leaf, <i>K. officinalis</i> fruit,	10, 14, 15, 17–19, 30,
		K. griffithii leaf, K. pauciflora stem, K. singapurensis root	36, 49 and 51
41	Kopsanone	K. arborea stem bark; K. fruticosa stem bark, K. jasminiflora stem	10, 14, 19, 22, 24, 29
		bark, K. hainanensis stem bark, K. pauciflora stem and stem bark, K.	and 31
		officinalis fruit	
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
10	Ropolatiunite O	K fruticosa aerial part	52
/	Konsiafrutine D	N. UMULING ACTAL DATE	34
40	Kopsiafrutine D	K frutiener aprial part	50
40	Kopsiafrutine D Kopsiafrutine E	<i>K. fruticosa</i> aerial part	52
40 47 48	Kopsiafrutine D Kopsiafrutine E Kopsiahainanin A	<i>K. fruticosa</i> aerial part <i>K. hainanensis</i> twig and leaf	52 53
40 47 48 49	Kopsiafrutine D Kopsiafrutine E Kopsiahainanin A Kopsiahainanin B	<i>K. fruticosa</i> aerial part <i>K. hainanensis</i> twig and leaf <i>K. hainanensis</i> twig and leaf	52 53 53

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	<i>K. arborea</i> aerial part	56
63	Kopsidarine	K. singapurensis leaf	48
64	Kopsidasine	K. dasvrachis leaf	57
65	Kopsidasine-N-oxide	K dasyrachis leaf	57
66	Konsidasinine	K. dasyrachis leaf	57
67	Kopsidine A	K. singanurensis leaf K teai leaf and stem bark	34 43 45 48 and 58
67	Kopsidine R	K. singupullisis leaf, K. Lebi leaf and stelli bark	24, 45, 45, 40 and 50
60	Kopsidine C	K. $icol \ ical$ K. singanuransis leaf K. taai leaf	34, 45 and 58
70	Kopsidine C. Nevide	K. singapurensis leaf	54, 46 anu 56
70	Kopsidine D	K. singapurensis leaf K tasi leaf	48
/1	Kopsidine D	K. singapurensis lear, K. teol lear	32, 34 and 58
72	Kopsidine E	<i>K. arborea</i> bark	59
73	Kopsifine	<i>K. arborea</i> stem bark, <i>K. dasyrachis</i> stem, <i>K. hainanensis</i> twig, <i>K. officinalis</i> stem, <i>K. pauciflora</i> stem and stem bark, <i>K. singapurensis</i> root	10–12, 18, 22, 49 and 60
74	Kopsiflorine	<i>K. arborea</i> stem bark; <i>K. dasyrachis</i> stem, <i>K. hainanensis</i> stem and leaf, <i>K. officinalis</i> leaf	7, 10, 12, 13, 18 and 61
75	Kopsiflorine <i>N</i> (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 sterio	12
86	Kopsihainin E	K hainanensis twig	12
80 87	Kopsihainin E	K. hainanansis twig	12
07	Kopsilasminino	K. taai stom bark	12
88	Kopsijasminine	K. <i>teol</i> stem bark	43
89	Kopsijasmine	K. Jasminifiora 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	10, 13, 15, 1/-19, 21,
		and stem bark, K. officinalis leaf, K. pauciflora stem	22 and 32
		K. singapurensis leaf	
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	Konsiloscine I	K. singanurensis leaf	23
102	Konsimaline A	K singapurensis leaf	23
10/	Konsimaline B	K. singapuronsis leaf	23
105	Konsimaline C	K. singapuransis leaf	23 12
105	Kopsimalina D	K. singuputensis leaf	20 22
100	Kopsimaline D	K. singupurensis lear	23
107	Kopsimaline E	K. singapurensis leat	23
108	s Kopsimaline F	K. singapurensis leaf	48

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
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 lea	f 32–34, 44, 45 and 48
113 Kopsinginine	<i>K. teoi</i> stem and stem bark	34, 43–45 and 47
114 Kopsinginol	<i>K. teol</i> stem and stem bark	34, 45 and 47
115 Kopsinidine A	<i>K. arborea</i> stem bark	10
116 Kopsiniaine B	K. arborea stem bark	10 11 12 16 24 20 and
117 Ropsmine acid (Ropsmie acid)	K. numunensis stem bark, K. <i>Jusminijiora</i> stem bark, K. <i>Ojjicinalis</i>	11, 13, 10, 24, 29 and
118 Konsinicine	K singanurensis leaf	23
119 Kopsinidine A	K arhorea stem hark K officinalis leaf	25 10 and 25
120 Kopsinidine B	<i>K. arborea</i> stem bark, <i>K. officinalis</i> leaf	10 and 25
121 Kopsinidine C	K. officinalis leaf and twig	16 and 25
122 Kopsinidine D	K. officinalis leaf and twig	16
<b>123</b> Kopsinidine E	K. officinalis leaf and twig	16
124 Kopsinilam	K. hainanensis stem bark and twig, K. jasminiflora stem bark, K.	11, 12, 14, 16, 24 and
1	officinalis stem, twig, leaf and fruit	29
125 Kopisininate	K. hainanensis stem and leaf	7
126 Kopsinine	K. arborea twig and stem bark, K. dasyrachis stem, K. fruticosa stem	n 7, 9–11, 13–19, 21–25,
	bark, K. jasminiflora stem bark, K. grandifolia stem bark, K. griffith	ii 28, 29, 32, 36, 42, 43,
	leaf and stem bark, K. hainanensis leaf, stem, stem bark and twig, K	. 48, 50, 51, 64–66 and
	larutensis stem, stem bark and leaf, K. officinalis root, stem, twig, leaf and fruit, K. singapurensis stem bark and leaf, K. pauciflora	68-72
	stem, stem bark and leaf, K. teoi stem bark	
<b>127</b> Kopsinine- <i>N</i> (4)-oxide	K. dasyrachis stem, K. griffithii stem bark, K. hainanensis stem and leaf, K. officinalis fruit and leaf, K. pauciflora stem, K. singapurensi bark	7, 13, 15, 18, 25 and 36 s
128 Kopsinine methochloride	<i>K. officinalis</i> 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	<i>K. teoi</i> 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 D	K. officinalis stem	11
141 Kopsiofficine E	K. officinalis stem	11
142 Kopsiofficine E	K. officinalis stem	11
143 Kopsiofficine I	K. officinalis stem	75
145 Kopsofinone	K. ojjuninus sun K. singanuransis leaf	73
146 Konsonoline	<i>K. teoi</i> stem bark	43
147 Kopsorinine	K. fruticosa leaf and stem bark	31
<b>148</b> Labadinine A	K. nauciflora leaf	76
<b>149</b> Lahadinine B	K. pauciflora leaf	76
150 Mersingine A	K. singapurensis leaf. K. teoi leaf	34. 49 and 74
<b>151</b> Mersingine B	<i>K. teoi</i> leaf	34 and 74
<b>152</b> N(1)-Methoxycarbonyl-11,12-	K. arborea stem bark, K. pauciflora stem	10, 19 and 51
dimethoxykopsinaline	· 1 J	
153 N(1)-Methoxycarbonyl-11,12-	K. officinalis leaf, twig, stem and root, K. pauciflora stem and leaf	11, 16, 42, 51, 69 and
methoxylenedioxykopsinaline		76
<b>154</b> $N(1)$ -Methoxycarbonyl-11,12-methylenedioxy- $\Delta^{16,17}$ -kopsinine	K. profunda stem	4
155 $N(1)$ -Methoxycarbonyl-12-methoxy- $\Delta^{16,17}$ - kopsinine	<i>K. griffithii</i> leaf, <i>K. pauciflora</i> stem, <i>K. profunda</i> stem and leaf, <i>K. tea</i> stem bark	<i>i</i> 4, 17, 19, 43, 51 and 77
<b>156</b> $N(1)$ -Methoxycarbonyl-12-methoxykopsinaline	K. officinalis root, stem, twig, leaf and fruit, K. pauciflora stem	11, 16, 25, 51 and 69

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No. Compounds	Species	References
<b>157</b> $N(1)$ -Methoxycarbonyl-11,12-methylenedioxy- $\Delta^{16,17}$ -kopsinine $N(4)$ oxide	K. profunda stem and leaf	77
<b>158</b> <i>N</i> (1)-Methoxycarbonyl-12-hydroxy- $\Delta^{16,17}$ - kopsinine	K. pauciflora stem, K. profunda stem and leaf	19 and 77
<b>159</b> $N(1)$ -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
<b>162</b> 11-Methoxykopsilongine <i>N</i> (4)-oxide	K. dasyrachis stem	18
<b>163</b> 11-Methoxy-12-hydroxy-kopsinol	<i>K. teoi</i> leaf	34
<b>164</b> 12-Methoxykopsidasinine	K. griffithu leat	17 12 16 42 and 60
<b>165</b> (-)-12-Methoxykopsinaline	K. officinalis leaf and twig	13, 16, 42 and 69
100 12-methoxykopsine	K. aubieu lear, K. jusminifiora stelli bark, K. officinalis foot and stelli K. pauciflora leaf	, 11, 22, 24 and 78
167 12-Methoxy-10-demethoxykopsidasinine	K. griffithii leaf, K. pauciflora stem	15, 51
168 12-Methoxypleiocarpine	<i>K. dasyrachis</i> stem and leaf, <i>K. hainanensis</i> stem and leaf, <i>K. griffithis</i> leaf, <i>K. pauciflora</i> stem	i 7, 15, 17–19 and 30
<b>169</b> (–)-Methylenedioxy-11,12-kopsinaline	K. arborea twig	7
170 <i>N</i> (4)-Methylkopsininate	<i>K. officinalis</i> leaf and twig	16
1/1 11,12-Methylenedioxykopsaporine	<i>K. singapurensis</i> bark, <i>K. teol</i> stem, stem bark and leaf	33, 34 and 79
172 (-)-11,12-Methylenedioxykopsinaline	<i>K. adsyrachis</i> stem, <i>K. officinalis</i> root, stem, lear, twig and fruit	11, 16, 18, 25 and 69
175 11,12-Methylenedioxykopsine	<i>K. grijjunii</i> stem bark, <i>K. ojjuniuis</i> stem, twig and lear	11, 15 and 10
	<i>pauciflora</i> stem bark	10, 11, 18 and 22
175 Nitaphylline	K. teol leaf	34, 46 and 80
176 5-Oxokopsinic acid	<i>K. jasminijiora</i> stem bark, <i>K. ojjuinans</i> twig and lear	16 allu 24
177 Faucidactine R	K. puulijoin stem bark	19 10 and 19
179 Paucidactine C	<i>K. arborea</i> stem bark, <i>K. pauciflora</i> stem bark	10 and 19
180 Paucidactine D	<i>K. pauciflora</i> stem bark	19
181 Paucidactine E	<i>K. pauciflora</i> stem bark	19
182 Paucidactinine	K. pauciflora stem bark	19
183 Paucidisine	<i>K. pauciflora</i> stem bark	19
184 Paucidirinine	<i>K. pauciflora</i> stem bark	19
185 Paucidirisine	<i>K. pauciflora</i> stem bark	19 11 and 10
186 Pauciduridine	K. officinalis stem, K. paucifiora stem bark	11 and 19
187 Paucifinine-Movide	K. pauciflora leaf	22 anu 76 76
189 Plejocarpine	<i>K. arborea</i> stem bark. <i>K. dasvrachis</i> stem and leaf. <i>K. griffithii</i> leaf. <i>K.</i>	10, 14, 15, 17–19, 25
	officinalis fruit, K. pauciflora stem,	and 30
<b>190</b> Pleiocarpine <i>N</i> -oxide	K. pauciflora stem	19
<b>191</b> Pseudokopsinine	<i>K. pauciflora</i> leaf and stem bark	22
<b>192</b> 5,6-Secokopsinine	<i>K. jasminiflora</i> stem bark	24
<b>193</b> Singapurensine A	K. singapurensis heat	36 79
195 Singapurensine B	K. singapurensis bark	79
<b>196</b> Singapurensine C	K. singapurensis bark	79
<b>197</b> Singapurensine D	K. singapurensis bark	79
<b>198</b> 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
<b>201</b> (–)-Venalstonine	<i>K. arborea</i> stem bark, <i>K. fruticosa</i> stem bark, <i>K. lapidilecta</i> stem and bark, <i>K. singapurensis</i> 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	K officinglis loof and trip	16
205 Unanoiruticosinic acid	K. officinalis leaf and twig	10
200 N <sub>1</sub> -Decarbonnethoxy chanoiruticosinic acid 207 11 12-Dimethoxydanuphylline	K. <i>numunensis</i> siem and lear	/ 3
<b>208</b> Flavisiamine A (prunifoline D)	K. arborea leaf. K. flavida leaf	82-84
<b>209</b> Flavisiamine B	<i>K. flavida</i> leaf	83

