A comprehensive review on phytochemistry and pharmacology of genus *Kopsia*: monoterpenoid 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*", "monoterpenoid 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 monoterpenoid alkaloids, five triterpenoids, and one sterol, were summarized, along with their resource. *Kopsia* monoterpenoid alkaloids presented in various skeletons, but aspidofractinines, eburnamines, and chanofruticosinates are the three major backbones. Mersinines and pauciflorines are new chemical classes of monoterpenoid alkaloids. With the rich content of monoterpenoid alkaloids, *Kopsia* constituents were also the main objects in pharmacological studies since the plant extracts and isolated compounds were proposed for antimicrobial, anti-inflammatory, anti-allergic, anti-diabetic, anti-manic, anti-nociceptive, acetylicholinesterase (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* Tsiaing & P. T. Li to treat rheumatoid arthritis, pharyngitis, tonsillitis, and dropsy.\(^4\) In Malaysia, the roots of four species, *K. larutensis* King & Gamble, *K. macrophylla* Hook.f., *K. singapurenensis* Ridl., and *K. paucifora* Hook.f., were applied as a poultice to ulcerate noses in tertiary syphilis.\(^5,6\) *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.\(^8\)–\(^1\) Though 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. lancebracteolata, K. lapidiflora, 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 monoterpenic alkaloids, in which they have induced a diversity of chemical skeletons, including aspidofractinines 1–204, chano-frutosinates 205–241, aspidospermingines 242–248, danuphylines 249–252, eburnamines 253–301, auammlines 302–322, sarpagines 323–326, aphydophyllines 327–331, strychnosin 332–356, stemmadenine 357, mersinines 358–378, pauciflorines 379–390, skytanthines 391–400, rhiadinols 401–409, lundurines 410–426, aspidospermas 427–431, catharinenines 432–436, leuconoxines 437–442, pericines 443–446, alstonines 447–449, quebrachamines 450–452, arbophyllines 453–454, arboflorines 455–456, andrasinines 457–458, corynantheines 459–460, carbolines 461–462, arbophyllidine 463, mersicarepine 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. jasminiflora, K. larutensis, K. macrophylla, K. officinalis, K. pauciflora, K. profunda, K. singapurensis, and K. teoi.47–79,81 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, epoxidation at carbons C-11 and C-12, and hydroxylation, or methylation at carbons C-11, C-12, C-16, C-17, and C-18. It was found that 5,22-dioxygenopane (17), kopsamine (39), kopsamine N-oxide (40), kopsanone (41), kopsifine (73), kopsilongine (91), kopsinonic acid (117), kopsinilam (124), kopsinine (126), kopsinine-N(4)-oxide (127), pleiocarpine (189), and (--)venalstonine (201) might be seen as characteristic metabolites in the group of Kopsia aspidofractinines. For instance, compound 126 was recorded to appear in K. arborea twig and stem bark, K. dasyrachis stem, K. fruticosa stem bark, K. jasminiflora stem bark, K. grandifolia stem bark, K. griffithii leaf and stem bark, K. hainanensis leaf, stem, stem bark and twig, K. larutensis stem, stem bark and leaf, K. officinalis root, stem, twig, leaf and fruit, K. singapurensis stem bark and leaf, K. pauciflora stem, stem bark and leaf, and K. teoi stem bark, whereas its N(4)-oxide (127) presented in K. dasyrachis stem, K. griffithii stem bark, K. hainanensis stem and leaf, K. officinalis fruit and leaf, K. pauciflora stem, and K. singapurensis bark.5,7–9,11,13–19,21–25,26,28,32,36,42,43,48,51,55,66,68–72

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 aspidofractinines 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,9–11,13,14,15,16 but aspidofractinin-1,3-dicarboxylic acid (4) was only detected in K. officinalis stem.17 [28,5β]-Aspidofractin-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-methoxykopsiline (5) and N-carbomethoxy-11-methoxy-12-hydroxykopsiline (6) were two new metabolites in nature.14–16 Dasyracrine (10) containing isokopnine 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 decarbomethoxykopsiline (11), decarbomethoxyisokopsiline (12), decarbomethoxykopsinol (13), N(1)-decarbomethoxykopsiline (14), Nα-demethoxy carbonyl-12-methoxykopsiline (15), and 10-demethoxykopsidasinine (16) are associated with the decarbomethoxylation at nitrogen N-116,18,19,20,21 Among them, compounds 13, 15, and 16 were new in nature. 