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## REVIEW

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

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

## 1. Introduction

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

*Kopsia* belongs to the subfamily Rauvolfioideae of the family Apocynaceae.[2] This genus, containing about 30 species, is widely distributed in Southeast Asia, China, Australia, and some islands of the Western Pacific.[3,4] *Kopsia* plants are recognized as a fertile reservoir of novel and bioactive secondary metabolite type alkaloids. Therefore, they have been traditionally used in each country. Chinese folk medicine deals with the use of parts of *K. officinalis* Tsiang & P. T. Li to treat rheumatoid arthritis, pharyngitis, tonsillitis, and dropsy.[4] In Malaysia, the roots of

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four species, *K. larutensis* King & Gamble, *K. macrophylla* Hook.f., *K. singapurensis* Ridl., and *K. paucifora* Hook.f., were applied as a poultice to ulcerate noses in tertiary syphilis.[2,5] *Kopsia* constituents are also well-known in pharmacological discoveries, in which they have a wide spectrum of pharmacological effects such as anticancer and anti-manic activities.[6,7]

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

## 2. Phytochemistry

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

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

## 2.1. Aspidofractinines

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

*grandifolia* stem bark, *K. griffithii* leaf and stem bark, *K. hainanensis* leaf, stem, stem bark and twig, *K. larutensis* stem, stem bark and leaf, *K. officinalis* root, stem, twig, leaf and fruit, *K. singapurensis* stem bark and leaf, *K. pauciflora* stem, stem bark and leaf, and *K. teoi* stem bark, whereas its *N*(4)-oxide (**127**) presented in *K. dasyrachis* stem, *K. griffithii* stem bark, *K. hainanensis* stem and leaf, *K. officinalis* fruit and leaf, *K. pauciflora* stem, and *K. singapurensis* bark.[5–7,9–11,13–19,21–25,28,29,32,36,42,43,48,51,65,66,68–72]

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

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

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

Table 1  (*Contd.*)

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

Table 1 (Contd.)

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

Table 1 (Contd.)

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

Table 1 (*Contd.*)

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

**Aspidospermines**

| No. | Compounds | Species | References |
|---|---|---|---|
| 242 | Aspidospermine | *K. pauciflora* leaf | 22 |
| 243 | (+)-1,2-Dehydroaspidospermine | *K. pauciflora* leaf | 22 |
| 244 | Eburenine | *K. arborea* aerial part | 90 |
| 245 | Kopsiofficine G | *K. officinalis* stem | 11 |
| 246 | Kopsiyunnanine G | *K. arborea* aerial part | 90 |
| 247 | Vincadifformine | *K. arborea* twig and stem bark, *K. officinalis* stem and fruit | 10, 11, 14 and 21 |
| 248 | Vincadifformine *N*(4)-oxide | *K. officinalis* stem | 11 |

**Danuphyllines**

| No. | Compounds | Species | References |
|---|---|---|---|
| 249 | Danuphylline | *K. dasyrachis* leaf | 30 and 91 |
| 250 | Danuphylline B | *K. arborea* leaf | 78 |
| 251 | 11,12-De(methylenedioxy)danuphylline | *K. officinalis* leaf | 13 |

Table 1 (*Contd.*)

| No. | Compounds | Species | References |
|---|---|---|---|
| 252 | Kopsihainin A | *K. hainanensis* stem | 65 |

**Eburnamines**

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

Table 1 (*Contd.*)

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

Table 1 (Contd.)

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

Table 1 (Contd.)

| No. | Compounds | Species | References |
|-----|-----------|---------|------------|
| 404 | Kopsiyunnanine C3 | *K. arborea* aerial part, *K. officinalis* aerial part | 96 and 114 |
| 405 | Leuconolam | *K. griffithii* leaf and stem bark, *K. hainanensis* twigs, stems and leaves, *K. officinalis* leaf, *K. pauciflora* leaf, *K. singapurensis* stem bark | 7, 9, 12, 15, 17, 22, 23, 25 and 32 |
| 406 | *O*-Methylleuconolam | *K. arborea* stem bark, *K. hainanensis* twig, *K. officinalis* stem | 10, 12 and 87 |
| 407 | Rhazinal | *K. dasyrachis* stem | 32 |
| 408 | Rhazinicine | *K. arborea* stem bark, *K. dasyrachis* stem, *K. singapurensis* root | 10, 18, 49 and 60 |
| 409 | Rhazinilam | *K. arborea* aerial part and stem bark, *K. officinalis* leaves and twigs, *K. pauciflora* leaves and stem bark, *K. singapurensis* leaf, bark and stem bark, *K. teoi* stem, stem bark and leaf | 16, 13, 22, 23, 25, 32–34, 36, 45, 47, 48 and 114 |

**Lundurines**

| No. | Compounds | Species | References |
|-----|-----------|---------|------------|
| 410 | Epilapidilectinol | *K. lapidilecta* stem and bark | 81 |
| 411 | Grandilodine A | *K. grandifolia* stem bark | 72 |
| 412 | Grandilodine B | *K. grandifolia* stem bark | 72 |
| 413 | Grandilodine C | *K. grandifolia* leaf | 72 |
| 414 | Isolapidilectine A | *K. grandifolia* leaf, *K. lapidilecta* stem and bark | 72 and 81 |
| 415 | Lapidilectam | *K. grandifolia* stem bark, *K. lapidilecta* stem and bark | 72 and 81 |
| 416 | Lapidilectine A | *K. grandifolia* stem bark, *K. lapidilecta* bark, stem and leaf | 72 and 115 |
| 417 | Lapidilectine B | *K. grandifolia* stem bark, *K. lapidilecta* bark, stem and leaf | 72 and 115 |
| 418 | Lapidilectinol | *K. lapidilecta* stem and bark | 81 |
| 419 | Lundurine A | *K. tenuis* leaf | 71 |
| 420 | Lundurine B | *K. tenuis* leaf | 71 |
| 421 | Lundurine C | *K. tenuis* leaf | 71 |
| 422 | Lundurine D | *K. tenuis* leaf | 71 |
| 423 | Tenuisine A | *K. tenuis* leaf | 116 and 117 |
| 424 | Tenuisine B | *K. tenuis* leaf | 71, 116 and 117 |
| 425 | Tenuisine C | *K. tenuis* leaf | 71, 116 and 117 |
| 426 | Tenuiphylline | *K. tenuis* leaf | 71 and 117 |

**Aspidospermas**

| No. | Compounds | Species | References |
|-----|-----------|---------|------------|
| 427 | Buchtienine | *K. griffithii* leaf and stem bark | 15 and 17 |
| 428 | Corynantheol | *K. hainanensis* twig and leaf | 9 |
| 429 | 19,20-Dihydroisositsirikine | *K. officinalis* stem | 75 |
| 430 | Dihydrocorynantheol | *K. hainanensis* twig and leaf | 9 |
| 431 | 16(*R*)-19,20-*E*-Isositsirikine | *K. griffithii* leaf, *K. pauciflora* leaf | 15, 17 and 22 |

**Catharinensines**

| No. | Compounds | Species | References |
|-----|-----------|---------|------------|
| 432 | Catharinensine | *K. pauciflora* leaf | 22 |
| 433 | Kopsirensine A | *K. pauciflora* leaf | 22 |
| 434 | Kopsirensine B | *K. pauciflora* leaf | 22 |
| 435 | Kopsirensine C | *K. pauciflora* leaf | 22 |
| 436 | Kopsiyunnanine B | *K. arborea* aerial part, *K. officinalis* aerial part | 96 and 97 |