No. Compounds	Species	References
<b>210</b> Flavisiamine C	K. arborea leaf, K. flavida leaf	83 and 84
<b>211</b> 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	<i>K. flavida</i> leaf	41
<b>214</b> 12-Hydroxylprunifoline A	K. lancibracteolata stem	85
215 12-Hydroxylprunifoline C	<i>K. lancibracteolata</i> stem	85
216 Kopreasin A	<i>K. arborea</i> leaf	84
217 Kopsia A (metnyi chanofruticosinate)	<i>k. aasyrachis</i> lear, <i>k. hainanensis</i> stem and lear, <i>k. officinalis</i> lear, twig, and stem, <i>K. pauciflora</i> leaf	7, 13, 16, 22, 25, 30, 75 and 86
<b>218</b> Kopsia B (des- <i>N</i> -(methoxycarbonyl) chanofruticosin-methyleste)	K. officinalis leaf	86
219 Kopsia C (6,7-methylendioxychanofruticosin- methylester or methyl 11,12- methylenedioxychanofruticosinate)	<i>K. arborea</i> leaf and stem bark, <i>K. dasyrachis</i> leaf, <i>K. officinalis</i> stem and leaf, twig and leaf, <i>K. pauciflora</i> stem bark and leaf	10, 16, 22, 30, 75, 84, 86 and 87
<b>220</b> Konsibainanine $\Delta$	K hainanensis leaf and stem	6
221 Kopsihainanine B	K. hainanensis leaf and stem	6
<b>222</b> 12-Methoxychanofruticosinic acid	K. officinalis leaf and twig	16
223 Methyl chanofruticosinate <i>N</i> (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
<b>225</b> 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
<b>226</b> Methyl $N_1$ -decarbomethoxy chanofruticosinate $N(4)$ -oxide	K. hainanensis stem and leaf	7
<b>227</b> Methyl 12-methoxy- $N_1$ -	K. arborea leaf, K. flavida leaf	83, 84, 88 and 89
<b>228</b> Methyl 12-methoxychanofruticosinate	K. arborea leaf and stem bark, K. flavida leaf, K. officinalis stem, twig	10, 16, 22, 75, 82, 84,
<b>229</b> Methyl 11,12-methylenedioxy- <i>N</i> <sub>1</sub> -	<i>K. arborea</i> stem bark and leaf, <i>K. dasyrachis</i> leaf, <i>K. flavida</i> leaf, <i>K.</i>	10, 16, 22, 25, 30, 42,
decarbomethoxychanofruticosinate	officinalis leaf, twig and stem, K. pauciflora leaf and stem bark	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
<b>231</b> Methyl (2β,11β,12β,19α)-6,7-didehydro-8,21-dioxo- 11,21-cycloaspidospermidine-2-carboxylate	K. officinalis leaf	13
<b>232</b> Methyl 3-oxo-12-methoxy- $N_1$ -decarbomethoxy- 14 15-didebudroghanofrutioosinate	<i>K. flavida</i> leaf	89
<b>233</b> Methyl 3-oxo-11.12-methylenedioxy-N <sub>4</sub> -	K. flavida leaf	89
decarbomethoxy-14,15- didebydrochanofruticocinate		
$2.34 \ \Delta^{1,2}$ -Methyldemethoxycarbonylchanofruticosinate	K. officinalis leaf	25
235 11.12-Methylenedioxychanofruticosinic acid	K. officinalis leaf and twig	16
236 3-Oxo-11,12-dimethoxy-N <sup>1</sup> -decarbomethoxy-14,15- didebydrochanofarticocinate	<i>K. fruticosa</i> 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 N(4)-ovide	K. arborea twig and stem bark, K. officinalis stem and truit	10, 11, 14 and 21
240 vincaunomine N(4)-0xiue	K. OJICHUHS SICH	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

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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
<b>255</b> (–)-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. terenggapensis bark	l 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
<b>260</b> (+)-Eburnamonine <i>N</i> (4)-oxide	<i>K. larutensis</i> leaf and stem	5 and 70
261 (–)-Eburnamonine	<i>K. jasminiflora</i> stem bark	24
262 (–)-O-Ethyleburnamine	K. arborea aerial part, K. larutensis stem	70 and 90
263 (+)-Ethylisoeburnamine	K. arborea aerial part	90
<b>264</b> 16α-Hydroxy-19-oxoeburnamine	K. officinalis leaf	25
<b>265</b> 16β-Hydroxy-19-oxoeburnamine	K. officinalis leaf	25
<b>266</b> (+)-19( <i>R</i> )-Hydroxyeburnamine	K. dasyrachis stem	18 and 93
267 19-Hydroxy-(–)-eburnamonine	K. arborea twig, K. larutensis leaf, K. officinalis twig	5, 7 and 42
<b>268</b> (–)-19( <i>R</i> )-Hydroxyisoeburnamine	K. dasyrachis stem, K. pauciflora stem and stem bark	19, 22 and 93
269 (+)-(19R)-19-Hydroxyeburnamine	K. officinalis leaf, K. pauciflora stem and stem bark	13, 19 and 22
270 (–)-19( <i>R</i> )-Hydroxyeburnamenine	K. pauciflora stem	19
271 (–)-(19 <i>R</i> )-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- $\Delta^{14}$ -vicamone	K. jasminiflora stem bark	24
274 (+)-Isoeburnamine	<i>K. arborea</i> aerial part, <i>K. dasyrachis</i> stem, <i>K. hainanensis</i> stem bark <i>K. larutensis</i> leaf, stem and stem bark, <i>K. teoi</i> stem bark and leaf, <i>K</i> officinalis leaf, <i>K. pauciflora</i> stem and stem bark, <i>K. terengganensis</i> 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	/5
282 Kopsomnol	K. aasyrachis stem, K. paucifiora stem	19 and 93
284 Larutenine	K. larutensis stem bark 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	<i>K. pauciflora</i> 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	n 18, 19, 22, 27 and 51
290 (+)-O-Methyleburnamine	K. officinalis stem	75
<b>291</b> (–)- <i>O</i> -Methylisoeburnamine ( <i>O</i> -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
<b>294</b> (–)-19-Oxoisoeburnamine	<i>K. pauciflora</i> 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
<b>299</b> Terengganensine B	K. terengganensis bark	92
$300 \Delta^{-}$ -Vicamone	<i>K. jasminijlora</i> stem bark	24
301 Yunnanoffine C	к. officinalis leat	25

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No. Compounds	Species	References
Akuammilines		
302 Akuammidine	K arborea stem bark K singanurensis root stem bark and leaf	10 23 32 48 and 49
202 Akuammiline	K. urboreu steni bark, K. singupurensis 1000, steni bark and real	10, 23, 32, 48 and 49
<b>204</b> Alguammilina $N(A)$ ovide	K. mucrophytiu bark, K. teol stelli aliu stelli bark	27, 54, 45, 45 and 47
205 vk Alguermicine	K. grujunu stem bark	15
<b>305</b> $\psi$ -Akuanningine <b>206</b> Descetulaluonmiline (rhazimel)	K. Juucosu stelli Dalk K. davarrai stom bark, K. griffithij loof and stom bark, K. macronhulla	31 15 17 02 07 24 45
306 Deacetylakuaininnine (mazimor)	<i>K. ueverrei</i> stem bark, <i>K. grijjunu</i> lear and stem bark, <i>K. mucrophytu</i>	13, 17, 23, 27, 34, 45, 47
	bark, K. singapurensis stem bark, K. teol stem and stem bark	47 and 94
307 Dregamine	K. macrophyua bark	27
308 16- <i>ept</i> -akuaminine	<i>K. singapurensis</i> leaf, stem bark and root, <i>K. teol</i> stem bark	23, 32, 36, 43 and 48
309 16-ept-deacetylakuammiline	<i>K. aeverrei</i> stem bark, <i>K. griffithil</i> stem bark, <i>K. fruticosa</i> stem bark,	15, 23, 31, 32, 34, 36
	<i>K. singupurensis</i> bark, stem bark and lear, <i>K. teol</i> stem and stem bark	43, 48 and 94
310 16-ept-deacetylakuammiline-N(4)-oxide	K. griffitnii stem bark, K. singapurensis bark	15 and 36
311 16-Hydroxymetnyl-pielocarpamine	K. aeverrei stem bark, K. fruticosa stem bark, K. singapurensis stem	23, 31, 43, 36 and 94
	bark and bark, K. teol stem bark	
312 <i>N</i> -Methylpleiocarpamine	K. singapurensis root	36
<b>313</b> 5-Methoxystrictamine	K. hainanensis twig and leaf	9
314 Rhazimal	<i>K. arborea</i> stem bark	10
<b>315</b> Rhazinaline <i>N</i> (4)-oxide	K. griffithii stem bark	15
316 Rhazinoline	<i>K. arborea</i> stem bark	10
317 Picralinal	K. hainanensis twig and leaf	9
318 Picramicine	K. fruticosa stem bark, K. singapurensis stem bark	23 and 31
<b>319</b> Pleiocarpamine	K. dasyrachis stem, K. deverrei stem bark, K. fruticosa stem bark, K.	18, 31, 36, 43 and 94
	singapurensis bark, K. teoi stem bark	
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	23, 31-34, 36, 43 and
	stem, stem bark and leaf	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	<i>K. arborea</i> stem bark	8
335 (E)-Condylocarpine	K. arborea aerial part, K. pauciflora leaf	22 and 95
<b>336</b> ( <i>E</i> )-Condylocarpine <i>N</i> -oxide	<i>K. arborea</i> aerial part	95
337 14α-Hydroxycondylocarpine	K. deverri stem bark, K. singapurensis stem bark	23 and 94
<b>338</b> 14α-Hydroxy- <i>N</i> (4)-methylcondylocarpine	K. singapurensis root	35 and 36
<b>339</b> 14( <i>S</i> )-Hydroxy-19( <i>R</i> )-methoxytubotaiwine	<i>K. jasminiflora</i> stem bark	24
<b>340</b> Isocondylocarpine	<i>K. arborea</i> aerial part	95
<b>341</b> Isocondylocarpine <i>N</i> -oxide	<i>K. arborea</i> aerial part	95
<b>342</b> Kopsivunnanine A	K. arborea aerial part, K. officinalis aerial part	96 and 97
343 Kopsiyunnanine I	<i>K. arborea</i> aerial part	98 and 99
344 Konsiyunnanine I1	<i>K. arborea</i> aerial part	99 and 100
	<i>K arborea</i> aerial part	99 and 100
45 Kopsiyunnanine I2	is alborou ucrial pare	
345 Kopsiyunnanine J2 346 Kopsiyunnanine L	K arborea aerial part	101 and 109
345 Kopsiyunnanine J2 346 Kopsiyunnanine L 347 Kopsiyunnanine M	K. arborea aerial part	101 and 102
345 Kopsiyunnanine J2 346 Kopsiyunnanine L 347 Kopsiyunnanine M 348 Kopsiyunnanine F1	<i>K. arborea</i> aerial part <i>K. arborea</i> aerial part <i>K. arborea</i> aerial part	101 and 102 101 and 102
<ul> <li>345 Kopsiyunnanine J2</li> <li>346 Kopsiyunnanine L</li> <li>347 Kopsiyunnanine M</li> <li>348 Kopsiyunnanine F1</li> <li>349 Kopsiyunnanine F2</li> </ul>	K. arborea aerial part K. arborea aerial part K. arborea aerial part	101 and 102 101 and 102 95 95

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No. Compounds	Species	References
<b>351</b> 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
53 19(S)-Methoxytubotaiwine	K. arborea aerial part and stem bark, K. hainanensis twig	10, 12 and 95
54 Mossambine	K. singapurensis stem bark	23
355 Precondylocarpine	K. pauciflora leaf	22
<b>356</b> Tubotaiwine	<i>K. arborea</i> aerial part, <i>K. hainanensis</i> stem and stem bark	29, 64 and 95
t <b>emmadenine</b> 57 Stemmadenine	K. nauciflora leaf	2.2
57 Stellindeenne		22
Mersinines	K singerungin last	102
58 Mersidasine A	K. singupurensis leaf	103
59 Mersidasine B	K. singapurensis leaf	103
60 Mersidasine C	K. singapurensis leaf	103
61 Mersidasine D	K. singapurensis leaf	103
62 Mersidasine E	K. singapurensis leaf	103
63 Mersidasine F	K. singapurensis leaf	103
64 Mersidasine G	K. singapurensis leaf	103
65 Mersifoline A	K. singapurensis leaf	103
66 Mersifoline B	K. singapurensis leaf	103
67 Mersifoline C	K. singapurensis leaf	103
68 Mersilongine	K singanurensis leaf	23 and 104
69 Mersiloscine	K singanurensis leaf	103 and 105
270 Mersiloscine A	K. singapurensis leaf	103 anu 103
70 Mershosche A	K. singupurensis leaf	103
/1 Mersiloscine B	K. singapurensis leaf	103
72 Mersinaline	K. singapurensis leaf	23 and 106
73 Mersinine A	K. fruticosa leaf, K. singapurensis leaf	103 and 105, 10
374 Mersinine B	K. singapurensis leaf	103 and 105
375 Mersinine C	K. singapurensis leaf	103
76 Mersiphyllines A	K. singapurensis leaf	108
577 Mersiphyllines B	K. singapurensis leaf	108
78 Mersirachine	K. singapurensis leaf	23 and 106
Pauciflorines		
<b>379</b> 11.12-Demethoxy-16-deoxypauciflorine	K. officinalis stem and leaf	109
<b>80</b> 20-Deoxykopsijasminilam	K jasminiflora leaf	40
181 Konsiarborines C	<i>K arborea</i> aerial part	56
82 Konsijasminilam	K. iasminiflora leaf	40
$^{02}$ $\Lambda^{14}$ Kongijagminilam	K. jasminiflora loof	40
$\Delta - Kopsijasinininani$	K. jusminijioru leal	40
84 Kopsionine A	<i>K. officinalis</i> stem and lear	109
85 Kopsioffine B	K. officinalis stem and leaf	109
<b>386</b> Kopsioffine C	K. officinalis stem and leaf	109
87 Pauciflorine A	K. pauciflora leaf	110
888 Pauciflorine B	K. pauciflora leaf	110
89 Pauciflorine C	K. pauciflora leaf	22
90 Paucifoline	K. pauciflora leaf	22
kytanthines		
91 Kinabalurine A (kinabalurine)	K. pauciflora leaf	111 and 112
<b>92</b> Kinabalurine B	K. pauciflora leaf	112
93 Kinabalurine C	K. pauciflora leaf	112
94 Kinabalurine D	K nauciflora leaf	112
95 Kinabalurine F	K nauciflora leaf	112
95 Kinabalurine E 06 Kinabalurine E	K. pauciflora leof	112
90 Kinabalullile F	K. puutijioru ieai	112
9/ Kinabalurine G	K. aasyrachis leat	30
98 Kopsilactone	K. macrophylla bark	27
99 Kopsirachine	K. dasyrachis leaf	30 and 113
400 Kopsone	K. macrophylla bark	27
Rhazinilams		
<b>01</b> 5,21-Dihydrorhazinilam	K. arborea stem bark, K. singapurensis stem bark and leaf	10, 23 and 48
02 Kopsiyunnanine C1	K. arborea aerial part, K. officinalis aerial part	96 and 114
<b>103</b> Kopsiyunnanine C2	K. arborea aerial part, K. officinalis aerial part	96 and 114

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No. Compounds	Species	References
<b>404</b> 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 x 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 409 Rhazinilam	<i>K. arborea</i> stem bark, <i>K. dasyrachis</i> stem, <i>K. singapurensis</i> root <i>K. arborea</i> aerial part and stem bark, <i>K. officinalis</i> leaves and twigs <i>K. pauciflora</i> leaves and stem bark, <i>K. singapurensis</i> leaf, bark and stem bark, <i>K. teoi</i> stem, stem bark and leaf	10, 18, 49 and 60 , 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
<b>420</b> Lundurine B	K. tenuis leaf	71
<b>421</b> Lundurine C	K. tenuis leaf	71
<b>422</b> Lundurine D	K. tenuis leaf	71
423 Tenuisine A	K. tenuis leaf	116 and 117
<b>424</b> Tenuisine B	K. tenuis leaf	71, 116 and 117
425 Tenuisine C	K. tenuis leaf	71, 116 and 117
<b>426</b> 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
<b>431</b> 16( <i>R</i> )-19,20- <i>E</i> -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
<b>436</b> Kopsiyunnanine B	K. arborea aerial part, K. officinalis aerial part	96 and 97
Leuconoxines		_
437 Arboloscine	<i>K. arborea</i> stem bark	10 and 118
438 Arboloscine A	K. pauciflora leaf	22
439 Leuconodine D	K. officinalis stem	75
<b>440</b> Leuconodine F (6-oxoleuconoxine)	K. griffithii leaf, K. pauciflora leaf	22 and 43
441 Leuconoxine	<i>K. arborea</i> stem bark, <i>K. griffithii</i> leaf and stem bark, <i>K. pauciflora</i> stem, stem bark and leaf, <i>K. singapurensis</i> stem bark, <i>K. teoi</i> stem bark	15, 17, 19, 22, 23 and 43
<b>442</b> 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 <i>N</i> -oxide	<i>K. arborea</i> stem bark	10
446 Valparicine	K. arborea stem bark	119 and 120
Alstonines		
447 Oxayohimban-16-carboxy acid	K. officinalis stem	75
<b>448</b> (–)-Tetrahydroalstonine	<i>K. arborea</i> stem bark, <i>K. dasyrachis</i> stem, <i>K. griffithii</i> leaf, <i>K. officinalis</i> root, twigs and leaves, <i>K. larutensis</i> stem bark and leaf, <i>K.</i>	10, 15, 17–19, 23, 25, 32, 42, 43, 66 and 69

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Table 1 (Contd.)