11,12-Dimethoxykopsiline (18) was a known metabolite found in K. dasyrachis leaves, but 11,12-dimethoxykopsiline (19) was a new one in the stem bark of K. pauciflora stem bark.22,23 Similarly, 16-epi-kopsinine (20), 16-epi-kopsilinam (21), 16-epi-17α-hydroxy-14,15-kopsinine (22), 14,15-β-epoxyskopin (23), N(1)-formylkopsinonic acid (24), N(1)-formylkopsinonic acid-N(4)-oxide (25), frucitosamine (26), frucitosamine A (27), and frucicosine (28) were new aspidofractinines, and found in genus Kopsia for the first time.11,20,24,29,31,37,39 The known metabolite 11-hydroxykopsilongine (29) has been detected in both the fruit and leaf of K. officinalis,12,25 while 11-hydroxykopsiline (30), 5β-hydroxykopsiline (31), and 15-hydroxykopsiline (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 kopsiline, respectively (Fig. 1). In the meantime, the structure of the new metabolite 35 is closely related to kopsiline 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 kopsijasminone (89), from the MeOH extract of K. jasminiflora leaves, whereas
| No. | Compounds                                      | Species                          | References                      |
|-----|------------------------------------------------|----------------------------------|---------------------------------|
| 1   | Arbolodinine A                                 | K. arborea stem bark             | 8                               |
| 2   | Aspidofractine                                 | 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-methoxykopsinylane | K. griffithii leaf, K. officinalis twig, leaf and fruit | 14–16                          |
| 6   | N-Carbomethoxy-11-methoxy-12-hydroxykopsinylane | K. officinalis fruit            | 14                              |
| 7   | N[1]-Carbomethoxy-11, 12-dimethoxykopsinylane | K. griffithii leaf, K. officinalis fruit | 14, 15 and 17                   |
| 8   | N-Carbomethoxy-12-methoxykopsinylane          | K. officinalis fruit            | 14                              |
| 9   | N-Carbomethoxy-5,22-dioxokopsane              | K. dasyrachis stem, K. paciflora 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  | Decarbomethoxykopsine                         | K. arborea twig, K. dasyrachis stem, K. paciflora leaf, K. officinalis leaf | 11, 18, 19, 21 and 22, stem and stem bark |
| 14  | N[1]-Decarbomethoxykopsamine                 | K. arborea stem twig, K. hainanensis stem and leaf, K. paciflora leaf, K. singapurensis leaf | 7, 10, 22 and 23                    |
| 15  | N[1]-Demethoxy-carbonyl-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 leaf | 11, 12, 14, 16, 19 and 19, root, stem, twig and fruit, K. paciflora stem bark | 27–29 |
| 18  | 11,12-Dimethoxykopsamine                      | K. dasyrachis leaf              | 30                              |
| 19  | 11,12-Dimethoxykopsinylane                   | K. paciflora 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-Δ⁴⁻¹⁵⁻kopsinine             | K. teo stem bark and leaf        | 33                              |
| 23  | 14,15-β-Epoxypokspingine                     | K. teo leaf                     | 34                              |
| 24  | N[1]-Formylkopsinonic acid                    | K. singapurensis root            | 35 and 36                        |
| 25  | N[1]-Formylkopsinonic acid-N(4)-oxide         | K. singapurensis root            | 35 and 36                        |
| 26  | Fruticosamine                                 | K. fruticosa leaf, K. jasminiflora leaf | 20 and 37–41                     |
| 27  | Fruticosamine A                               | K. fruticosa leaf               | 41                              |
| 28  | Fruticosine                                   | K. jasminiflora leaf, K. fruticosa leaf, K. officinalis twig | 20 and 37–42                        |
| 29  | 11-Hydroxykopsiavidine                        | K. officinalis fruit and leaf    | 13 and 25                        |
| 30  | 11-Hydroxykopsipingine                        | K. teo 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 leaf | 10, 31 and 36                        |
| 34  | 17α-Hydroxykopsinine                          | K. teo stem bark                | 43                              |