**Leuconoxines**

| No. | Compounds | Species | References |
|-----|-----------|---------|------------|
| 437 | Arboloscine | *K. arborea* stem bark | 10 and 118 |
| 438 | Arboloscine A | *K. pauciflora* leaf | 22 |
| 439 | Leuconodine D | *K. officinalis* stem | 75 |
| 440 | Leuconodine F (6-oxoleuconoxine) | *K. griffithii* leaf, *K. pauciflora* leaf | 22 and 43 |
| 441 | Leuconoxine | *K. arborea* stem bark, *K. griffithii* leaf and stem bark, *K. pauciflora* stem, stem bark and leaf, *K. singapurensis* stem bark, *K. teoi* stem bark | 15, 17, 19, 22, 23 and 43 |
| 442 | Melodinine E | *K. arborea* twig | 21 |

**Pericines**

| No. | Compounds | Species | References |
|-----|-----------|---------|------------|
| 443 | Pericidine | *K. arborea* stem bark | 10 and 118 |
| 444 | Pericine | *K. arborea* stem bark | 10 |
| 445 | Pericine *N*-oxide | *K. arborea* stem bark | 10 |
| 446 | Valparicine | *K. arborea* stem bark | 119 and 120 |

**Alstonines**

| No. | Compounds | Species | References |
|-----|-----------|---------|------------|
| 447 | Oxayohimban-16-carboxy acid | *K. officinalis* stem | 75 |
| 448 | (−)-Tetrahydroalstonine | *K. arborea* stem bark, *K. dasyrachis* stem, *K. griffithii* leaf, *K. officinalis* root, twigs and leaves, *K. larutensis* stem bark and leaf, *K.* | 10, 15, 17–19, 23, 25, 32, 42, 43, 66 and 69 |

Table 1 (*Contd.*)

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

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

To search for bioactive metabolites from *Kopsia* plants, Long *et al.* (2018) isolated five new aspidofractinines kopsiafrutines A–E (**43–47**) from the 80% EtOH extract of *K. fruticosa* aerial part.[52] Eleven new analogs, kopsiahainanins A–F (**48–53**) and kopsiahainins A–E (**54–58**) were among the new compounds found in the 80% EtOH extract of *K. hainanensis* twigs and leaves.[53,54] In another approach, chromatographic separation of the 95% EtOH extract of *K. officinalis* aerial part can lead to the

isolation of three new metabolites (**59–61**), which named kopsiaofficines A–C.[55] From *K. arborea* aerial part, the new compound kopsiarborines A (**62**) was isolated.[56] Three new metabolites, kopsidasine (**64**), kopsidasine-N-oxide (**65**), and kopsidasinine (**66**) were separated from *K. dasyrachis* leaves and structurally confirmed by the NMR analysis and Hofmann reaction.[57] Thirteen previously undescribed metabolites kopsidines A–D (**67–69** and **71**), kopsinitarines B–D (**132–134**), mersingines A–B (**150–151**), 11-methoxykopsingine (**160**), 11-methoxy-12-hydroxy-kopsinol (**163**), 11,12-

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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**).[33,34,43–45,73,74,80] Kopsidarine (**63**), kopsidine C *N*-oxide (**70**), and singaporentine A (**193**) were three new compounds existed in *K. singapurensis* leaf, whereas its bark encompassed four new

others singapurensines A–D (**194–197**)[36,48,58,79] In two years 2007 and 2008, primarily based on CC approach, Subramaniam *et al.* successfully isolated nineteen new aspidofractinines, including kopsilongine-*N*-oxide (**92**), kopsiloscines A–J (**93–102**), kopsinalines A–F (**103–108**), kopsinicine (**118**), and kopsofinone (**145**) from *K. singapurensis* leaf or stem bark (Table 1 and Fig. 1).[23,32,48] Kopsiflorine (**74**) is now available in the genus *Kopsia*, but its *N*(4)-oxide (**75**) and kopsinarine (**109**) were new in

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

Phytochemical analysis aided by NMR structural elucidation on the CHCl₃ and *n*-BuOH extracts of *K. officinalis* leaf and twig has resulted in the isolation of eight new compounds kopsinidines C–E (**121–123**), *N*(1)-methoxycarbonyl-11,12-methoxylenedioxykopsinaline (**153**), *N*(1)-methoxycarbonyl-12-methoxykopsinaline (**156**), *N*(4)-methylkopsininate (**170**), (−)-11,12-methylenedioxykopsinaline (**172**), and 5-oxokopsinic acid (**176**), in addition to seven known compounds kopsinilam (**124**), kopsinine (**126**), kopsinine methochloride (**128**), kopsinine B (**129**), (−)-kopsinoline (**137**), (−)-12-methoxykopsinaline (**165**), and 11,12-methylenedioxykopsinaline *N*(4)-oxide (**173**).[16] Among the isolates from *K. hainanensis* stem and leaves, the new compound kopsininate (**125**) itself displayed an interesting feature since it contained a carboxylate group ($\delta_C$ 181.6 ppm in CD₃OD).[7] Besides known compounds, the application of NMR and MS tools would take a good advance in the natural product chemistry field, by which the chemical structures of seven new aspidofractinines kopsiofficines A–F and L (**138–144**) from *K. officinalis* stem and three new analogs yunnanoffines A–C (**202–204**) from *K. officinalis* leaf have been determined.[11,25,75] Aspidofractinines were further observed in other *Kopsia* plants. For instance, apart from known compounds, five new derivatives *N*(1)-methoxycarbonyl-11,12-methylenedioxy-Δ^{16,17}-kopsinine (**154**), *N*(1)-methoxycarbonyl-12-methoxy-Δ^{16,17}-kopsinine (**155**), *N*(1)-methoxycarbonyl-11,12-methylenedioxy-Δ^{16,17}-kopsinine *N*(4) oxide (**157**), *N*(1)-methoxycarbonyl-12-hydroxy-Δ^{16,17}-kopsinine (**158**), and *N*(1)-methoxycarbonyl-12-methoxy-Δ^{16,17}-kopsinine *N*(4) oxide (**159**) were characteristics of *K. profunda*,[4,77] or lahadinines A–B (**145–146**), 12-methoxy-10-demethoxykopsidasinine (**167**), paucidactines D–E (**180–181**), paucidactinine (**182**), paucidisine (**183**), paucidirinine (**184**), paucidirisine (**185**), pauciduridine (**186**), paucifinine (**187**), and paucifinine-*N*-oxide (**188**) were new metabolites isolated from the parts of *K. pauciflora*.[19,51,76]