No. Compounds	Species	References
	pauciflora stem, stem bark and leaf, K. singapurensis stem bark; K.	
	<i>teoi</i> 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	<i>K. arborea</i> aerial part, <i>K. hainanensis</i> twig and leaf, <i>K. officinalis</i> root, <i>K. pauciflora</i> leaf	9, 22, 69 and 114
Arbophyllinines		
453 Arbophyllinine A	<i>K. arborea</i> bark	59
<b>454</b> Arbophyllinine B	<i>K. arborea</i> bark	59
Arboflorines		
455 Arboflorine	K. arborea stem bark	10
<b>456</b> 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		
<b>467</b> β-Amyrin	K. singapurensis leaf and bark	122
<b>468</b> β-Amyrin acetate	K. singapurensis leaf and bark	122
<b>469</b> 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.<sup>10,40</sup>

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.<sup>52</sup> 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.<sup>53,54</sup> 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.<sup>55</sup> From *K. arborea* aerial part, the new compound kopsiarborines A (**62**) was isolated.<sup>56</sup> 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.<sup>57</sup> 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-

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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).<sup>33,34,43–45,73,74,80</sup> 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).<sup>23,32,48</sup> 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.<sup>43,66</sup> 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.<sup>18,20,38,39,41,67</sup> 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.<sup>10</sup>

Phytochemical analysis aided by NMR structural elucidation on the CHCl<sub>3</sub> and *n*-BuOH extracts of *K. officinalis* leaf and twig has resulted in the isolation of eight new compounds kop-(121 - 123),N(1)-methoxycarbonyl-11,12sinidines C-E methoxylenedioxykopsinaline (153), N(1)-methoxycarbonyl-12methoxykopsinaline (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).<sup>16</sup> 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 ( $\delta_{\rm C}$ 181.6 ppm in CD<sub>3</sub>OD).<sup>7</sup> 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 vunnanoffines 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-11,12methylenedioxy- $\Delta^{16,17}$ -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.<sup>3,6,7,10,13,16,22,25,30,41,42,65,75,82-89</sup> From Table 1, kopsia A (217), kopsia C (219), methyl 11,12-dimethoxychanofruticosinate (224),methyl N<sub>1</sub>-decarbomethoxychanofruticosinate (225), methyl 12-methoxychanofruticosinate (228), methyl 11,12-methylenedioxy-N1-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).<sup>13,16,86</sup> 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.<sup>6,7</sup> 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).<sup>3</sup> The MeOH extract of *K. flavida* leaf consisted of serial new alkaloids type chanofruticosinates flavisiamines A–F (208–213).<sup>41,83</sup> 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).<sup>82,84</sup> 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.<sup>85</sup>

Regarding aspidospermines, the acidic EtOH extract of *K. pauciflora* leaf contained aspidospermine (242), and its (+)-1,2dehydro derivatives (243).<sup>22</sup> 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).<sup>90</sup> Similarly, new compound kopsiofficine G (245), together with two known ones, vincadifformine (247) and vincadifformine *N*(4)-oxide (248) represented for *K. officinalis* stem.<sup>11</sup>

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).<sup>13,30,65,78,91</sup> 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*.<sup>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.</sup> (–)-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.<sup>5,13,18,19,22,29,33,51,68,70,90,92,93</sup>

(-)-Demethylnorpleiomutine (253), (-)-eburnaminol (258), (-)-O-ethyleburnamine (262), 19-hydroxy-(-)-eburnamonine (267), (-)-19(*R*)-hydroxyisoeburnamine (268), (+)-(19*R*)-19hydroxyeburnamine (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),



(–)-eburnamonine (261), (+)-ethylisoeburnamine (263), 16 $\alpha$ hydroxy-19-oxoeburnamine (264), 16 $\beta$ -hydroxy-19oxoeburnamine (265), melohenine B (287), (–)-methyleburnamine (288), (+)-O-methyleburnamine (290), and O-methyl-16*epi*-vincanol (295), and  $\Delta^{14}$ -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.* 



*officinalis, K. singapurensis*, and *K. teoi* were main resource of these phyto-constituents.<sup>9,10,15-17,23,27,31,32,34-36,43,45,47-49,94</sup> 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*.<sup>10,23,27,32,34,43,45,47-49</sup> 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.<sup>15</sup>  $\psi$ -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.<sup>9,10,15,16,27,31,36</sup> Lastly, two new metabolites, rhazinoline (316) and singaporentinidine (322), were purified from the extracts of *K. arborea* stem bark, *K. singapurensis* root, respectively.<sup>10,35</sup>

A list of four alkaloidal sarpagines **323–326** has been updated in Table 1 and Fig. 4.<sup>9,27,50</sup> 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*.<sup>9</sup> Perivine (**324**) and tabernaemontanine (**325**) were two known sarpagines derived from *K. officinalis* root and stem and *K. macrophylla* bark, respectively.<sup>27,50</sup>

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.<sup>23,32,34,36,43,48,49</sup> 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.<sup>32,48</sup> 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.<sup>23,31-34,36,43,48</sup>



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*.<sup>8,10,12,22–24,29,35,36,64,94–102</sup> 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.<sup>8</sup> Compound 335 is a known compound,<sup>22,95</sup> but its 14 $\alpha$ -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.<sup>35,94</sup> Mossambine (354) was another new *strychnos* found in *K. singapurensis* stem bark.<sup>23</sup> *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 (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.<sup>24,29,64,95</sup> Stemmadenine (**357**) from *K. pauciflora* leaves was the only stemmadenine detected in the genus *Kopsia*.<sup>22</sup>

## 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).<sup>23,103–108</sup> 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.<sup>103</sup> Their stereo-chemistry 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**).<sup>23,106,108</sup>

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.<sup>22,40,56,109,110</sup>



Fig. 6 Mersinines and pauciflorines from genus Kopsia.

Besides aspidofractinines, the MeOH extract of *K. jasmini-flora* leaf has associated with the presence of three novel pauciflorines 20-deoxykopsijasminilam (**380**), kopsijasminilam (**382**), and  $\Delta^{14}$ -kopsijasminilam (**383**).<sup>40</sup> 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.<sup>109</sup> Pauciflorines A–B (**387–388**) reached 0.22 and 0.03 g kg<sup>-1</sup> in *K. pauciflora* leaf.<sup>110</sup> 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.<sup>22</sup> 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.<sup>123</sup> 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.<sup>27,30,112,113</sup> Two publications in 1996 and 1997 by Kam and partners successfully reported the structures of serial new skytanthines kinabalurines



A-F (**391–396**) from *K. pauciflora* leaves.<sup>111,112</sup> while their following congener kinabalurine G (**397**) was derived from *K. dasyrachis* leaf.<sup>30</sup> 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.<sup>113</sup> 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.<sup>27</sup> 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.<sup>124</sup> It was then isolated from the shrub of the other Apocynaceae plant *Rhazya stricta* as well as other organisms.<sup>125</sup> 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.<sup>13,16,22,23,25,32-34,36,45,47,48,114</sup> 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.<sup>7,9,12,15,17,22,23,25,32</sup> As shown in Table 1, known compound 5,21-dihydrorhazinilam (**401**) existed in *K. arborea* stem bark and *K. singapurensis* stem bark and leaves.<sup>10,23,48</sup> 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**).<sup>96,114</sup> *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.<sup>10,12,18,32,49,60,87</sup> 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.<sup>72</sup> 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*.<sup>15,17</sup> The MeOH extract of *K. hainanensis* twig and leaf consisted of two aspidospermas, corynantheol (**428**) and dihydrocorynantheol (**430**).<sup>9</sup> 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*.<sup>15,17,22</sup> 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.*<sup>126</sup> 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<sub>3</sub>–MeOH is appropriate to isolate alkaloidal catharinensines.<sup>22</sup> 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.<sup>22</sup> 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.<sup>96,97</sup>

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.<sup>15,17,19,22,23,43</sup> 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.<sup>10,21,118</sup> 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**.<sup>22</sup> 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.<sup>22,43,75</sup>

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.<sup>10,118,119</sup>

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.<sup>75</sup> 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.<sup>10,15,17–19,22,23,25,32,42,43,66</sup> Compound 449, a pseudoindoxyl derivative of compound 448, was identified to be a new constituent from the acidic EtOH extract of *K. pauciflora* leaves.<sup>22</sup>

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.<sup>9,22,69,114</sup> However, kopsiyunnanines D and H (450–451) from *K. arborea* aerial part were confirmed to be two new analogs.<sup>90,114</sup>

## 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).<sup>59</sup> 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.<sup>10,96,99,121</sup> Besides the main constituents, the EtOH extract of K. pauciflora leaves has composed of a new component, and ransinine 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.<sup>10</sup> It was then further found in K. pauciflora leaves and K. singapurensis stem bark.22,23 Two final alkaloids, a new alkaloid type, azepanefused tetrahydro-\beta-carboline kopsiyunnanine K (465) and a known alkaloid type and ranginine (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  $\beta$ -amyrin (467),  $\beta$ -amyrin acetate (468),  $\beta$ -amyrone (469), lupeol (470), lupeol acetate (471), and one sterol stigmasterol (472) (Table 1 and Fig. 10).<sup>122</sup> 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.<sup>127,128</sup> 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.<sup>49</sup> Among them, kopsifine (**73**) induced the lowest  $CD_{50}$  value of 0.9 µg mL<sup>-1</sup> against HL-60 cells in referencing with the positive control vincristine ( $CD_{50}$  **1.8** µg mL<sup>-1</sup>).<sup>49</sup>

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<sub>50</sub> values of 7.3–9.5  $\mu$ M.<sup>52</sup> Meanwhile, its congeners kopsiafrutines C-D (45–46) containing a hydroxyl group at carbon C-15 have shown to associate with the respective IC<sub>50</sub> values of 10.3–12.5 and 11.8–13.8  $\mu$ M, but kopsiafrutines A–B (43–44) and kopsifoline A (76) did not inhibit cancer cell growth (IC<sub>50</sub> > 20  $\mu$ M).<sup>52</sup> In the same way, the following new aspido-fractinines kopsiahainanins A–B (48–49) with a lactone bridge have induced the respective IC<sub>50</sub> values of 9.4–11.7 and 12.2–15.9  $\mu$ M against A-549, BGC-823, HepG-2, HL-60, MCF-7, SMMC-7721, and W-480 cells.<sup>53</sup> However, four new analogous kopsiahainanins C–F (50–53) accompanied by the IC<sub>50</sub> values of >20  $\mu$ M.<sup>53</sup>

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<sub>50</sub> values of  $\leq 10 \ \mu$ M.<sup>54</sup> Similarly, in the N(4)-oxide group, new alkaloid 237 possessed the IC<sub>50</sub> values from 7.2 to 8.9  $\mu M$  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  $\mu M).^{85}$ 

The new metabolite kopsia officines C (61) showed the IC<sub>50</sub> values of <10  $\mu$ M 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<sub>50</sub>  $\leq$  20  $\mu$ M) and 60 (IC<sub>50</sub> > 20  $\mu$ M).<sup>55</sup> 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<sub>50</sub> values ranging from 1.3 to 9.6  $\mu$ g mL<sup>-1</sup>, while arbolodinines A and C (1 and 334) failed to do so.<sup>8</sup>