| 35  | 17α-Hydroxy-Δ⁴⁻¹⁵⁻kopsinine                   | K. singapurensis stem bark and leaf, K. teo 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. paciflora stem and stem bark, K. singapurensis leaf and root, K. teo 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. paciflora 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. paciflora stem and stem bark, K. officinalis fruit | 10, 14, 19, 22, 24, 29, 31 |
| 42  | Kopsaporine                                   | K. singapurensis stem bark, K. teo 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                              |
| 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  | Kopsiaofficeine A            | K. officinalis aerial part       | 55         |
| 60  | Kopsiaofficeine B            | K. officinalis aerial part       | 55         |
| 61  | Kopsiaofficeine C            | K. officinalis aerial part       | 55         |
| 62  | Kopsiarborines A             | K. arborea aerial part           | 56         |
| 63  | Kopsidarine                 | K. singapurensis leaf            | 48         |
| 64  | Kopsidamine                  | K. dasyrychis leaf               | 57         |
| 65  | Kopsidamine-N-oxide          | K. dasyrychis leaf               | 57         |
| 66  | Kopsidamine                  | K. dasyrychis 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. dasyrychis 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. dasyrychis stem, K. hainanensis stem and leaf, K. officinalis leaf | 7, 10, 12, 13, 18 and 61 |
| 75  | Kopsiflorine N(4)-oxide      | K. dasyrychis 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. dasyrychis stem, K. griffithii leaf and stem bark, K. officinalis leaf, K. pauciflora stem | 10, 13, 15, 17–19, 21, 22 and 32 |
| 92  | Kopsilongine-N-oxide        | K. singapurensis leaf            | 32         |
| 93  | Kopsiloscin A                | K. singapurensis leaf            | 32         |
| 94  | Kopsiloscin B                | K. singapurensis leaf            | 32         |
| 95  | Kopsiloscin C                | K. singapurensis leaf and stem bark | 32 and 48 |
| 96  | Kopsiloscin D                | K. singapurensis leaf            | 32         |
| 97  | Kopsiloscin E                | K. singapurensis leaf            | 32         |
| 98  | Kopsiloscin F                | K. singapurensis leaf            | 32         |
| 99  | Kopsiloscin G                | K. singapurensis stem bark and leaf | 23 and 48 |
|100  | Kopsiloscin H                | K. singapurensis stem bark       | 23         |
|101  | Kopsiloscin I                | K. hainanensis stem and leaf, K. singapurensis stem bark | 7 and 23 |
|102  | Kopsiloscin 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         |
| No. | Compounds                  | Species                                    | References |
|-----|---------------------------|--------------------------------------------|------------|
| 109 | Kopsinarine               | *K. dasyrachis* stem, *K. hainanensis* twig | 12, 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, bark and leaf | 32, 34, 43, 45, 47 and 48 |
| 112 | Kopsingingine             | *K. singapurensis* leaf and stem bark, *K. teoi* stem, bark and leaf | 32-34, 44, 45 and 48 |
| 113 | Kopsinginine              | *K. teoi* stem and bark                     | 34, 43–45 and 47 |
| 114 | Kopsinginol               | *K. teoi* stem and bark                     | 34, 45 and 47 |
| 115 | Kopsinidine A             | *K. arborea* stem bark                      | 10         |
| 116 | Kopsinidine B             | *K. arborea* stem bark                      | 10         |
| 117 | Kopsinonic acid (kopsinic acid) | *K. hainanensis* stem bark, *K. officinalis* stem, twig and leaf, *K. singapurensis* bark and leaf | 11, 13, 16, 24, 29 and 36 |
| 118 | Kopsinine                 | *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 | Kopsiniam                 | *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 | Kopsisinolate             | *K. hainanensis* stem and leaf              | 7          |
| 126 | Kopsinine                 | *K. arborea* twig and stem bark, *K. dasyrachis* stem, *K. fruticosa* stem, *K. singapurensis* stem bark and leaf, *K. grandifolia* stem bark, *K. griffithii* stem bark, *K. jasminiflora* stem bark, *K. kopsinoides* stem bark, *K. jasminiflora* stem bark, *K. hainanensis* stem, bark and leaf, *K. singapurensis* stem bark and leaf, *K. fruticosa* stem, *K. hainanensis* stem, bark and leaf, *K. officinalis* stem bark and leaf, *K. teoi* stem and leaf, *K. pauci* stem, bark and leaf, *K. teoi* stem and leaf, *K. officinalis* fruit and leaf, *K. pauci* stem and leaf, *K. singapurensis* stem bark and leaf, *K. officinalis* stem, twig, leaf and fruit, *K. singapurensis* stem bark and leaf, *K. pauci* stem and leaf, *K. teoi* stem and leaf | 7, 13, 15, 18, 25 and 36 |