## 2.2. Chanofruticosinates, aspidospermines, and danuphyllines

In general, *Kopsia* chanofruticosinate derivatives **205–241** have established a similarity in the chemical structural skeleton with aspidofractinines (Table 1 and Fig. 2). However, fragment C-2–C-16–C-17–C-20 in aspidofractinines was replaced by a carbon bridge between C-6 and C-20 in chanofruticosinates. To date, these phytochemicals occurred in *K. arborea*, *K. dasyrachis*, *K. fruticosa*, *K. flavida*, *K. hainanensis*, *K. lancibracteolata*, *K. officinalis*, and *K. pauciflora*.[3,6,7,10,13,16,22,25,30,41,42,65,75,82–89] From Table 1, kopsia A (**217**), kopsia C (**219**), methyl 11,12-dimethoxychanofruticosinate (**224**), methyl *N₁*-decarbomethoxychanofruticosinate (**225**), methyl 12-methoxychanofruticosinate (**228**), methyl 11,12-methylenedioxy-*N₁*-decarbomethoxychanofruticosinate (**229**), and methyl 11,12-methylenedioxy-*N₁*-decarbomethoxy-Δ^{14,15}-chanofruticosinate (**230**) were major components in the group of *Kopsia* chanofruticosinates. Analyzing chemical composition further, the rich alkaloid fraction of *K. officinalis* leaf and twig have also contained five new derivatives, chanofruticosinic acid (**205**), kopsias A–C (**217–219**), 12-methoxychanofruticosinic acid (**222**), and methyl (2β,11β,12β,19α)-6,7-didehydro-8,21-dioxo-11,21-cycloaspidospermidine-2-carboxylate (**231**).[13,16,86] According to the phytochemical report of Chen and partners, *N₁*-decarbomethoxy chanofruticosinic acid (**206**), kopsihainanines A–B (**220–221**), methyl chanofruticosinate *N*(4)-oxide (**223**), and methyl *N₁*-decarbomethoxy chanofruticosinate *N*(4)-oxide (**226**) were previously unrecorded compounds and found in *K. hainanensis* stem and leaf for the first time.[6,7] The application of HPLC chromatographic procedure to the 70% EtOH extract of *K. fruticosa* aerial part has resulted in the isolation of two new substances, 11,12-dimethoxydanuphylline (**207**) and 3-oxo-11,12-dimethoxy-*N*¹-decarbomethoxy-14,15-didehydrochanofruticosinate (**236**).[3] The MeOH extract of *K. flavida* leaf consisted of serial new alkaloids type chanofruticosinates flavisiamines A–F (**208–213**).[41,83] Besides known compounds, the chromatographic isolation of the alcoholic extracts of *K. arborea* leaves has allowed to identify the appearance of seven new methyl chanofruticosinate alkaloids, kopreasin A (**216**), and prunifolines A–F (**208, 211,** and **238–241**).[82,84] Finally, three new derivatives 12-hydroxylprunifoline A (**214**), 12-hydroxylprunifoline A (**215**), and *N*(4)-oxide prunifoline D (**3**) were purified from the 70% EtOH extract of *K. lancibracteolata* stem.[85]

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

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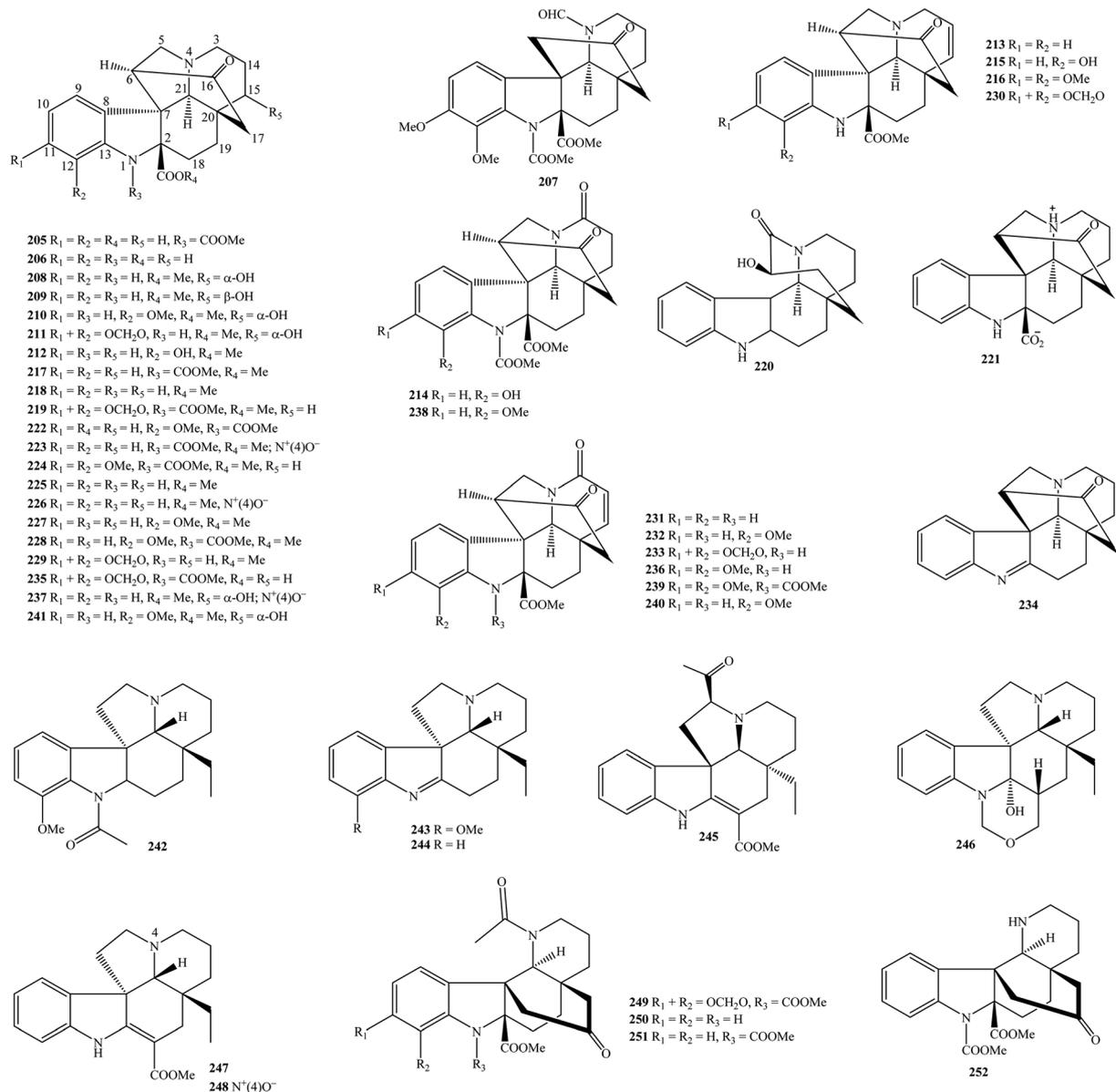
**Fig. 2** Chanofruticosinates, aspidospermines and danuphyllines from genus *Kopsia*.