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

Vincristine, a renowned chemotherapy medication, is usually used in combining with other drugs to treat many types of cancers.<sup>132</sup> 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 ( $10 \mu g m L^{-1}$ ) showed reversal of multiple drug resistance (MRD) by suppressing the bound of [3H]azidopine to *P*-glycoprotein.<sup>61</sup> Alkaloidal compounds **88**, **102–107**, **411**, **413**, **417**, **434**, and **438** exhibited no appreciable cytotoxic activity against KB (VJ300) cells.<sup>22,23,43,72</sup> However, they possessed IC<sub>50</sub> 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 acti	ivity				
39	In vitro	$CD_{50}$ $>$ 60 $\mu g~mL^{-1}/NIH/3T3$ and HeLa cells $CD_{50}=$ 6.9 $\mu g~mL^{-1}/HL$ -60 cells	Vincristine	$CD_{50} > 60 \ \mu g \ mL^{-1}/NIH/3T3 \ cells$ $CD_{50} = 1.8 \ \mu g \ mL^{-1}/HL-60 \ cells$	49
40	<b>T</b>	$c_{\rm D} = c_{\rm D} = 1$ (NIII) (2772) (11, c_{\rm D} = 1) (11, 1) (11, 1)	<b>TT</b> <sup>1</sup>	$CD_{50} = 0.4 \ \mu g \ mL^{-1}/HeLa \ cells$	10
40	In vitro	$CD_{50} > 60 \ \mu g \ mL^{-7}/NIH/313$ , HL-60 and HeLa cells	vincristine	$CD_{50} > 60 \ \mu g \ mL^{-1}/MH/313 \ cells$	49
				$CD_{50} = 1.8 \ \mu g \ \text{mL}^{-1}/\text{HeL} \text{ a cells}$	
13	In vitro	$IC_{ro} = 33.7 \mu M/HS-1$ cells	Adiamycin	$IC_{ro} = 17.8  \mu M/HS-1$ cells	52
10	111 01110	$IC_{50} = 28.4 \ \mu M/HS-4 \ cells$	nalalityelli	$IC_{50} = 24.7 \ \mu M/HS 4 \ cells$	02
		$IC_{50} = 32.4 \ \mu M/SCL-1 \ cells$		$IC_{50} = 21.8 \ \mu M/SCL-1 \ cells$	
		$IC_{50} = 29.7 \ \mu M/A-431 \ cells$		$IC_{50} = 33.7 \ \mu M/A-431 \ cells$	
		$IC_{50} = 30.9 \ \mu M/BGC-823 \ cells$		$IC_{50} = 28.4 \ \mu M/BGC-823 \ cells$	
		$IC_{50} = 27.1 \ \mu M/MCF$ -7 cells		$IC_{50} = 37.6 \ \mu M/MCF-7 \ cells$	
		$IC_{50} = 31.2 \ \mu M/W-480 \ cells$		$IC_{50} = 14.1 \ \mu M$ /W-480 cells	
44	In vitro	$IC_{50} = 34.9 \ \mu M/HS-1 \ cells$	Adiamycin	$IC_{50} = 17.8 \ \mu$ M/HS-1 cells	52
		$IC_{50} = 29.9 \ \mu M/HS-4 \ cells$		$IC_{50} = 24.7 \ \mu M/HS-4 \ cells$	
		$IC_{50} = 33.1 \mu M/SCL-1 \text{ cells}$		$IC_{50} = 21.8 \ \mu M/SCL-1 \ cells$	
		$IC_{50} = 30.1 \ \mu M/A-431 \ cells$		$IC_{50} = 33.7 \ \mu M/A-431 \ cells$	
		$IC_{50} = 35.5 \ \mu M/BGC-823 \ cells$		$IC_{50} = 28.4 \mu\text{M/BGC-823}$ cells	
		$IC_{50} = 31.2 \mu\text{M/M}/\text{M}\text{CF-7}$ cells		$IC_{50} = 37.6 \mu\text{M/MCF-7}$ cells	
15	In vitro	$IC_{50} = 32.0 \ \mu\text{M}/\text{W} - 480 \ \text{cens}$ $IC_{50} = 12.4 \ \mu\text{M}/\text{HS} - 1 \ \text{cells}$	Adjamycin	$IC_{50} = 14.1 \ \mu M/W-480 \ cens$ $IC_{50} = 17.8 \ \mu M/HS-1 \ cells$	52
15	111 11110	$IC_{50} = 12.3 \ \mu M/HS-4 \text{ and } BGC-823 \text{ cells}$	Autamyem	$IC_{50} = 24.7 \text{ µM/HS} + \text{cells}$	52
		$IC_{50} = 12.9 \ \mu M/SCL-1 \ cells$		$IC_{50} = 21.8 \ \mu M/SCL-1 \ cells$	
		$IC_{50} = 11.8 \ \mu M/A-431 \ cells$		$IC_{50} = 33.7 \ \mu M/A-431 \ cells$	
		$IC_{50} = 12.6 \ \mu M/MCF-7 \ cells$		$IC_{50} = 28.4 \ \mu M/BGC-823 \ cells$	
		$IC_{50} = 13.8 \ \mu M/W-480 \ cells$		$IC_{50} = 37.6 \ \mu M/MCF-7 \ cells$	
				$IC_{50} = 14.1 \ \mu M/W-480 \ cells$	
46	In vitro	$IC_{50} = 11.6 \ \mu M/HS-1 \ cells$	Adiamycin	$IC_{50} = 17.8 \ \mu M/HS-1 \ cells$	52
		$IC_{50} = 11.4 \ \mu M/HS-4 \ cells$		$IC_{50} = 24.7 \ \mu M/HS-4 \ cells$	
		$IC_{50} = 12.1 \ \mu M/SCL-1 \ cells$		$IC_{50} = 21.8 \ \mu M/SCL-1 \ cells$	
		$IC_{50} = 10.3 \ \mu M/A-431 \ cells$		$IC_{50} = 33.7 \ \mu M/A-431 \ cells$	
		$IC_{50} = 11.7 \ \mu M/BGC-823 \ cells$		$IC_{50} = 28.4 \ \mu M/BGC-823 \ cells$	
		$IC_{50} = 10.4 \ \mu M/MCF/ \ cells$		$IC_{50} = 3/.6 \ \mu M/MCF-7 \ cells$	
17	In witho	$IC_{50} = 12.5 \ \mu\text{M}/\text{W} - 480 \ \text{cells}$	Adiamusin	$IC_{50} = 14.1 \ \mu M/W - 480 \ cens$	50
±/	111 11110	$IC_{50} = 7.5 \ \mu\text{M/HS-1}$ cells $IC_{} = 8.6 \ \mu\text{M/HS-4}$ and MCE-7 cells	Autamychi	$IC_{50} = 17.8 \ \mu M/HS-1 \ cells$	32
		$IC_{50} = 8.2 \ \mu\text{M/SCL-1}$ cells		$IC_{50} = 24.7 \ \mu M/SCL-1 \ cells$	
		$IC_{50} = 9.5 \mu M/A431$ cells		$IC_{50} = 33.7 \mu$ M/A-431 cells	
		$IC_{50} = 8.9 \ \mu\text{M/BGC-823 cells}$		$IC_{50} = 28.4 \ \mu M/BGC-823 \ cells$	
		$IC_{50} = 9.2 \ \mu M/W-480 \ cells$		$IC_{50} = 37.6 \ \mu M/MCF-7 \ cells$	
				$IC_{50} = 14.1 \ \mu M/W-480 \ cells$	
18	In vitro	$IC_{50} = 11.3 \ \mu M/A-549 \ cells$	Doxorubicin	$IC_{50} = 0.02 \ \mu M/A-549$ , HepG-2 and V	V- 53
				480 cells	
		$IC_{50} = 9.4 \ \mu M/BGC-823 \ cells$		$IC_{50} = 0.01 \ \mu M/BGC-823 \ cells$	
		$IC_{50} = 10.1 \ \mu M/HepG-2 \ cells$		$IC_{50} = 0.03 \ \mu M/HL-60 \ cells$	
		$IC_{50} = 11.1 \ \mu M/HL-60 \ cells$		$IC_{50} = 0.04 \ \mu M/SMMC-7721 \ cells$	
		$IC_{50} = 10.4 \ \mu M/MCF-7 \ cells$			
		$IC_{50} = 9.7 \ \mu M/SMMC-7721 \ cells$			
	<b>.</b> .,	$IC_{50} = 11.7 \ \mu M/W-480 \ cells$	D 111		
19	In vitro	$IC_{50} = 12.7 \ \mu M/A-549 \ cells$	Doxorubicin	$IC_{50} = 0.02 \ \mu$ M/A-549, HepG-2 and V 480 cells	V- 53
		$IC_{50} = 12.2 \ \mu M/BGC-823 \ cells$		$IC_{50} = 0.01 \ \mu M/BGC-823 \ cells$	
		$IC_{50} = 12.8 \ \mu\text{M/HepG-2 cells}$		$IC_{50} = 0.03 \ \mu M/HL-60 \ cells$	
		$IC_{50} = 13.8 \ \mu\text{M/HL}{-60}$ cells		$IC_{50} = 0.04 \ \mu M/SMMC-7/21 \ cells$	
		$IC_{50} = 14.3 \ \mu\text{M/M}/\text{MCF-7}$ and SMMC-7/21 cells			
50	In vitro	$IC_{50} = 31.9 \ \mu\text{M/A}{-}549 \ \text{cells}$	Doxorubicin	$IC_{50} = 0.02 \ \mu$ M/A-549, HepG-2 and V	V- 53
				480 cells	
		$IC_{50} = 31.2 \ \mu M/BGC-823 \ cells$		$IC_{50}=0.01\;\mu\text{M}/\text{BGC-823}$ cells	
		$IC_{50} = 30.7 \ \mu M/HepG-2 \ cells$		$IC_{50} = 0.03 \ \mu M/HL-60 \ cells$	
		$IC_{50} = 32.2 \ \mu M/HL-60 \ cells$		$IC_{50} = 0.04 \ \mu M/SMMC$ -7721 cells	
		$IC_{50} = 28.1 \ \mu M/MCF-7 \ cells$			

Compounds	Models	s Effect	Positive control	Effect	References
		IC <sub>50</sub> = 29.9 μM/SMMC-7721 cells			
		$IC_{50} = 27.6 \ \mu M/W-480 \ cells$			
51	In vitro	$IC_{50} = 29.7 \ \mu M/A-549 \ cells$	Doxorubicin	$IC_{50}=0.02~\mu\text{M}/\text{A-549},$ HepG-2 and W-	53
				480 cells	
		$IC_{50} = 29.6 \ \mu M/BGC-823 \ cells$		$IC_{50} = 0.01 \ \mu M/BGC-823 \ cells$	
		$IC_{50} = 29.4 \ \mu$ M/HepG-2 and HL-60 cells		$IC_{50} = 0.03 \ \mu M/HL-60 \ cells$	
		$IC_{50} = 27.1 \ \mu M/MCF-7 \ cells$		$IC_{50} = 0.04 \ \mu M/SMMC$ -7721 cells	
		$IC_{50} = 30.1 \ \mu M/SMMC$ -7721 cells			
		$IC_{50} = 24.9 \ \mu M/W-480 \ cells$			
52	In vitro	$IC_{50} = 76.3 \ \mu M/A-549 \ cells$	Doxorubicin	$IC_{50}=0.02~\mu\text{M}/\text{A-549},$ HepG-2 and W-	53
				480 cells	
		$IC_{50} = 68.7 \ \mu M/BGC-823 \ cells$		$IC_{50} = 0.01 \ \mu M/BGC-823 \ cells$	
		$IC_{50} = 66.8 \ \mu M/HepG-2 \ cells$		$IC_{50} = 0.03 \ \mu M/HL-60 \ cells$	
		$IC_{50} = 72.3 \ \mu$ M/HL-60 cells		$IC_{50} = 0.04 \ \mu M/SMMC$ -7721 cells	
		$IC_{50} = 76.2 \ \mu M/MCF-7 \ cells$			
		$IC_{50} = 70.8 \ \mu M/SMMC$ -7721 cells			
		$IC_{50} = 69.4 \ \mu M/W-480 \ cells$			
53	In vitro	$IC_{50} = 80.2 \ \mu M/A-549 \ cells$	Doxorubicin	$IC_{50} = 0.02 \ \mu$ M/A-549, HepG-2 and W-	53
				480 cells	
		$IC_{50} = 78.8 \ \mu M/BGC-823 \ cells$		$IC_{50} = 0.01 \ \mu M/BGC-823 \ cells$	
		$IC_{50} = 79.4 \ \mu M/HepG-2 \ cells$		$IC_{50} = 0.03 \ \mu$ M/HL-60 cells	
		$IC_{50} = 80.3 \ \mu M/HL-60 \ cells$		$IC_{50} = 0.04 \ \mu M/SMMC-7721 \ cells$	
		$IC_{50} = 80.5 \ \mu M/MCF-7 \ cells$			
		$IC_{50} = 81.6 \ \mu M/SMMC-7721 \ cells$			
		$IC_{50} = 81.8 \ \mu M/W-480 \ cells$			
54	In vitro	$IC_{50} = 15.8 \ \mu M/BGC-823 \ cells$	Doxorubicin	$IC_{50} = 0.02 \ \mu M/BGC-823 \ cells$	54
		$IC_{50} = 16.8 \ \mu M/HepG-2 \ cells$		$IC_{50} = 0.01 \ \mu$ M/HepG-2 and SK-OV-3	
		-		cells	
		$IC_{50} = 16.5 \ \mu M/MCF-7 \ cells$		$IC_{50} = 0.06 \ \mu M/MCF-7 \ cells$	
		$IC_{50} = 18.7 \ \mu M/SGC-7901 \ cells$		$IC_{50} = 0.05 \ \mu M/SGC-7901 \ cells$	
		$IC_{50} = 19.7 \ \mu M/SK-MEL-2 \ cells$		$IC_{50} = 0.03 \ \mu M/SK-MEL-2 \ cells$	
		$IC_{50} = 17.6 \ \mu M/SK-OV-3 \ cells$			
55	In vitro	$IC_{50} = 13.8 \ \mu M/BGC-823 \ cells$	Doxorubicin	$IC_{50} = 0.02 \ \mu M/BGC-823 \ cells$	54
		$IC_{50} = 12.4 \ \mu M/HepG-2 \ cells$		$IC_{50} = 0.01 \ \mu$ M/HepG-2 and SK-OV-3	
				cells	
		$IC_{50} = 14.8 \ \mu M/MCF-7 \ cells$		$IC_{50} = 0.06 \ \mu M/MCF-7 \ cells$	
		$IC_{50} = 13.9 \ \mu M/SGC$ -7901 and SK-OV-3 cells		$IC_{50} = 0.05 \ \mu M/SGC$ -7901 cells	
		$IC_{50} = 12.6 \ \mu M/SK-MEL-2 \ cells$		$IC_{50} = 0.03 \ \mu M/SK-MEL-2 \ cells$	
56	In vitro	$IC_{50} = 7.3 \ \mu M/BGC-823 \ cells$	Doxorubicin	$IC_{50} = 0.02 \ \mu M/BGC-823 \ cells$	54
		$IC_{50} = 8.6 \ \mu M/HepG-2 \ cells$		$IC_{50} = 0.01 \ \mu$ M/HepG-2 and SK-OV-3	
				cells	
		$IC_{50} = 8.2 \ \mu M/MCF-7 \ cells$		$IC_{50} = 0.06 \ \mu M/MCF-7 \ cells$	
		$IC_{50} = 9.5 \ \mu M/SGC-7901 \ cells$		$IC_{50} = 0.05 \ \mu M/SGC-7901 \ cells$	
		$IC_{50} = 8.9 \ \mu M/SK-MEL-2 \ cells$		$IC_{50} = 0.03 \ \mu M/SK-MEL-2 \ cells$	
		$IC_{50} = 8.6 \ \mu M/SK-OV-3 \ cells$			
57	In vitro	$IC_{50} = 9.5 \ \mu M/BGC-823 \ cells$	Doxorubicin	$IC_{50} = 0.02 \ \mu M/BGC-823 \ cells$	54
		$IC_{50} = 10.6 \ \mu M/HepG-2 \ cells$		$IC_{50} = 0.01 \ \mu M/HepG-2$ and SK-OV-3	
		··· ·		cells	
		$IC_{50} = 9.3 \ \mu M/MCF-7 \ cells$		$IC_{50} = 0.06 \ \mu M/MCF-7 \ cells$	
		$IC_{50} = 10.4 \ \mu M/SGC-7901 \ cells$		$IC_{50} = 0.05 \ \mu M/SGC-7901 \ cells$	
		$IC_{50} = 9.2 \ \mu M/SK-MEL-2 \ cells$		$IC_{50} = 0.03 \ \mu M/SK-MEL-2 \ cells$	
		$IC_{50} = 10.3 \ \mu M/SK-OV-3 \ cells$			
58	In vitro	$IC_{50} = 33.1 \ \mu M/BGC-823 \ cells$	Doxorubicin	$IC_{50} = 0.02 \ \mu M/BGC-823 \ cells$	54
		$IC_{50} = 32.4 \ \mu M/HepG-2 \ cells$		$IC_{50} = 0.01 \mu\text{M/HepG-2}$ and SK-OV-3	
				cells	
		$IC_{50} = 29.7 \ \mu M/MCF-7 \ cells$		$IC_{50} = 0.06 \ \mu M/MCF-7 \ cells$	
		$IC_{50} = 30.9 \ \mu M/SGC-7901 \ cells$		$IC_{50} = 0.05 \ \mu M/SGC-7901 \ cells$	
		$IC_{50} = 27.1 \mu\text{M/SK-MEL-2}$ cells		$IC_{50} = 0.03 \ \mu M/SK-MEL-2 \ cells$	
		$IC_{50} = 30.1 \ \mu M/SK-OV-3 \ cells$			
59	In vitro	$IC_{50} = 12.9 \mu\text{M}/95\text{-D cells}$	Doxorubicin	$IC_{50} = 24.7 \ \mu M/95-D$ cells	55
	,	$IC_{50} = 12.4 \ \mu M/A-549 \ cells$		$IC_{50} = 21.8 \ \mu M/A-549 \ cells$	
		$IC_{50} = 13.8 \mu\text{M/ATCC}$ cells		$IC_{50} = 33.7 \mu M/ATCC$ cells	
		$IC_{ro} = 14.8 \mu\text{M/H-446 cells}$		$IC_{50} = 22.3 \ \mu M/H-446 \ cells$	
		$10_{50} - 11.0 \mu m/11 - 110 ccms$		$10_{50} - 22.0 \mu m/11 440 cms$	