| 127 | Kopsinine-N(4)-oxide      | *K. dasyrachis* stem, *K. griffithii* stem bark, *K. hainanensis* stem and leaf, *K. officinalis* fruit and leaf, *K. pauci* stem, *K. singapurensis* stem bark and leaf | 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 | Kopsinitaritine A         | *K. singapurensis* leaf, *K. teoi* leaf     | 34, 48, 73 and 74 |
| 132 | Kopsinitaritine B         | *K. singapurensis* leaf, *K. teoi* leaf     | 34, 48, 73 and 74 |
| 133 | Kopsinitaritine C         | *K. teoi* leaf                             | 34, 73 and 74 |
| 134 | Kopsinitaritine D         | *K. teoi* leaf                             | 34 and 74  |
| 135 | Kopsinitaritine E         | *K. teoi* stem bark                        | 43         |
| 136 | Kopsinol                  | *K. teoi* stem and bark                     | 34, 45 and 47 |
| 137 | (--) Kopsinoline          | *K. hainanensis* stem bark, *K. officinalis* stem, twig and leaf | 11, 16 and 29 |
| 138 | Kopsiofifitine A          | *K. officinalis* stem                      | 11         |
| 139 | Kopsiofifitine B          | *K. officinalis* stem                      | 11         |
| 140 | Kopsiofifitine C          | *K. officinalis* stem                      | 11         |
| 141 | Kopsiofifitine D          | *K. officinalis* stem                      | 11         |
| 142 | Kopsiofifitine E          | *K. officinalis* stem                      | 11         |
| 143 | Kopsiofifitine F          | *K. officinalis* stem                      | 11         |
| 144 | Kopsiofifitine L          | *K. officinalis* stem                      | 75         |
| 145 | Kopsinofine               | *K. singapurensis* leaf                    | 23         |
| 146 | Kopsonoline               | *K. teoi* stem                            | 43         |
| 147 | Kopsoninone               | *K. teoi* stem                            | 43         |
| 148 | Lahadinine A              | *K. pauci* leaf                           | 76         |
| 149 | Lahadinine B              | *K. pauci* 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)-Methoxy carbonyl-11,12-dimethoxykopsinaline | *K. arborea* stem bark, *K. pauci* stem | 10, 19 and 51 |
| 153 | N(1)-Methoxy carbonyl-11,12-methoxylendioxypsinaline | *K. officinalis* leaf, twig and stem, *K. pauci* stem and leaf | 11, 16, 42, 51, 69 and 76 |
| 154 | N(1)-Methoxy carbonyl-11,12-methylenedioxy-Δ16,17-kopsinidine | *K. profunda* stem | 4 |
| 155 | N(1)-Methoxy carbonyl-12-methoxy-Δ16,17-kopsinidine | *K. griffithii* leaf, *K. pauci* stem, *K. profunda* stem and leaf, *K. teoi* stem | 4, 17, 19, 43, 51 and 77 |
| 156 | N(1)-Methoxy carbonyl-12-methoxykopsinidine | *K. officinalis* root, stem, twig, leaf and fruit, *K. pauci* 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 (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 (4)-oxide | K. profunda stem and leaf | 77 |
| 160 | 11-Methoxykopsingingine | K. tei leaf | 34 |
| 161 | 11-Methoxypseudoisinol | K. dasyrachis stem, K. officinalis stem and leaf | 11, 13 and 18 |
| 162 | 11-Methoxypseudoisinol N(4)-oxide | K. dasyrachis stem | 18 |
| 163 | 11-Methoxy-12-hydroxy-kopsinol | K. tei 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, K. pauciflora leaf, K. jasminiflora stem bark | 7, 15, 17-19 and 30 |
| 169 | (--)Methylenedioxy-11,12-kopsinol | K. arborea twig | 7 |
| 170 | (4)-Methylkopsininate | K. officinalis leaf and twig | 16 |
| 171 | 11,12-Methylenedioxykopsaporine | K. singapurensis bark, K. tei 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-Methylenedioxykopsinol N(4)-oxide | K. griffithii stem bark, K. officinalis stem, twig and leaf | 11, 15 and 16 |
| 174 | K. arborea stem bark, K. dasyrachis stem, K. officinalis stem, K. pauciflora stem bark | K. pauciflora stem bark | 11, 18 and 22 |
| 175 | Nitaphylline | K. tei leaf | 34, 46 and 80 |
| 176 | 5-Oxokopsininc 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 | Pauclusidine | K. pauciflora stem bark | 19 |