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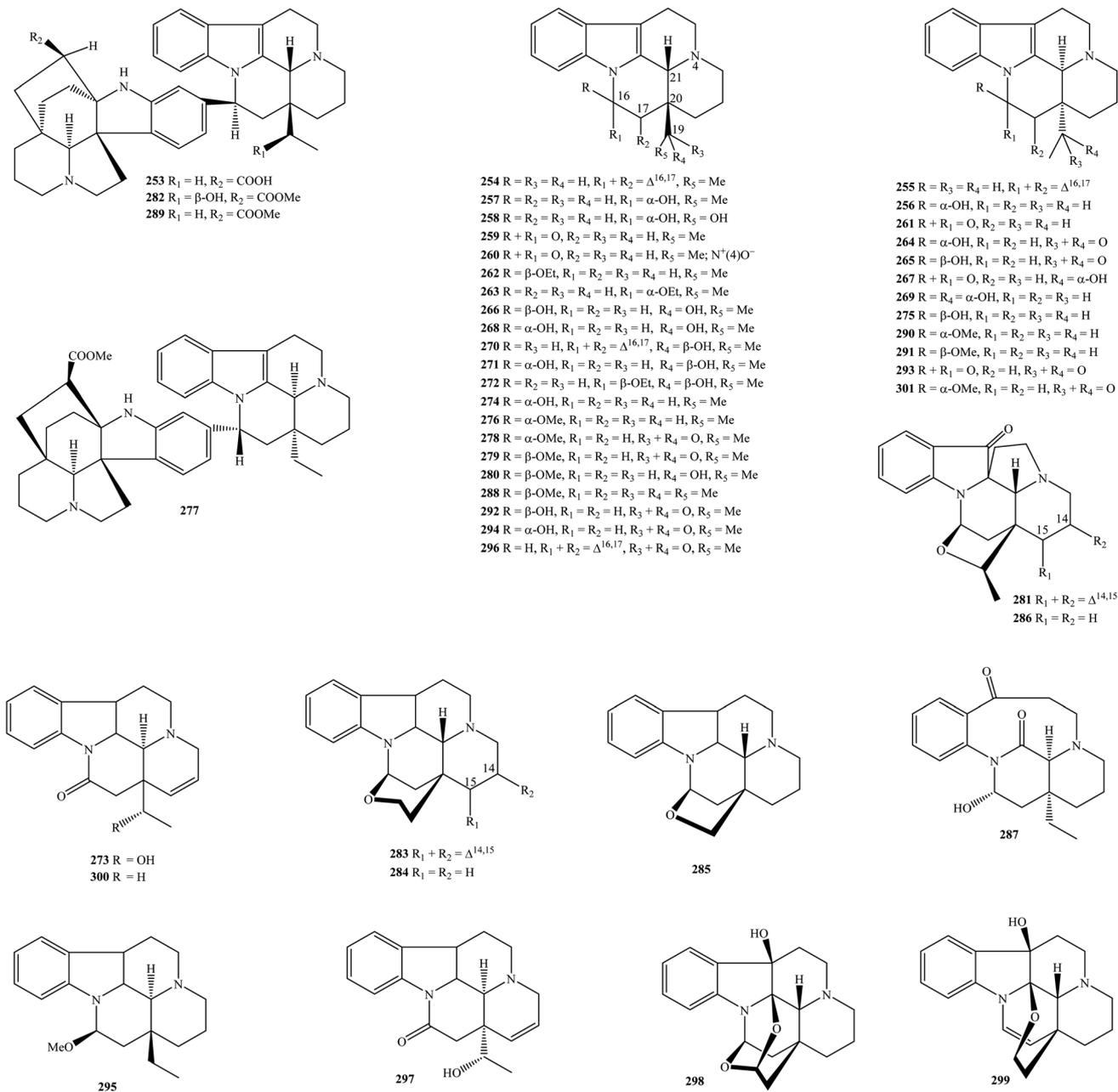
### 2.3. Eburnamines

As can be seen from Table 1 and Fig. 3, eburnamines are also a crucial phytochemical class of the genus *Kopsia*. Forty-nine compounds **253–301** were isolated to date, and they were mainly derived from *K. arborea*, *K. dasyrachis*, *K. griffithii*, *K. hainanensis*, *K. hainanensis*, *K. jasminiflora*, *K. larutensis*, *K. macrophylla*, *K. officinalis*, *K. pauciflora*, *K. singapurensis*, *K. teoi*, and *K. terengganensis*.[5,9,13–15,17–19,21–25,27–29,33,42,50,51,66,68–70,75,90,92,93] *Kopsia* eburnamines appeared in both monomer and dimer forms, but not to have connected with sugar units.

(−)-Eburnamenine (**255**), (−)-eburnamine (**257**), (+)-eburnamonine (**259**), (+)-isoeburnamine (**274**), and larutenine (**284**) were isolated frequently, *e.g.*, compound **274** was detected in *K. arborea* aerial part, *K. dasyrachis* stem, *K. hainanensis* stem bark, *K. larutensis* leaf, stem and stem bark, *K. teoi* stem bark and leaf, *K. officinalis* leaf, *K. pauciflora* stem and stem bark, and *K. terengganensis* bark.[5,13,18,19,22,29,33,51,68,70,90,92,93]

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

**Fig. 3** Eburnamines from genus *Kopsia*.

(−)-eburnamonine (**261**), (+)-ethylisoeburnamine (**263**), 16α-hydroxy-19-oxoeburnamine (**264**), 16β-hydroxy-19-oxoeburnamine (**265**), melohenine B (**287**), (−)-methyleburnamine (**288**), (+)-*O*-methyleburnamine (**290**), and *O*-methyl-16-*epi*-vincanol (**295**), and Δ¹⁴-vicamone (**300**) have never been observed in genus *Kopsia* before. Especially, (−)-eburnaminol (**258**), (+)-eburnamonine *N*(4)-oxide (**260**), (+)-19(*R*)-hydroxyeburnamine (**266**), (−)-19(*R*)-hydroxyisoeburnamine (**268**), (−)-19(*R*)-hydroxyeburnamenine (**270**), (−)-(19*R*)-19-hydroxyisoeburnamine (**271**), (−)-19(*R*)-hydroxy-*O*-ethylisoeburnamine (**272**), (−)-isoeburnamine (**275**), kopsiofficines H–K (**278–281**), (+)-larutensine (**283**), larutenine (**284**), larutenines A–B (**285–**286), (−)-norpleiomutine (**289**), (+)-19-oxoeburnamine (**292**), (−)-19-oxoisoeburnamine (**294**), 20-oxo-eburnamenine (**296**), phutdonginin (**297**), terengganensines A–B (**298–299**), and yunnanoffine C (**301**) were new in literature and isolated from genus *Kopsia* for the first time. Eburnamines is now abundant in genus *Kopsia*, but this chemical class was only found in the family Apocynaceae.