Compounds	Models	s Effect	Positive control	Effect	References
		$IC_{50} = 13.3 \ \mu$ M/H-460 cells		$IC_{50} = 14.1 \ \mu\text{M/H-460 cells}$	
		$IC_{50} = 12.6 \ \mu M/H-292 \ cells$		$IC_{50} = 13.7 \ \mu M/H-292 \ cells$	
		$IC_{50} = 13.9 \ \mu M/SPCA-1 \ cells$		$IC_{50} = 14.1 \ \mu M/SPCA-1 \ cells$	
60	In vitro	$IC_{50} = 46.8 \ \mu M/95$ -D cells	Doxorubicin	$IC_{50} = 24.7 \ \mu M/95$ -D cells	55
		$IC_{50} = 47.1 \ \mu M/ATCC \ cells$		$IC_{50} = 33.7 \ \mu M/ATCC \ cells$	
		$IC_{50} = 46.6 \ \mu M/H-446 \ cells$		$IC_{50} = 22.3 \ \mu$ M/H-446 cells	
		$IC_{50} = 45.9 \ \mu M/H-292 \ cells$		$IC_{50} = 13.7 \ \mu M/H-292 \ cells$	
61	In vitro	$IC_{50} = 9.5 \ \mu M/95$ -D cells	Doxorubicin	$IC_{50} = 24.7 \ \mu M/95$ -D cells	55
		$IC_{50} = 8.6 \ \mu M/A-549 \ cells$		$IC_{50} = 21.8 \ \mu M/A-549 \ cells$	
		$IC_{50} = 9.3 \ \mu M/ATCC$ and H-292 cells		$IC_{50} = 33.7 \ \mu M/ATCC \ cells$	
		$IC_{50} = 9.4 \ \mu M/H 446 \ cells$		$IC_{50} = 22.3 \ \mu M/H - 446 \ cells$	
		$IC_{50} = 9.2 \ \mu M/H-460 \ cells$		$IC_{50} = 14.1 \mu\text{M/H} \cdot 460 \text{cells}$	
		$IC_{50} = 9.7 \ \mu M/SPCA-1$ cens		$IC_{50} = 13.7 \mu M/H-292$ cells	
72	In nitro	CD = 20.7 ug mI $^{-1}$ /NIH/2T2 colla	Vincristino	$CD > 60 \text{ ug m} I^{-1}/\text{NIH}/2\text{T}2$ colls	40
73	111 11110	$CD_{50} = 20.7 \ \mu g \ \text{mL}^{-1}/\text{HI} \ 60 \ \text{cells}$	vincristine	$CD_{50} > 60 \ \mu g \ \text{IIL} / \text{NIH} / 313 \ \text{cens}$	49
		$CD_{50} = 0.9 \ \mu g \ \text{mL}^{-1}/\text{HeI a cells}$		$CD_{50} = 1.8 \ \mu g \ \text{mL}^{-1}/\text{Hel a cells}$	
74	In vitro	$CD_{50} = 50.5 \ \mu g \ \text{mL}^{-1} / \text{ReLa cens}$		$CD_{50} = 0.4 \ \mu g \ \text{mL}$ /HeLa cens	61
74	111 11110	alveonrotein			01
76	In vitro	$IC_{ro} = 67.3 \mu\text{M/HS-4 cells}$	Adiamycin	$IC_{50} = 24.7 \mu\text{M/HS-4 cells}$	52
	110 00000	$IC_{50} = 74.2 \ \mu M/A-431 \ cells$	i iaiaiii j eiii	$IC_{50} = 33.7 \mu\text{M/A-431 cells}$	02
		$IC_{50} = 66.2 \ \mu M/W-480 \ cells$		$IC_{50} = 14.1  \mu\text{M}/\text{W}-480 \text{ cells}$	
88	In vitro	$IC_{50} = 38.7 \text{ ug mL}^{-1}/\text{KB} (VI300) + 0.1 \text{ ug mL}^{-1}$	Vincristine	$IC_{50} = 1.0 \text{ µg mL}^{-1}/\text{KB} (VI300)$	43
		vincristine			
93	In vitro	$IC_{50} = 19.5 \ \mu g \ mL^{-1}/KB \ cells$	Vincristine	$IC_{50} = 1.0 \ \mu g \ mL^{-1}/KB \ (VJ300)$	32
		$IC_{50} = 18.0 \ \mu g \ mL^{-1}/KB \ (VJ300) \ cells$			
		$IC_{50} = 3.80 \ \mu g \ mL^{-1}/KB \ (VJ300) + 0.1 \ \mu g \ mL^{-1}$			
		vincristine			
102	In vitro	$IC_{50} = 15.0 \ \mu g \ mL^{-1}/KB \ (VJ300) + 0.1 \ \mu g \ mL^{-1}$	Vincristine	$IC_{50} = 1.0 \ \mu g \ mL^{-1}/KB \ (VJ300)$	23
		vincristine			
103	In vitro	$IC_{50} = 3.9 \ \mu g \ mL^{-1}/KB \ (VJ300) + 0.1 \ \mu g \ mL^{-1}$	Vincristine	$IC_{50} = 1.0 \ \mu g \ mL^{-1}/KB \ (VJ300)$	23
		vincristine			
104	In vitro	$IC_{50} = 13.0 \ \mu g \ mL^{-1}/KB \ (VJ300) + 0.1 \ \mu g \ mL^{-1}$	Vincristine	$IC_{50} = 1.0 \ \mu g \ mL^{-1}/KB \ (VJ300)$	23
		vincristine		1	
105	In vitro	$IC_{50} = 18.2 \ \mu g \ mL^{-1}/KB \ (VJ300) + 0.1 \ \mu g \ mL^{-1}$	Vincristine	$IC_{50} = 1.0 \ \mu g \ mL^{-1}/KB \ (VJ300)$	23
		vincristine			
106	In vitro	$IC_{50} = 9.2 \ \mu g \ mL^{-7}/KB \ (VJ300) + 0.1 \ \mu g \ mL^{-7}$	Vincristine	$IC_{50} = 1.0 \ \mu g \ mL^{-7}/KB \ (VJ300)$	23
107	T.,	vincristine $I_{0}^{-1} = \frac{10.0 \text{ mm} \text{m} I_{0}^{-1}}{10.0 \text{ mm} \text{m} I_{0}^{-1}} = 0.1 \text{ mm} \text{m} I_{0}^{-1}$	Tin mintin a	$10 - 10 = 10^{-1}/100 (M200)$	22
107	In vitro	$IC_{50} = 18.0 \ \mu g \ mL \ /KB (VJ300) + 0.1 \ \mu g \ mL$	vincristine	$IC_{50} = 1.0 \ \mu g \ mL \ /KB \ (VJ300)$	23
014	In nitro	Vinclisting $I_{C} = 20.7 \text{ mM/PCC}$ 222 colls	Dovorubicin	IC = 20.7  wM/BCC 822  colls	05
214	111 11110	$IC_{50} = 27.6 \mu$ M/HepG-2 cells	Doxorubiciii	$IC_{50} = 27.7 \mu$ M/BOC-023 cells	85
		$IC_{50} = 37.0 \mu\text{M/HepG}/2 \text{cells}$		$IC_{50} = 37.0 \mu$ M/HCF-7 cells	
		$IC_{50} = 35.8 \mu\text{M/MOL}^{-7}$ certs		$IC_{50} = 35.8 \mu \text{M/MOL}^{-7}$ certs $IC_{50} = 36.8 \mu \text{M/SGC}$ -7901 cells	
		$IC_{ro} = 36.5 \mu\text{M/SGO} / 501 \text{cells}$		$IC_{50} = 36.5 \mu$ M/SK-MEL-2 cells	
215	In vitro	$IC_{50} = 32.1 \text{ µM/BGC-823 cells}$	Doxorubicin	$IC_{50} = 29.7 \mu M/BGC-823$ cells	85
215	111 11110	$IC_{ro} = 29.8 \mu\text{M/HepG-2, cells}$	Doxorubiciii	$IC_{50} = 37.6 \mu$ M/HepG-2 cells	05
		$IC_{ro} = 31.9 \mu\text{M/MCF-7}$ cells		$IC_{50} = 35.8 \mu\text{M/MCF-7 cells}$	
		$IC_{50} = 27.9 \mu\text{M/SGC-7901}$ cells		$IC_{50} = 36.8 \mu\text{M/SGC-7901}$ cells	
		$IC_{50} = 33.3 \ \mu\text{M/SK-MEL-2 cells}$		$IC_{50} = 36.5 \ \mu$ M/SK-MEL-2 cells	
237	In vitro	$IC_{50} = 8.6 \ \mu M/BGC-823 \ cells$	Doxorubicin	$IC_{50} = 29.7 \ \mu M/BGC-823 \ cells$	85
		$IC_{50} = 7.2 \ \mu M/HepG-2 \ cells$		$IC_{50} = 37.6 \ \mu M/HepG-2 \ cells$	
		$IC_{50} = 8.3 \ \mu M/MCF-7 \ cells$		$IC_{50} = 35.8 \ \mu M/MCF-7 \ cells$	
		$IC_{50} = 8.2 \ \mu M/SGC-7901 \ cells$		$IC_{50} = 36.8 \ \mu M/SGC-7901 \ cells$	
		$IC_{50} = 8.9 \ \mu M/SK-MEL-2 \ cells$		$IC_{50} = 36.5 \ \mu M/SK-MEL-2 \ cells$	
282	In vitro	$IC_{50} = 9.7 \ \mu g \ mL^{-1}/PC-3 \ cells$	Cisplatin	$IC_{50} = 1.5 \ \mu g \ mL^{-1}/PC-3 \ cells$	19
		$IC_{50} = 15.9 \mu\text{g mL}^{-1}/\text{HCT-116}$ cells	-	$IC_{50} = 3.2 \ \mu g \ mL^{-1}/HCT$ -116 cells	
		$IC_{50} = 14.1 \ \mu g \ mL^{-1}/MCF$ -7 cells		$IC_{50} = 4.2 \ \mu g \ mL^{-1}/MCF-7 \ cells$	
		$IC_{50} > 25 \ \mu g \ m L^{-1}/A-549$ and KB (VJ300) cells		$IC_{50} = 4.3 \ \mu g \ mL^{-1}/A-549 \ cells$	
		$IC_{50} = 8.6 \ \mu g \ mL^{-1}/KB \ (VJ300) + 0.1 \ \mu g \ mL^{-1}$	Verapamil	$IC_{50} = 4.7 \ \mu g \ mL^{-1}/KB \ (VJ300) + 0.1 \ \mu s$	r.
		vincristine	-	mL <sup>-1</sup> vincristine	
289	In vitro	$IC_{50} = 7.1 \ \mu g \ mL^{-1}/PC-3 \ cells$	Cisplatin	$\mathrm{IC}_{50} = 1.5~\mu\mathrm{g~mL}^{-1}$ /PC-3 cells	19
		$IC_{50} = 7.6 \ \mu g \ m L^{-1} / HCT-116 \ cells$		$IC_{50} = 3.2 \ \mu g \ mL^{-1}/HCT-116 \ cells$	

Compounds	Models	Effect	Positive control	Effect	References
		$IC_{50} = 9.7 \ \mu g \ mL^{-1}/MCF-7 \ cells$ $IC_{50} = 20.4 \ \mu g \ mL^{-1}/A-549 \ cells$ $IC_{$		$\begin{split} \mathrm{IC}_{50} &= 4.2 \ \mu g \ m L^{-1} / \text{MCF-7 cells} \\ \mathrm{IC}_{50} &= 4.3 \ \mu g \ m L^{-1} / \text{A-549 cells} \end{split}$	
		$IC_{50} = 23 \ \mu g \ mL^{-1}/KB \ (VJ300) \ ens$ $IC_{50} = 4.80 \ \mu g \ mL^{-1}/KB \ (VJ300) + 0.1 \ \mu g \ mL^{-1}$ vincristine	Verapamil	$IC_{50} = 4.7 \ \mu g \ mL^{-1}/KB \ (VJ300) + 0.1 \ \mu g$ mL <sup>-1</sup> vincristine	
302	In vitro	$CD_{50} > 60 \ \mu g \ mL^{-1}/NIH/3T3 \ cells$ $CD_{50} = 30.2 \ \mu g \ mL^{-1}/HL-60 \ cells$	Vincristine	$CD_{50} > 60 \ \mu g \ mL^{-1}/NIH/3T3 \ cells$ $CD_{50} = 1.8 \ \mu g \ mL^{-1}/HL-60 \ cells$	49
327	In vitro	$\begin{split} & \text{CD}_{50} = 2.8 \ \text{\mu g} \ \text{mL}^{-1} / \text{HeLa cells} \\ & \text{CD}_{50} = 6.4 \ \text{\mu g} \ \text{mL}^{-1} / \text{NIH} / 3\text{T3} \ \text{cells} \\ & \text{CD}_{50} > 60 \ \text{\mu g} \ \text{mL}^{-1} / \text{HL-60 cells} \end{split}$	Vincristine	$\begin{split} & \text{CD}_{50} = 0.4 \ \text{\mug mL}^{-1} / \text{HeLa cells} \\ & \text{CD}_{50} > 60 \ \text{\mug mL}^{-1} / \text{NIH} / 3\text{T3 cells} \\ & \text{CD}_{50} = 1.8 \ \text{\mug mL}^{-1} / \text{HL-60 cells} \end{split}$	49
333	In vitro	$CD_{50} = 7.5 \ \mu g \ mL^{-1}/HeLa \ cells$ $IC_{50} = 1.3 \ \mu g \ mL^{-1}/HT-29 \ cells$ $IC_{70} = 4.9 \ \mu g \ mL^{-1}/MCF-7 \ cells$	Cisplatin	$CD_{50} = 0.4 \ \mu g \ mL^{-1}/HeLa \ cells$ $IC_{50} = 8.8 \ \mu g \ mL^{-1}/HT-29 \ cells$ $IC_{70} = 6.6 \ \mu g \ mL^{-1}/MCF-7 \ cells$	8
		$\begin{split} &\text{IC}_{50} = 4.7 \ \mu\text{g mL}^{-1}/\text{PC-3} \ \text{cells} \\ &\text{IC}_{50} = 4.7 \ \mu\text{g mL}^{-1}/\text{PC-3} \ \text{cells} \\ &\text{IC}_{50} = 7.0 \ \mu\text{g mL}^{-1}/\text{MDA-MB} \ \text{-231 cells} \\ &\text{IC}_{50} = 7.3 \ \mu\text{g mL}^{-1}/\text{HCT-116 cells} \\ &\text{IC}_{50} = 9.6 \ \mu\text{g mL}^{-1}/\text{A-549 cells} \\ &\text{IC}_{50} = 3.0 \ \mu\text{g mL}^{-1}/\text{KB} \ (\text{VJ300}) \ \text{cells} \end{split}$	Vincristine	$\begin{split} &\text{IC}_{50} = 0.0 \ \mu\text{g mL}^{-1}/\text{PC-3} \ \text{cells} \\ &\text{IC}_{50} = 4.2 \ \mu\text{g mL}^{-1}/\text{PC-3} \ \text{cells} \\ &\text{IC}_{50} = 2.1 \ \mu\text{g mL}^{-1}/\text{MDA-MB} \ \text{-}231 \ \text{cells} \\ &\text{IC}_{50} = 4.6 \ \mu\text{g mL}^{-1}/\text{HCT-116} \ \text{cells} \\ &\text{IC}_{50} = 5.4 \ \mu\text{g mL}^{-1}/\text{A-549} \ \text{cells} \\ &\text{IC}_{50} = 0.8 \ \mu\text{g mL}^{-1}/\text{KB} \ (\text{VJ300}) \ \text{cells} \end{split}$	
366	In vitro	$\label{eq:IC50} \begin{split} IC_{50} &= 3.70 \ \mu g \ m L^{-1} / \text{KB} \ \text{(VJ}300\text{)} + 0.1 \ \mu g \ m L^{-1} \\ \text{vincristine} \end{split}$	Vincristine	$IC_{50} = 1.0 \ \mu g \ mL^{-1}/KB \ (VJ300)$	103
367	In vitro	$IC_{50} = 7.0 \ \mu g \ mL^{-1}/KB \ (VJ300) + 0.1 \ \mu g \ mL^{-1}$ vincristine	Vincristine	$IC_{50} = 1.0 \ \mu g \ mL^{-1}/KB \ (VJ300)$	103
373	In vitro	$IC_{50} = 4.1 \ \mu g \ mL^{-1}/KB \ (VJ300) + 0.1 \ \mu g \ mL^{-1}$ vincristine	Vincristine	$IC_{50} = 1.0 \ \mu g \ mL^{-1}/KB \ (VJ300)$	103
374	In vitro	$IC_{50} = 3.2 \ \mu g \ mL^{-1}/KB \ (VJ300) + 0.1 \ \mu g \ mL^{-1}$ vincristine	Vincristine	$IC_{50} = 1.0 \ \mu g \ mL^{-1}/KB \ (VJ300)$	103
375	In vitro	$IC_{50} = 11.2 \ \mu g \ mL^{-1}/KB \ (VJ300) + 0.1 \ \mu g \ mL^{-1}$ vincristine	Vincristine	$IC_{50} = 1.0 \ \mu g \ mL^{-1}/KB \ (VJ300)$	103
402	In vitro	$\begin{split} \mathrm{IC}_{50} &= 5.38 \ \mu\text{M/A-549 cells} \\ \mathrm{IC}_{50} &= 4.67 \ \mu\text{M/HT-29 cells} \end{split}$	Docetaxel	$\begin{split} IC_{50} &= 4.95 \times 10^{-4} \ \mu\text{M/A-549 cells} \\ IC_{50} &= 3.34 \times 10^{-4} \ \mu\text{M/HT-29 cells} \end{split}$	114
403	In vitro	$\begin{split} IC_{50} &= 7.44 \; \mu\text{M/A-549 cells} \\ IC_{50} &= 6.39 \; \mu\text{M/HT-29 cells} \end{split}$	Docetaxel	$\begin{split} IC_{50} &= 4.95 \times 10^{-4} \; \mu\text{M/A-549 cells} \\ IC_{50} &= 3.34 \times 10^{-4} \; \mu\text{M/HT-29 cells} \end{split}$	114
404	In vitro	$\begin{split} IC_{50} &= 8.21 \ \mu\text{M/A-549 cells} \\ IC_{50} &= 8.89 \ \mu\text{M/HT-29 cells} \end{split}$	Docetaxel	$\begin{split} \text{IC}_{50} &= 4.95 \times 10^{-4}  \mu\text{M/A-549 cells} \\ \text{IC}_{50} &= 3.34 \times 10^{-4}  \mu\text{M/HT-29 cells} \end{split}$	114
407	In vitro	$\begin{split} & IC_{50} = 0.24 \ \mu g \ mL^{-1} / KB \ cells \\ & IC_{50} = 0.25 \ \mu g \ mL^{-1} / KB \ (VJ300) \ cells \\ & IC_{50} = 0.30 \ \mu g \ mL^{-1} / KB \ (VJ300) + 0.1 \ \mu g \ mL^{-1} \\ & vincristine \end{split}$	Vincristine	$IC_{50} = 1.0 \ \mu g \ m L^{-1} / KB \ (VJ300)$	32
408	In vitro	$CD_{50} = 20.8 \ \mu g \ mL^{-1}/NIH/3T3 \ cells$ $CD_{50} > 60 \ \mu g \ mL^{-1}/HL-60 \ cells$ $CD_{50} = 2.9 \ \mu g \ mL^{-1}/HeLa \ cells$	Vincristine	$CD_{50} > 60 \ \mu g \ mL^{-1}/NIH/3T3 \ cells$ $CD_{50} = 1.8 \ \mu g \ mL^{-1}/HL-60 \ cells$ $CD_{50} = 0.4 \ \mu g \ mL^{-1}/HeLa \ cells$	49
		$\begin{split} & IC_{50} = 0.19 \ \mu g \ m L^{-1} / KB \ cells \\ & IC_{50} = 0.25 \ \mu g \ m L^{-1} / KB \ (VJ300) \ cells \\ & IC_{50} = 0.34 \ \mu g \ m L^{-1} / KB \ (VJ300) + 0.1 \ \mu g \ m L^{-1} \\ & vincristine \end{split}$	Vincristine	$IC_{50} = 1.0 \ \mu g \ mL^{-1}/KB \ (VJ300)$	32
409	In vitro	$IC_{50} = 0.35 \ \mu$ M/A-549 and HT-29 cells $IC_{50} = 1.25 \ \mu$ g mL <sup>-1</sup> /KB cells	Docetaxel	$\begin{split} IC_{50} &= 4.95 \times 10^{-4} \; \mu \text{M/A-549 cells} \\ IC_{50} &= 3.34 \times 10^{-4} \; \mu \text{M/HT-29 cells} \end{split}$	114
		$\begin{split} IC_{50} &= 2.50 \ \mu g \ mL^{-1} / KB \ (VJ300) \ cells \\ IC_{50} &= 1.85 \ \mu g \ mL^{-1} / KB \ (VJ300) + 0.1 \ \mu g \ mL^{-1} \\ vincristine \end{split}$	Vincristine	$\rm{IC}_{50} = 1.0 \ \mu g \ m L^{-1} / KB \ (VJ300)$	32
411	In vitro	$\label{eq:IC50} IC_{50} = 4.35 \ \mu g \ m L^{-1} / \text{KB} \ \text{(VJ300)} + 0.1 \ \mu g \ m L^{-1}$ vincristine	Vincristine	$IC_{50} = 1.0 \ \mu g \ m L^{-1} / KB \ (VJ300)$	72
413	In vitro	$IC_{50} = 4.11 \ \mu g \ m L^{-1} / KB \ (VJ300) + 0.1 \ \mu g \ m L^{-1}$ vincristine	Vincristine	$IC_{50} = 1.0 \ \mu g \ m L^{-1} / KB \ (VJ300)$	72
417	In vitro	$\label{eq:IC50} \begin{split} IC_{50} &= 0.39 \ \mu g \ m L^{-1} / \text{KB} \ (\text{VJ}300) + 0.1 \ \mu g \ m L^{-1} \\ \text{vincristine} \end{split}$	Vincristine	$IC_{50} = 1.0 \ \mu g \ m L^{-1} / KB \ (VJ300)$	72
434	In vitro	$\label{eq:IC50} IC_{50} = 21.8 \ \mu g \ m L^{-1} / KB \ (VJ300) + 0.1 \ \mu g \ m L^{-1}$ vincristine	Vincristine	$IC_{50} = 1.0 \ \mu g \ m L^{-1} / KB \ (VJ300)$	22
437	In vitro	$\begin{split} & IC_{50} = 15.0 \ \mu g \ m L^{-1} / KB \ cells \\ & IC_{50} = 11.0 \ \mu g \ m L^{-1} / KB \ (VJ300) \ cells \\ & IC_{50} = 3.8 \ \mu g \ m L^{-1} / KB \ (VJ300) + 0.1 \ \mu g \ m L^{-1} \\ & vincristine \end{split}$	Vincadifformine	$ \begin{split} & {\rm IC}_{50} = 10.2 \ \mu g \ m L^{-1} / {\rm KB} \ {\rm cells} \\ & {\rm IC}_{50} = 6.3 \ \mu g \ m L^{-1} / {\rm KB} \ ({\rm VJ300}) \ {\rm cells} \\ & {\rm IC}_{50} = 4.5 \ \mu g \ m L^{-1} / {\rm KB} \ ({\rm VJ300}) + 0.1 \ \mu g \\ & {\rm m L}^{-1} \ {\rm vincristine} \end{split} $	10