### 2.4. Akuammilines, sarpagines, and aspidophyllines

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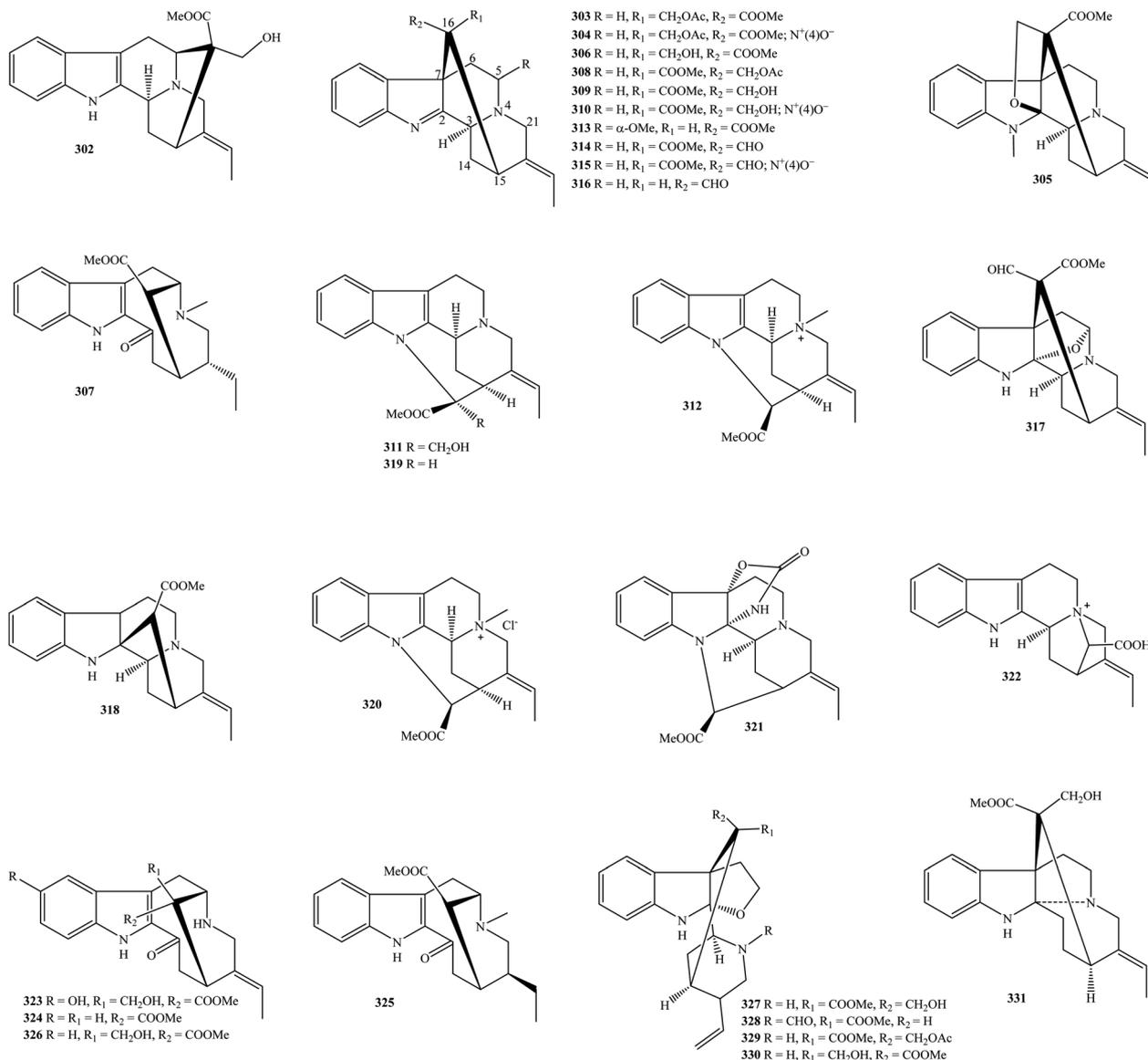
**Fig. 4** Akuammilines, sarpagines and aspidophyllines from genus *Kopsia*.

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

The first compound akuammidine (302) was originated from *K. arborea* stem bark, *K. singapurensis* root, stem bark, and leaves, while akuammiline (303) presented in the aerial part of *K. macrophylla* and *K. teoi*.[10,23,27,32,34,43,45,47–49] Akuammiline *N*(4)-oxide (304) and 16-*epi*-deacetylakuammiline-*N*(4)-oxide (310) were reported to be two new derivatives, which were separated from the rich alkaloidal fraction of *K. griffithii* stem bark.[15] ψ-Akuammigine (305), dregamine (307), *N*-methylpleiocarpamine (312), 5-methoxystrictamine (313), rhazimal (314), rhazinaline *N*(4)-oxide (315), picralinal (317), pleiocarpamine

methochloride (320), and pleiomalicine (321) were isolated from genus *Kopsia* for the first time.[9,10,15,16,27,31,36] Lastly, two new metabolites, rhazinoline (316) and singaporentinidine (322), were purified from the extracts of *K. arborea* stem bark, *K. singapurensis* root, respectively.[10,35]

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

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

Aspidodasycarpine (**327**) was recorded by various authors and was detected in *K. singapurensis* root and stem bark, *K. teoi* stem, and stem bark.[23,32,34,36,43,48,49] Two new phyto constituents aspidophyllines A–B (**328–329**), were determined to exist in *K. singapurensis* stem bark, while the new analog vincophylline (**331**)

was found in its leaves.[32,48] It can be concluded that lonicerine (**330**) was a major component in the group of aspidophyllines because it has occurred in various *Kopsia* plants such as *K. fruticosa* stem bark, *K. singapurensis* bark and stem bark, and *K. teoi* stem, stem bark and leaf.[23,31–34,36,43,48]
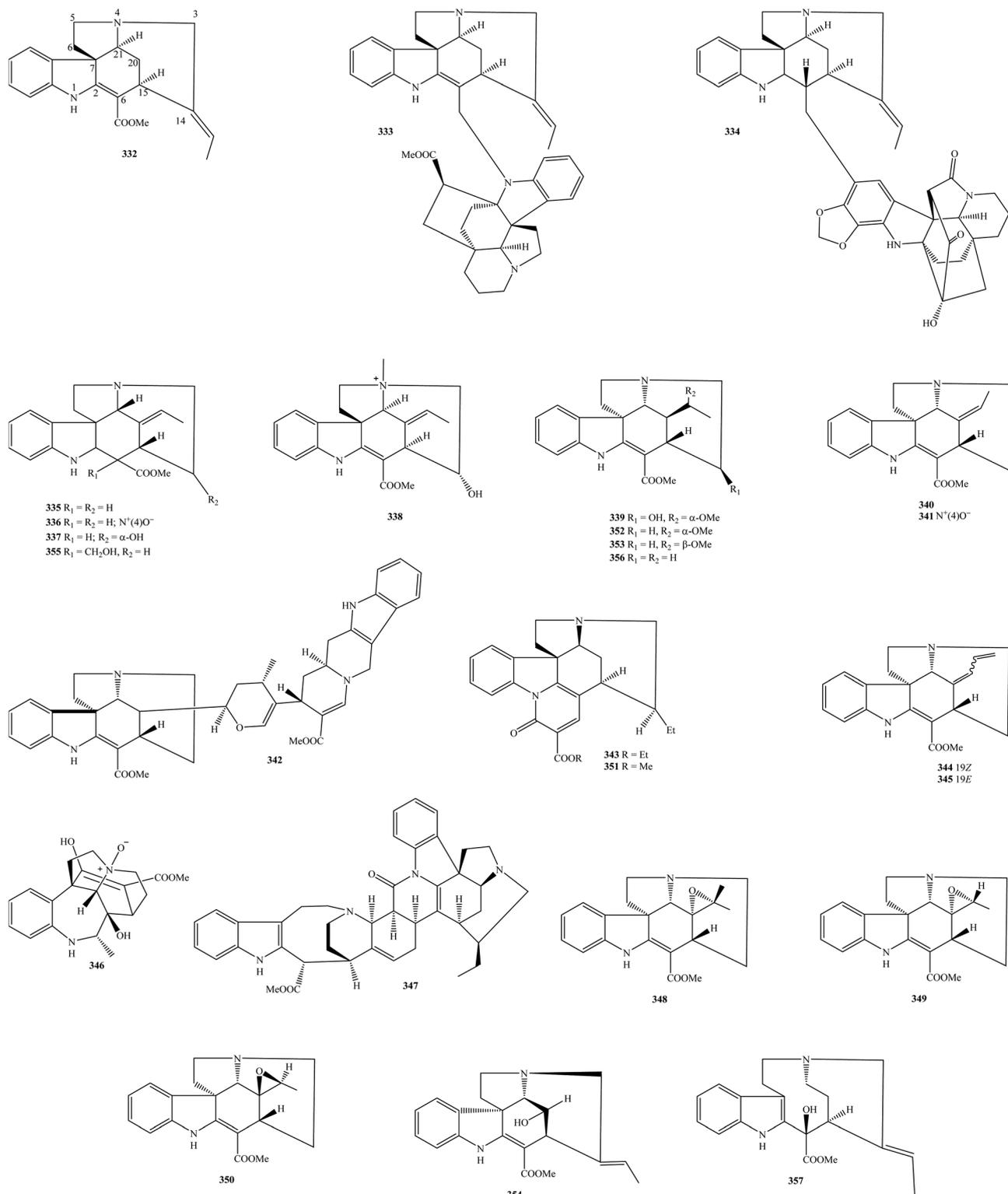


Fig. 5  Strychnoses and stemmadenine from genus *Kopsia*.