Compounds	Models	s Effect	Positive control	Effect	References
438	In vitro	$IC_{50} = 6.4 \ \mu g \ mL^{-1}/KB \ (VJ300) + 0.1 \ \mu g \ mL^{-1}$ vincristine	Vincristine	$\rm{IC}_{50} = 1.0 \ \mu g \ m L^{-1} / KB \ (VJ300)$	22
446	In vitro	$\begin{split} & IC_{50} = 0.25 \ \mu g \ m L^{-1} / Jurkat \ cells \\ & IC_{50} = 3.6 \ \mu g \ m L^{-1} / KB \ cells \\ & IC_{50} = 0.75 \ \mu g \ m L^{-1} / KB \ (VJ300) \ cells \\ & IC_{50} = 0.46 \ \mu g \ m L^{-1} / KB \ (VJ300) + 0.1 \ \mu g \ m L^{-1} \\ & vinceiting \end{split}$	Vincadifformine	$\begin{split} & IC_{50} = 21.8 \ \mu g \ mL^{-1} / Jurkat \ cells \\ & IC_{50} = 10.2 \ \mu g \ mL^{-1} / KB \ cells \\ & IC_{50} = 6.3 \ \mu g \ mL^{-1} / KB \ (VJ300) \ cells \\ & IC_{50} = 4.5 \ \mu g \ mL^{-1} / KB \ (VJ300) + 0.1 \ \mu g \\ & mL^{-1} \ u in origination \end{split}$	10
450 and 452	In vitro	$IC_{50} > 30 \ \mu\text{M/A-549}$ cells $IC_{50} = 30 \ \mu\text{M/HT-29}$ cells	Docetaxel	III. Vincristine $IC_{50} = 4.95 \times 10^{-4} \mu\text{M/A-549}$ cells $IC_{50} = 3.34 \times 10^{-4} \mu\text{M/HT-29}$ cells	114
463	In vitro	$IC_{50} = 6.2 \text{ µM/HT} - 29 \text{ cells}$		$1050 = 0.01 \times 10^{-1} \mu m/m = 25$ cents	59
467	In vitro	$IC_{50} = 15.5 \ \mu g \ m L^{-1} / MCF-7 \ cells$			122
468	In vitro	$IC_{50} = 22.5 \ \mu g \ m L^{-1} / MCF-7 \ cells$			122
469	In vitro	$IC_{50} = 21.5 \ \mu g \ mL^{-1}/MCF$ -7 cells			122
470	In vitro	$IC_{50} = 17 \ \mu g \ mL^{-1}/MCF$ -7 cells			122
471	In vitro	$IC_{50} = 26 \ \mu g \ m L^{-1}/MCF$ -7 cells			122
472	In vitro	$IC_{50} = 14.5 \ \mu g \ mL^{-1}/MCF$ -7 cells			122
Anti-microbial a	activity				
14	In vitro	MIC = $31.3 \ \mu g \ mL^{-1}/E$ . coli, E. carotovra, B. subtilis, B. cereus, and S. aureus MIC = $15.5 \ \mu g \ mL^{-1}/E$ . carotovra	Ampicillin	$\begin{split} MIC &= 100 \ \mu g \ mL^{-1}/\textit{E. coli} \ and \ \textit{E.} \\ carotovra \\ MIC &= 12.5 \ \mu g \ mL^{-1}/\textit{B. subtilis} \\ MIC &= 25.0 \ \mu g \ mL^{-1}/\textit{B. cereus} \ and \ \textit{S.} \end{split}$	7
		$EC_{50}=33.3~\mu g~mL^{-1}/\textit{R. solani}$ $EC_{50}=29.2~\mu g~mL^{-1}/\textit{P. italicum}$ $EC_{50}=16.3~\mu g~mL^{-1}/\textit{F. oxysporum}$ f. sp. Cubense	Mildothane	$EC_{50} = 17.0 \ \mu g \ mL^{-1}/R. \ solani$ $EC_{50} = 7.8 \ \mu g \ mL^{-1}/P. \ italicum$ $EC_{50} = 57.0 \ \mu g \ mL^{-1}/F. \ oxysporum \ f.$	
		$EC_{50}=31.8~\mu g~mL^{-1}\/\ensuremath{\textit{F}}$ . oxysporum f. sp. Niveum		Sp. Cubense $EC_{50} = 101.0 \ \mu g \ mL^{-1}/F.$ oxysporum f.	
43	In vitro	IZ = 11  mm/K. pneumoniae	Sanguinarine	IZ = 25  mm/S. mutans and S. viridans	52
		IZ = 10  mm/E.  coli,  S.  aureus and  S.  viridans IZ = 9  mm/C.  glabrata,  E.  cloacae and  S.  mutans	Netilmicin	IZ = 21  mm/S. aureus IZ = 8  mm/S. epidermidis and K.	
		IZ = 8  mm/S. epidermidis and S. dysenteriae IZ = 7  mm/C. albicans, C. tropicalis and P. aeruginosa		IZ = 24  mm/E.  coli $IZ = 22  mm/E.  cloacae$	
				IZ = 23 mm/ <i>P. aeruginosa</i> and <i>S. dysenteriae</i>	
44	In vitro	IZ = 12  mm/P. aeruginosa and S. mutans IZ = 11  mm/E. coli	Sanguinarine Netilmicin	IZ = 25  mm/s. mutans and s. viridans IZ = 21  mm/s. aureus	52
		1Z = 10  mm/C. glabrata		IZ = 8  mm/S. epidermidis and K. pneumoniae	
		<ul> <li>IZ = 9 mm/E. cloacae, S. aureus and S. dysenteriae</li> <li>IZ = 8 mm/C. albicans, K. pneumoniae and S. epidermidis</li> </ul>		IZ = 24  mm/E. coli IZ = 22  mm/E. cloacae	
		IZ = 7 mm/C. tropicalis and S. viridans		IZ = 23 mm/ <i>P. aeruginosa</i> and <i>S. dysenteriae</i>	
45	In vitro	IZ = 18  mm and $MIC = 0.77  mM/$ K. pneumoniae	Sanguinarine	$\mathrm{IZ}=25$ mm/S. mutans and S. viridans	52
		IZ = 18  mm and $MIC = 0.87  mM/S.$ viridans	Netilmicin	IZ = 21  mm/S. aureus	
		IZ = 17  mm  and  MIC = 0.89  mM/E.  coli		IZ = 8  mm/S. epidermidis and K.	
				pneumoniae	
		IZ = 18  mm  and  MIC = 0.97  mM/S. aureus  and  S.		IZ = 24 mm/E. coli	
		epidermidis			
		IZ = 18 mm and MIC = 0.97 mM/ <i>E. cloacae</i> IZ = 19 mm and MIC = 1.01 mM/ <i>P. aeruginosa</i>		IZ = 22  mm/E.  cloacae IZ = 23  mm/P.  aeruginosa and S. dysenteriae	
		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			
		$\mathrm{IZ}=17~\mathrm{mm}$ and $\mathrm{MIC}=3.09~\mathrm{mM}/\mathit{C}.$ glabrata			
46	In vitro	IZ = 20  mm  and  MIC = 0.72  mM/E.  coli	Sanguinarine	IZ = 25  mm/S. mutans and S. viridans	52
		IZ = 20  mm and $MIC = 0.82  mM/S$ mutans			

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Compounds	Models Effect	Positive control	Effect	References
	IZ = 20  mm and $MIC = 0.91  mM/S. epidermidisIZ = 20  mm$ and $MIC = 1.03  mM/S. dysenteriaeIZ = 20  mm$ and $MIC = 1.11  mM/S. viridansIZ = 20  mm$ and $MIC = 1.18  mM/P. aeruginosaIZ = 19  mm$ and $MIC = 1.20  mM/E. cloacaeIZ = 20  mm$ and $MIC = 1.23  mM/C. tropicalis$ a	Netilmicin nd	IZ = 21 mm/S. aureus IZ = 8 mm/S. epidermidis and K. pneumoniae IZ = 24 mm/E. coli	
	S. aureus IZ = 17 mm and MIC = $1.32 \text{ mM/C}$ . glabrata IZ = 21 mm and MIC = $1.37 \text{ mM/K}$ . pneumonia	е	IZ = 22 mm/E. cloacae IZ = 23 mm/P. aeruginosa and S. dysenteriae	
47	IZ = 17 mm and MIC = 2.87 mM/C. albicans 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 a	Sanguinarine nd	IZ = 25 mm/S. mutans and S. viridans	52
	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. pneumonia IZ = 23 mm and MIC = 0.87 mM/S. viridans	Netilmicin e	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	
48	IZ = 24 mm and MIC = $1.14 \text{ mM/S.}$ mutans In vitro IZ = 23 mm and MIC = $0.12 \text{ mM/K.}$ pneumonia IZ = 24 mm and MIC = $0.12 \text{ mM/S.}$ dysenteriae IZ = 24 mm and MIC = $0.13 \text{ mM/P.}$ aeruginosa IZ = 23 mm and MIC = $0.15 \text{ mM/E.}$ cloacae IZ = 23 mm and MIC = $0.16 \text{ mM/S.}$ epidermidis IZ = 24 mm and MIC = $0.18 \text{ mM/S.}$ aureus IZ = 24 mm and MIC = $0.23 \text{ mM/E.}$ coli	e 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.	53
49	In vitro IZ = 24 mm and MIC = 0.14 mM/K. pneumonia 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	e 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	IZ = 24 mm and MIC = 0.26 mM/ <i>E. coli</i> In vitro IZ = 18 mm and MIC = 0.94 mM/ <i>P. aeruginosa</i> IZ = 17 mm and MIC = 1.10 mM/ <i>E. cloacae</i> IZ = 17 mm and MIC = 1.12 mM/ <i>K. pneumonia</i> and <i>S. dysenteriae</i> IZ = 18 mm and MIC = 1.20 mM/ <i>S. aureus</i> IZ = 19 mm and MIC = 1.23 mM/ <i>S. epidermidis</i>	Netilmicin e	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

Compounds	Models	Effect	Positive control	Effect	References
		$\mathrm{IZ}=18~\mathrm{mm}$ and $\mathrm{MIC}=1.32~\mathrm{mM}/\mathrm{\textit{E.}}$ coli		IZ = 25  mm and $MIC = 0.004  mM/S$ . epidermidis IZ = 24  mm and $MIC = 0.015  mM/E$ . coli	
51	In vitro	$\mathrm{IZ}=17~\mathrm{mm}$ and $\mathrm{MIC}=0.92~\mathrm{mM}/\textit{P.}$ aeruginosa	Netilmicin	IZ = 23  mm  and  MIC = 0.015  mM/P. aeruginosa	53
		$\mathrm{IZ}=18~\mathrm{mm}$ and $\mathrm{MIC}=1.01~\mathrm{mM/\textit{E}}.$ cloacae		IZ = 22  mm  and  MIC = 0.01  mM/E. cloacae	
		$\mathrm{IZ}=19~\mathrm{mm}$ and $\mathrm{MIC}=1.02~\mathrm{mM}/\mathrm{S}.$ dysenteriae		IZ = 23  mm and $MIC = 0.011  mM/S$ . <i>dysenteriae</i>	
		$\mathrm{IZ}=18~\mathrm{mm}$ and MIC = 1.09 mM/K. pneumoniae		IZ = 25  mm and $MIC = 0.009  mM/K$ .	
		$\mathrm{IZ}=19~\mathrm{mm}$ and MIC = 1.15 mM/S. epidermidis		IZ = 25  mm and $MIC = 0.004  mM/S$ . <i>epidermidis</i>	
		$\mathrm{IZ}=20~\mathrm{mm}$ and MIC = 1.18 mM/S. aureus		IZ = 21  mm and MIC = 0.005  mM/S. aureus	
		$\mathrm{IZ}=17~\mathrm{mm}$ and MIC = 1.24 mM/E. coli		IZ = 24  mm  and  MIC = 0.015  mM/E. <i>coli</i>	
52	In vitro	$\mathrm{IZ}=17~\mathrm{mm}$ and MIC = 1.19 mM/K. pneumoniae	Netilmicin	IZ = 25  mm  and  MIC = 0.009  mM/K. pneumoniae	53
		$\mathrm{IZ}=18~\mathrm{mm}$ and $\mathrm{MIC}=1.21~\mathrm{mM}/\!\mathit{E.~coli}$		IZ = 24  mm  and  MIC = 0.015  mM/E.	
		$\mathrm{IZ}=17\ \mathrm{mm}$ and $\mathrm{MIC}=1.21\ \mathrm{mM}/\text{P.}$ aeruginosa		IZ = 23  mm and MIC = 0.015  mM/P.	
		$\mathrm{IZ}=17\ \mathrm{mm}$ and $\mathrm{MIC}=1.31\ \mathrm{mM}/\!\mathit{E.}$ cloacae		IZ = 22  mm  and  MIC = 0.01  mM/E.	
		$\mathrm{IZ}=15~\mathrm{mm}$ and $\mathrm{MIC}=1.31~\mathrm{mM}/\!\mathit{S}.$ dysenteriae		IZ = 23  mm  and  MIC = 0.011  mM/s.	
53	In vitro	$\mathrm{IZ}=16~\mathrm{mm}$ and $\mathrm{MIC}=0.99~\mathrm{mM}/\textit{K}.$ pneumoniae	Netilmicin	IZ = 25  mm and MIC = 0.009  mM/K.	53
		$\mathrm{IZ}=18~\mathrm{mm}$ and $\mathrm{MIC}=1.01~\mathrm{mM}/\mathrm{S}.$ dysenteriae		IZ = 23  mm  and  MIC = 0.011  mM/s.	
		$\mathrm{IZ}=17\ \mathrm{mm}$ and $\mathrm{MIC}=1.24\ \mathrm{mM}/\mathrm{P}.\ aeruginosa$		IZ = 23  mm  and  MIC = 0.015  mM/P.	
		$\rm IZ=15~mm$ and $\rm MIC=1.31~mM/{\it E.~coli}$		IZ = 24  mm and  MIC = 0.015  mM/E.	
		$\mathrm{IZ}=17~\mathrm{mm}$ and $\mathrm{MIC}=1.32~\mathrm{mM}/\!\mathit{E.}$ cloacae		IZ = 22  mm and  MIC = 0.01  mM/E.	
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	Kanamycin	IZ = 24.7  mm/S. aureus	12
		IZ = 12 mm/S. epidermidis	sulfate		
		IZ = 9  mm/C. albicans and C. glabrata			
		IZ = 8  mm/C. tropicalis, S. mutans and S. dysenteriae			
95	In witten	LZ = / mm/E. coll and K. pneumoniae	Kanamusin	IZ = 24.7  mm/S gurance	10
80 86	In vitro	IZ = 0.1  mm/s gurans	sulfate	1L = 24.7  mm/s. aureus	12
80	In vitro	IZ = 10.2  mm/S. <i>aureus</i>	sulfate	1L = 24.7  mm/s. aureus	12
ð/	in vitro	1L = 10.3  mm/s.  dureus	sulfate	12 = 24.7  mm/s. aureus	12
206	In vitro	MIC = 15.5 µg mL <sup>-</sup> / <i>E.</i> coll, Erwinia carotovra, Bacillus subtilis, B. cereus, and S. aureus MIC = 7.8 µg mL <sup>-1</sup> / <i>E.</i> carotovra	Ampicillin	$MIC = 100 \ \mu g \ mL^{-}/E. \ coli \ and \ E. carotovra$	1
		$EC_{50} = 21.9 \ \mu g \ mL^{-1}/R. \ solani$	Mildothane	MIC = 12.5 $\mu g \text{ mL}^{-1}/B$ . subtilis	
		$EC_{50} = 19.4 \ \mu g \ mL^{-1}/P. \ italicum$		$MIC = 25.0 \ \mu g \ mL^{-1}/B.$ cereus and S. aureus	
		$EC_{50} = 15.2 \ \mu g \ mL^{-1}/F.$ oxysporum f. sp. Cubense		$EC_{50} = 17.0 \ \mu g \ mL^{-1}/R. \ solani$	
		$EC_{50} = 43.8 \ \mu g \ mL^{-1}/F.$ oxysporum f. sp. Niveum		$\begin{split} & \mathrm{EC}_{50} = 7.8 \ \mathrm{\mu g} \ \mathrm{mL}^{-1}/P. \ italicum \\ & \mathrm{EC}_{50} = 57.0 \ \mathrm{\mu g} \ \mathrm{mL}^{-1}/F. \ oxysporum \ f. \end{split}$	
				sp. Cubense EC <sub>50</sub> = 101.0 $\mu$ g mL <sup>-1</sup> / <i>F. oxysporum</i> f. sp. Niveum	

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Table 2 (Contd)

Compounds	Models	Effect	Positive control	Effect	Reference
267 and 297	In vitro	$MIC = 32 \ \mu g \ mL^{-1} / \textit{E. coli}$			21
Anti-inflammator	y activity				
11	In vitro	$IC_{50} = 25.4 \ \mu M/T$ cell inhibition			16
170	In vitro	$IC_{50} = 21.6 \ \mu M/T$ cell inhibition			16
222	In vitro	$IC_{50} = 27.8 \ \mu M/T$ cell inhibition			16
409	In vitro	$IC_{50} = 1.0 \ \mu M/T$ cell inhibition			16
		To arrest the G2/M phase of the T cell cycle			
		To decrease IL-6 and IL-17 levels in T cells			
219, 225, 228,	In vitro	The inhibitory effects on IL-1 $\beta$ and TNF- $\alpha$ , and			75
279–280, 291, and	1	PGE2 were comparable with positive control			
439		dexamethasone			
Anti-alleroic activ	itv				
90	In vitro	$IC_{10} = 3.73 \ \mu g \ m L^{-1}/histamine and \beta$ -	Ketotifen	$IC_{10} = 1.37 \ \mu g \ m L^{-1}/histomine and \beta$ -	66
		hexosaminidase inhibition in RBL-2H3 cell	fumarate	hexosaminidase inhibition in RBL-	
				2H3 cell	
.26	In vitro	$IC_{10} = 7.06 \ \mu g \ m L^{-1}$ /histamine and $\beta$ -	Ketotifen	$IC_{10}=1.37~\mu g~mL^{-1}/histamine$ and $\beta$	66
		hexosaminidase inhibition in RBL-2H3 cell	fumarate	hexosaminidase inhibition in RBL-	
				2H3 cell	
57	In vitro	$IC_{10} = 5.51 \ \mu g \ m L^{-1}$ /histamine and $\beta$ -	Ketotifen	$IC_{10}=1.37~\mu g~mL^{-1}/histamine$ and $\beta\text{-}$	66
		hexosaminidase inhibition in RBL-2H3 cell	fumarate	hexosaminidase inhibition in RBL-	
				2H3 cell	
48	In vitro	$IC_{10} = 11.78 \ \mu g \ mL^{-1}/histamine and \beta$ -	Ketotifen	$IC_{10} = 1.37 \ \mu g \ mL^{-1}/histamine and \beta$ -	66
		hexosaminidase inhibition in RBL-2H3 cell	fumarate	hexosaminidase inhibition in RBL-	
_		1		2H3 cell	
he MeOH extrac	t In vitro	$IC_{10} = 2.17 \ \mu g \ mL^{-1}/histomine and \beta$ -	Ketotifen	$IC_{10} = 1.37 \ \mu g \ mL^{-1}/histomine and \beta$ -	66
f K. larutensis		hexosaminidase inhibition in RBL-2H3 cell	fumarate	hexosaminidase inhibition in RBL-	
ark		$r_{2} = r_{2} = r_{1} + r_{2} + r_{2} + r_{3} + r_{3$	TT 1 110	2H3  cell	
he MeOH extrac	t In vitro	$IC_{10} = 3.82 \ \mu g \ mL^{-7}$ /histamine and $\beta$ -	Ketotifen	$IC_{10} = 1.37 \ \mu g \ mL^{-7}$ /histamine and $\beta$ -	129
I K. <i>arborea</i> barr	C	nexosaminidase inhibition in RBL-2H3 cell	rumarate	and a sell	
be MeOU extrac	t In vitro	IC = 2.01 $\mu$ g mI <sup>-1</sup> /bistamine and B	Ketotifen	$2H3$ cell $IC = 1.27$ up mI $^{-1}$ /bistamine and $\beta_{-}$	66
f K larutensis lea	f	$R_{10} = 3.01 \mu g \text{mL}^2$ /instantine and p-	fumarate	$R_{10} = 1.37 \ \mu g \ \text{mL}^2$ /installine and p-	00
I K. IUTUIETISIS ICA	1	nexosaninindase initibilion in KBL-2115 cen	Tullialate	2H3 cell	
'he MeOH extrac	t In vitro	$IC_{ro} = 2.58 \text{ µg mL}^{-1}/\text{bistamine and }\beta$ -	Ketotifen	$IC_{10} = 1.37 \text{ µg mL}^{-1}/\text{histamine and }\beta$ -	129
of K arborea leaf		hexosaminidase inhibition in RBL-2H3 cell	fumarate	$h_{10} = 1.57 \ \mu g \ m L$ (instantine and p)	125
i K. urborcu icai		nexosaninindase initibilion in KBE 2115 cen	Tulliarate	2H3 cell	
he MeOH extrac	t <i>In vitro</i>	$IC_{10} = 1.61 \text{ µg mL}^{-1}/\text{histamine and }\beta$ -	Ketotifen	$IC_{10} = 1.37 \text{ µg mL}^{-1}/\text{histamine and }\beta$ -	66
of K. larutensis		hexosaminidase inhibition in RBL-2H3 cell	fumarate	hexosaminidase inhibition in RBL-	00
oot				2H3 cell	
he MeOH extrac	t <i>In vitro</i>	$IC_{10} = 4.32 \text{ ug mL}^{-1}/\text{histamine}$ and $\beta$ -	Ketotifen	$IC_{10} = 1.37 \text{ µg mL}^{-1}/\text{histamine and }\beta$ -	129
of K. arborea root		hexosaminidase inhibition in RBL-2H3 cell	fumarate	hexosaminidase inhibition in RBL-	
				2H3 cell	
Inti-diabetic activ	vity				
29	In vitro	$EC_{50} = 24.5 \ \mu M/glucose-evoked podocyte injury$	Astragaloside IV	$EC_{50} = 15.4 \mu\text{M/glucose-evoked}$	25
26	T.,	Inhibition		FC 15 4 v M (shapped such ad	25
26	In vitro	$EC_{50} = 3.0 \mu\text{M/glucose-evoked podocyte injury}$	Astragaloside IV	$EC_{50} = 15.4 \mu$ M/glucose-evoked	25
24	In vitro	$\frac{1}{1000} = 10.2 \text{ m}/c \text{luces a welled pole with injury}$	Astrogalogida IV	FC = 15.4  wM/glucose evolved	25
/ <b>2*1</b>	111 VIII'0	$E_{50} = 10.2 \mu \text{M/gracose-evoked polycyte Injury}$	Astragaloside IV	$10_{50} - 13.4 \mu w/gradose-evoked$	23
64	In vitro	FC = 12.0  uM/glucose-evoked podogyte injury	Astrogaloside IV	FC = 15.4  uM/glucose-evolved	25
UT	111 VIII 0	inhibition	Astragalosite IV	podocyte injury inhibition	23
~-	In vitro	$EC_{50} = 3.80 \mu M/glucose-evoked podocyte injury$	Astragaloside IV	$EC_{50} = 15.4 \mu M/glucose-evoked$	25
05	<b>III VIUIU</b>	200 0.00 min Success croited podocyte injury	. Stragarobiae IV	2000 - 1011 min Statobe croned	-0
.05		inhibition		podocyte injury inhibition	
105 179 and 384-386	In vitro	inhibition IC <sub>50</sub> > 50 $\mu$ M/α-glucosidase inhibition		podocyte injury inhibition	109

AChE inhibitory activity

39	In vitro MIR = 12.5 $\mu$ g/AChE inhibition	Galanthamine	$MIR = 0.004 \ \mu g/AChE$ inhibition
220	In vitro $IC_{50} = 12.5 \ \mu g/AChE$ inhibition		
221	In vitro $IC_{50} = 12.5 \ \mu g/AChE$ inhibition		

216 6

Compounds	Models	Effect	Positive control	Effect	References
Anti-manic activi	ty				
165	In vitro	$IC_{50} = 12.5 \text{ mg mL}^{-1}$ /anti-manic activity in Drosophila			13
Anti-tussive activi	ity				
126	In vivo	88% Cough inhibition/citric acid activated Guine pig cough model	a		65
250	In vivo	Interaction to δ-opioid receptor 76% Cough inhibition/citric acid activated Guine pig cough model	a		65
Anti-nociceptive a	activity				
The alkaloidal extract of <i>K.</i> macrophylla	In vivo	To decrease in the number of contortion and stretching <i>via</i> peripheral mechanism			130
Cardiovascular ar	nd vasore	laxant activities			
112	In vivo	To decrease arterial blood pressure and heart rat	e		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

 $\mu$ g mL<sup>-1</sup> against KB (VJ300) cells in the presence of 0.1  $\mu$ g mL<sup>-1</sup> 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  $\mu$ g mL<sup>-1</sup> vincristine.<sup>32</sup>

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  $\mu$ g mL<sup>-1</sup> vincristine, better than its analogous dimer kopsoffinol (289).<sup>19</sup> 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<sub>50</sub> values of 3.2–11.2  $\mu$ g mL<sup>-1</sup>.<sup>103</sup> Valparicine (446) would be superior to the positive control vincadifformine in a cytotoxic assay against Jurkat cell growth.<sup>10</sup> In addition, this compound and arboloscine (437) showed positive signals to resist the growth of KB (VJ300) and KB (VJ300) + 0.1  $\mu$ g mL<sup>-1</sup> vincristine (Table 2).<sup>10</sup>

## 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.<sup>52,53</sup> 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.<sup>12</sup> In an antimicrobial assay against *E. coli, Erwinia carotovra, Bacillus subtilis, B. cereus*, and *S. aureus*, two best agents *N*-decarbomethoxykopsamine (14) and *N*<sub>1</sub>-decarbomethoxy chanofruticosinic acid (206) were associated with the MIC values of 7.8–15.5 and 15.5–31.3  $\mu$ g mL<sup>-1</sup>, respectively.<sup>7</sup> These two molecules further showed antifungal activity against

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*Rhizoctonia solani, Penicillium italicum, Fusarium oxysporum* f. sp. Cubense, and *F. oxysporum* f. sp. Niveum (Table 2).<sup>7</sup> 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  $\mu$ g mL<sup>-1.21</sup>

## 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.<sup>133-135</sup> *K. officinalis* constituents are such useful agents to treat autoimmune diseases due to their inhibition of human T cell proliferation and proinflammatory cytokines.<sup>16</sup> Indeed, *K. officinalis* constituents decarbomethoxykopsine (**11**), *N*(4)-methylkopsininate (**170**), 12-methoxychanofruticosinic acid (**222**), and rhazinilam (**409**) inhibited T cell growth with the IC<sub>50</sub> values of 25.4, 21.6, 27.8, and 1.0  $\mu$ M, respectively.<sup>16</sup> 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.<sup>16</sup>

The secretion of cytokines IL-1 $\beta$  and TNF- $\alpha$  or PGE2 levels has mainly caused inflammatory reactions. When LPSstimulated RAW 264.7 cells, at the concentration of 5 µg mL<sup>-1</sup>, kopsia C (**219**), methyl *N*<sub>1</sub>-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-1 $\beta$  and TNF- $\alpha$ , and PGE2, and comparable with positive control dexamethasone at the concentration of 10 µg mL<sup>-1</sup>.<sup>75</sup>

## 3.4. Anti-allergic and antidiabetic activities

Naturally occurring compounds have been recognized as potential antiallergic agents. In an experiment against histamine and  $\beta$ -hexosaminidase in RBL-2H3 cells, the IC<sub>10</sub> values of 3.73–11.78 µg mL<sup>-1</sup> were assigned to four alkaloids kopsilarutensinine (90), kopsinine (126), (–)-eburnamine (257), and (–)-tetrahydroalstonine (448).<sup>66</sup> In the same model against histamine and  $\beta$ -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).<sup>66,129</sup>

For antidiabetic activity, among tested compounds for the high glucose-evoked podocyte injury inhibition, the EC<sub>50</sub> values were orderly run as kopsinine **126** (3.0  $\mu$ M) > leuconolam **405** (3.8  $\mu$ M) > methyl 11,12-dimethoxychanofruticosinate **224** (10.2  $\mu$ M) > 16 $\alpha$ -hydroxy-19-oxoeburnamine **264** (12.0  $\mu$ M) > reference compound astragaloside IV (15.4  $\mu$ M) > 11-hydroxykopsilongine **29** (24.5  $\mu$ M).<sup>25</sup> However, four pauciflorine derivatives 11,12-demethoxy-16-deoxypauciflorine (**379**) and kopsioffines A–C (**384–386**) failed to suppress enzyme  $\alpha$ -glucosidase (IC<sub>50</sub> > 50  $\mu$ M).<sup>109</sup>

## 3.5. AChE inhibitory, anti-manic, anti-tussive, and antinociceptive activities

In Alzheimer's disease treatment based AChE inhibitory examination, kopsamine (**39**) has the minimum inhibitory requirement (MIR) value of 12.5  $\mu$ g, as compared with that of the reference compound galanthamine (MIR 0.004  $\mu$ g).<sup>21</sup> Meanwhile, two novel chanofruticosinates, kopsihainanines A–B (**220–221**), displayed weak AChE inhibitory activity with the respective IC<sub>50</sub> values of 38.5 and 50.6  $\mu$ M.<sup>6</sup> (–)-12-Methoxykopsinaline (**165**) with the IC<sub>50</sub> value of 12.5 mg mL<sup>-1</sup>, showed anti-manic activity in *Drosophila*.<sup>13</sup>

Kopsinine **126** (70 mg kg<sup>-1</sup>, i.p.) and methyl  $N_1$ -decarbomethoxychanofruticosinate **225** (250 mg kg<sup>-1</sup>, i.p.) exhibited 88 and 76% cough inhibition in the antitussive assays when citric acid activated guinea pig cough model.<sup>65</sup> In addition, antitussive effect of compound **126** was due to its interaction with  $\delta$ -opioid receptors.<sup>65</sup>

The alkaloidal extract of *K. macrophylla* (400 mg kg<sup>-1</sup>, 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.<sup>130</sup>

#### 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.<sup>136</sup> Drug discovery for CVD started from the 18<sup>th</sup> century at least.<sup>137</sup> To consider *Kopsia* constituents for cardiovascular treatment, at doses of 0.2–10.0 mg kg<sup>-1</sup> intravenous injection, kopsingine (**112**) caused decreases in arterial blood pressure and heart rate when hypertensive mice were anesthetized.<sup>123</sup> 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.<sup>123</sup>

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

# 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 <sub>50</sub>	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.

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