## 2.5. Strychnoses

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

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

hydroxy-19(*R*)-methoxy derivative 339 isolated from the MeOH extract of *K. jasminiflora* stem bark has been determined as a new metabolite.[24,29,64,95] Stemmadenine (357) from *K. pauciflora* leaves was the only stemmadenine detected in the genus *Kopsia*.[22]

## 2.6. Mersinines and pauciflorines

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

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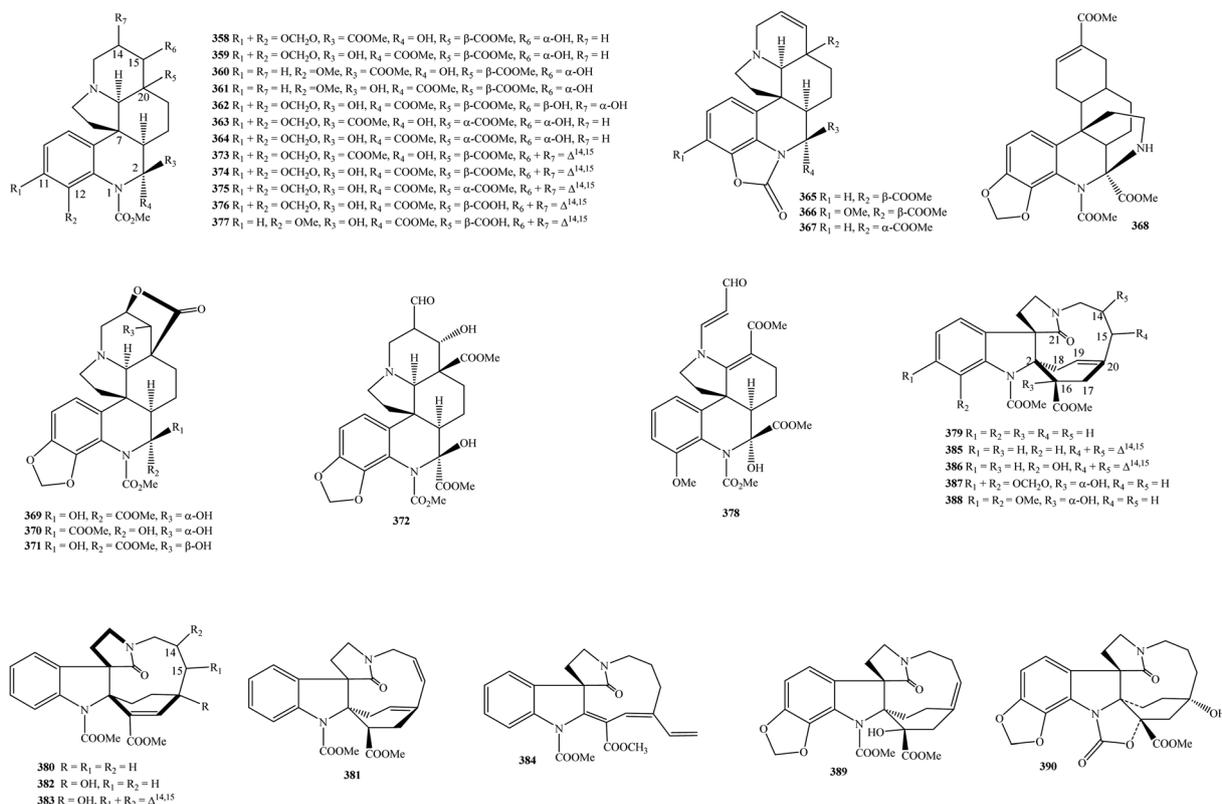


**Fig. 6** Mersinines and pauciflorines from genus *Kopsia*.

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

## 2.7. Skytanthines, rhazinilams, and lundurines

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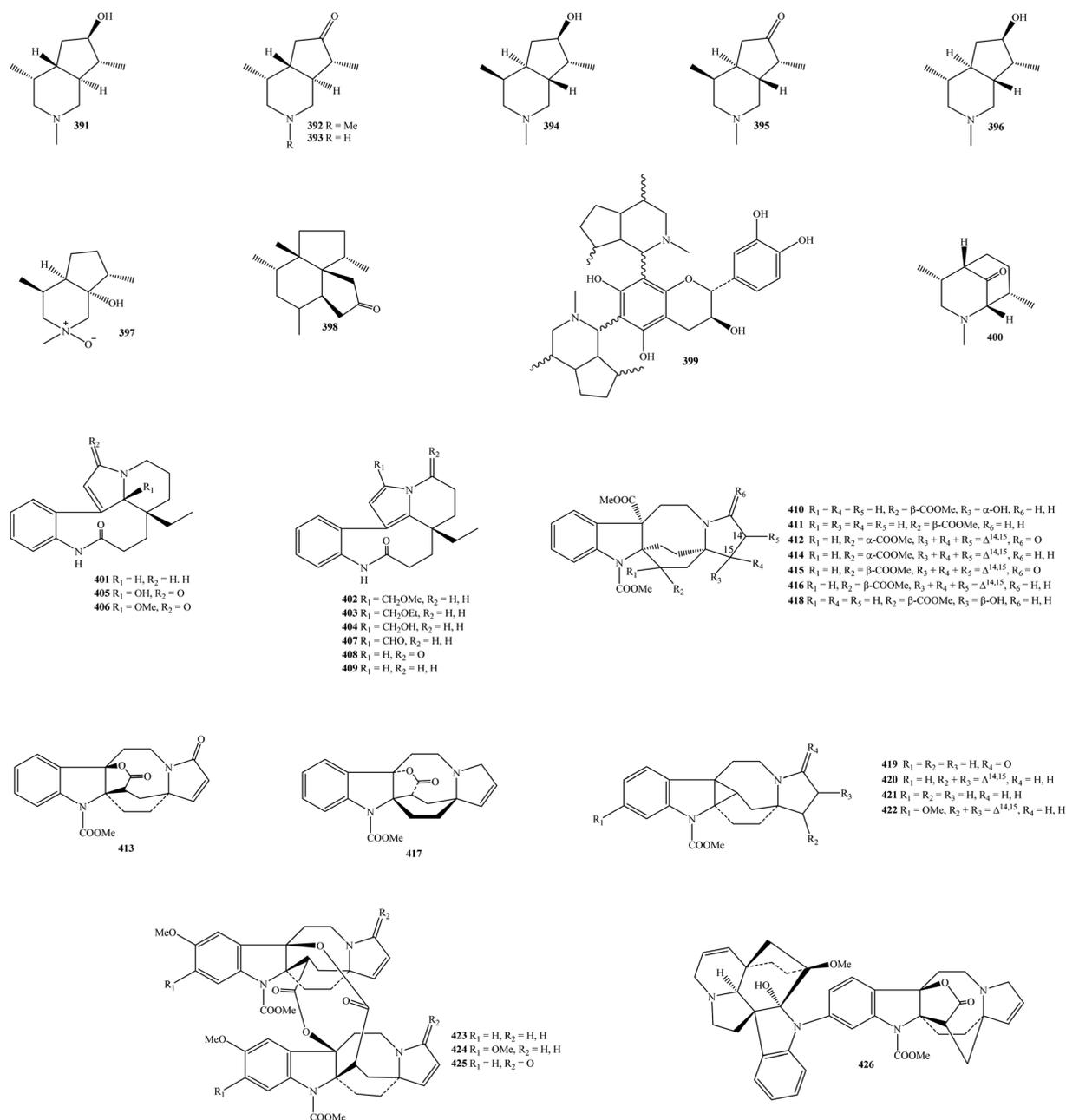


Fig. 7 Skytanthines, rhazinilams and lundurines from genus *Kopsia*.

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

Apocynaceae plants, especially between genera *Skytanthus* and *Kopsia*.

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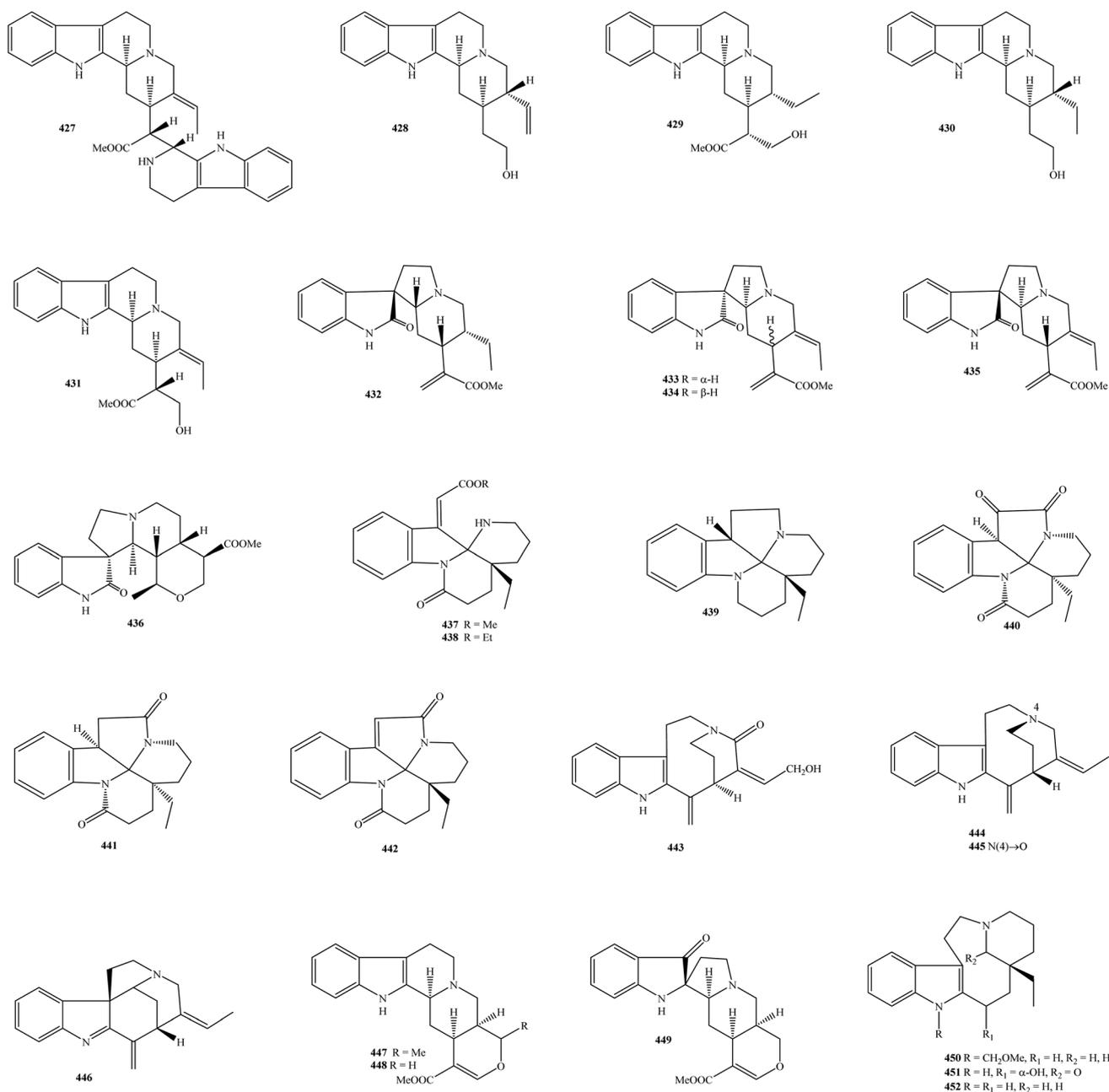


**Fig. 8** Aspidospermas, catharinensines, leuconoxines, pericines, alstonines and quebrachamines from genus *Kopsia*.

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

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

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

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

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

Catharinensines, which belong to the group of oxindole alkaloids, can be found in several higher plants, such as

*Peschiera catharinensis*.[126] In *Kopsia* plants, five catharinensines 432–436 were detected (Table 1 and Fig. 8). Phytochemical research conducted by Gan and partners revealed that the use of mobile phase CHCl$_3$–MeOH is appropriate to isolate alkaloidal catharinensines.[22] By this approach, three new compounds, kopsirensines A–C (433–435), together with known analog catharinensine (432), have been successfully purified from the acidic EtOH extract of *K. pauciflora* leaves.[22] New catharinensine kopsiyunnanine B (436) was first collected as a light yellow solid from the alcoholic extract of *K. officinalis* aerial part, and then was detected in the *K. arborea* aerial part.[96,97]

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

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

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

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

## 2.9. Others indole alkaloids and non-alkaloids

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

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

To date, there have not been many results on the separation of non-alkaloidal constituents from the plants of the genus *Kopsia*. A phytochemical report from Shan and partner (2017) identified that

the *n*-hexane extract of *K. singapurensis* dried leaf and bark has accompanied with the existence of five triterpenoids β-amyrin (**467**), β-amyrin acetate (**468**), β-amyrone (**469**), lupeol (**470**), lupeol acetate (**471**), and one sterol stigmasterol (**472**) (Table 1 and Fig. 10).[122] This is the first time to observe these compounds in the genus *Kopsia*.

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

# 3. Pharmacological activities

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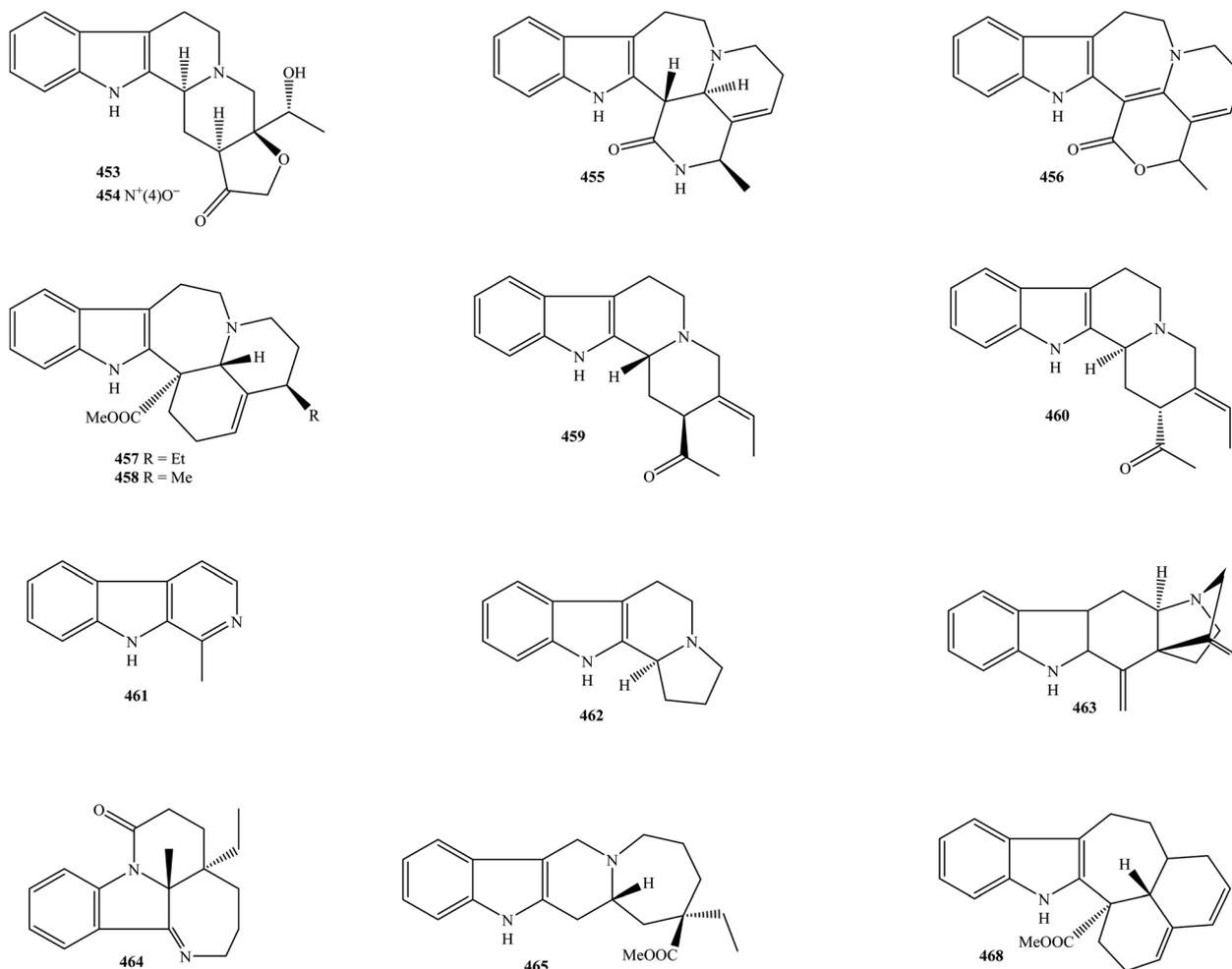


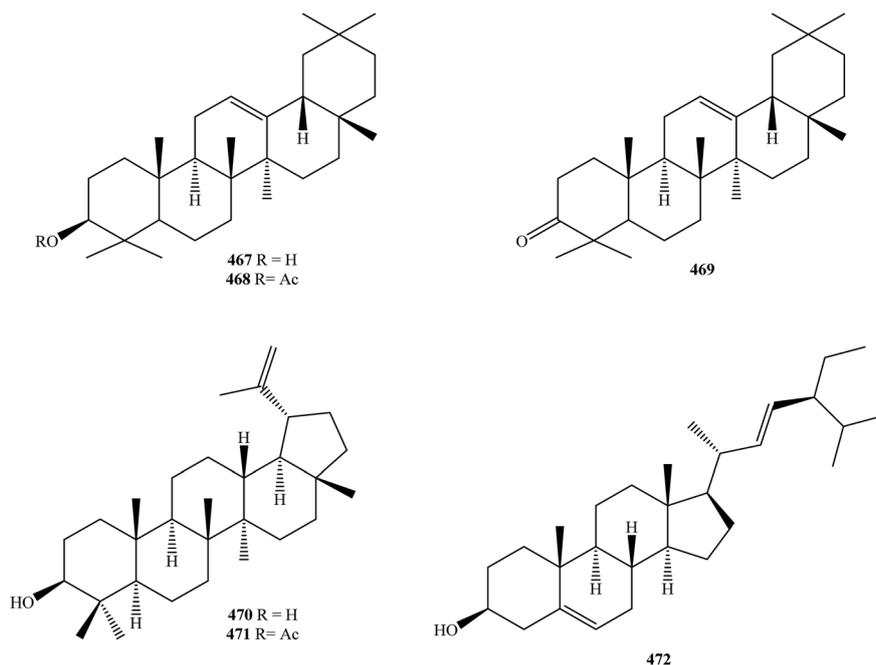Fig. 9 Others type indole alkaloids from genus *Kopsia*.

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

### 3.1. Cytotoxic activity

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

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

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

from 7.2 to 8.9 µM to inhibit BGC-823, HepG-2, MCF-7, SGC-7901, and SK-MEL-2 cells, but new metabolites **214–215** was inactive ($IC_{50}$ > 20 µM).[85]

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

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

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

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

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

**Table 2** (Contd.)

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

Table 2 (Contd.)

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

**Table 2** (*Contd.*)

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

Table 2 (Contd.)

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

**Table 2**  (*Contd.*)

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

Table 2 (Contd.)

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

Table 2  (Contd.)

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

**Table 2** (*Contd.*)

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

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

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

### 3.2. Anti-microbial activity

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

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

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

### 3.3. Anti-inflammatory activity

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

The secretion of cytokines IL-1β and TNF-α or PGE2 levels has mainly caused inflammatory reactions. When LPS-stimulated RAW 264.7 cells, at the concentration of 5 μg mL$^{-1}$, kopsia C (**219**), methyl *N*$_1$-decarbomethoxychanofruticosinate (**225**), methyl 12-methoxychanofruticosinate (**228**), kopsiofficines I–J (**279–280**), (+)-*O*-methyleburnamine (**290**), (−)-*O*-methylisoeburnamine (**291**), and leuconodine D (**439**) have remarkable anti-inflammatory effects on IL-1β and TNF-α, and PGE2, and comparable with positive control dexamethasone at the concentration of 10 μg mL$^{-1}$.[75]

### 3.4. Anti-allergic and antidiabetic activities

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

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

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

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

Kopsinine **126** (70 mg kg$^{-1}$, i.p.) and methyl *N*$_1$-decarbomethoxychanofruticosinate **225** (250 mg kg$^{-1}$, i.p.) exhibited 88 and 76% cough inhibition in the antitussive assays when citric acid activated guinea pig cough model.[65] In addition, antitussive effect of compound **126** was due to its interaction with δ-opioid receptors.[65]

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

### 3.6. Cardiovascular and vasorelaxant activities

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

Vasodilators can be used for cerebral vasospasm and hypertension treatments, as well as to enhance peripheral circulation.[138,139] Flavisiamines A, C, and D (**208** and **210–211**), kopreasin A (**216**), methyl 11,12-methylenedioxychanofruticosinate (**219**), methyl *N*$_1$-decarbomethoxychanofruticosinate (**225**), methyl 12-methoxy-*N*$_1$-decarbomethoxychanofruticosinate (**227**), methyl 12-methoxychanofruticosinate (**228**), methyl 11,12-methylenedioxy-*N*$_1$-decarbomethoxychanofruticosinate (**229**), methyl 11,12-methylenedioxy-*N*$_1$-decarbomethoxy-Δ$^{14,15}$-chanofruticosinate (**230**), and prunifoline B (**239**) at the concentration of 3 × 10$^{-5}$ M showed a moderate vasorelaxant effect of 14–41% when phenylephrine (3 × 10$^{-7}$ M) precontracted rat aortic rings.[84]

## 4. Conclusion and future perspectives

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

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

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

## Abbreviations

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

## Conflicts of interest

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

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