| 184 | Pauclidirinine | K. pauciflora stem bark | 19 |
| 185 | Pauclidirisine | K. pauciflora stem bark | 19 |
| 186 | Paucliduridine | K. officinalis stem, K. pauciflora stem bark | 11 and 19 |
| 187 | Pauclifinine | K. pauciflora stem and bark | 22 and 76 |
| 188 | Pauclifinine-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, K. jasminiflora stem bark, K. officinalis twig and leaf, K. pauciflora stem bark | 10, 14, 15, 17-19, 25 |
| 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 leaf | 79 |
| 195 | Singapurensine B | K. singapurensis leaf | 79 |
| 196 | Singapurensine C | K. singapurensis leaf | 79 |
| 197 | Singapurensine D | K. singapurensis leaf | 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 leaf | 10, 31, 36 and 81 |
| 202 | Yunnanofficine A | K. officinalis leaf | 25 |
| 203 | Yunnanofficine B | K. officinalis leaf | 25 |
| 204 | Yunnanofficine D | K. officinalis leaf | 25 |

Chanosfruticosinates

| 205 | Chanosfruticosic acid | K. officinalis leaf and twig | 16 |
| 206 | N\(_\text{2}\)-Decarbomethoxy chanosfruticosic 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 |
| 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. lancebacteolata* stem                   | 85                    |
| 215 | 12-Hydroxylprunifoline C                      | *K. lancebacteolata* stem                   | 85                    |
| 216 | Kopreatin A                                   | *K. arborea* leaf                           | 84                    |
| 217 | Kopsia A (methyl chanofruticosinate)          | *K. dasyrachis* leaf, *K. hainanensis* stem and leaf, *K. officialis* leaf, twig, and stem, *K. pauciflora* leaf | 7, 13, 16, 22, 25, 30, 75 and 86 |
| 218 | Kopsia B (des-Ne-methoxy carbonyl) chanofruticosin-methylster | *K. officialis* leaf                        | 86                    |
| 219 | Kopsia C (6,7-methylenedioxy chanofruticosin-methylster or methyl 11,12-methylenedioxy chanofruticosin) | *K. arborea* leaf and stem bark, *K. dasyrachis* leaf, *K. flavida* leaf, *K. officialis* stem and leaf, *K. pauciflora* stem bark and leaf | 10, 16, 22, 30, 75, 84, and 86 |
| 220 | Kopsihainanine A                              | *K. hainanensis* leaf and stem               | 6                     |
| 221 | Kopsihainanine B                              | *K. hainanensis* leaf and stem               | 6                     |
| 222 | 12-Methoxy chanofruticosin acid              | *K. officialis* leaf and twig                | 16                    |
| 223 | Methyl chanofruticosin N(4)-oxide             | *K. hainanensis* stem and leaf               | 7                     |
| 224 | Methyl 11,12-dimethoxy chanofruticosin        | *K. arborea* leaf, *K. flavida* leaf, *K. officialis* leaf | 13, 22, 25, 82, 88 and 89 |
| 225 | Methyl N1-decarbomethoxy chanofruticosin     | *K. arborea* leaf and stem bark, *K. dasyrachis* leaf, *K. flavida* 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 N1-decarbomethoxy chanofofruticosin N(4)-oxide | *K. hainanensis* stem and leaf               | 7                     |
| 227 | Methyl 12-methoxy-N1-decarbomethoxy chanofofruticosin | *K. arborea* leaf, *K. flavida* leaf         | 83, 84, 88 and 89     |
| 228 | Methyl 12-methoxy chanofofruticosin           | *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-N1-decarbomethoxy chanofofruticosin | *K. arborea* stem bark and leaf, *K. dasyrachis* leaf, *K. flavida* leaf, *K. officinalis* 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-N1-decarbomethoxy-Δ14,15-chanofofruticosin | *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,19αs)-6,7-didehydro-8,21-dioxo-11,21-cycloaspidospermidine-2-carboxylate | *K. officinalis* leaf                         | 13                    |
| 232 | Methyl 3-oxo-12-methoxy-N1-decarbomethoxy-14,15-didehydro chanofofruticosin | *K. flavida* leaf                            | 89                    |
| 233 | Methyl 3-oxo-11,12-methylenedioxy-N1-decarbomethoxy-14,15-didehydro chanofofruticosin | *K. flavida* leaf                            | 89                    |
| 234 | Δ1,2-Methyldemethoxy carbonyl chanofofruticosin | *K. officinalis* leaf                         | 25                    |
| 235 | 11,12-Methylenedioxy chanofofruticosin acid  | *K. officinalis* leaf and twig                | 16                    |
| 236 | 3-Oxo-11,12-dimethoxy-N6-decarbomethoxy-14,15-didehydro chanofofruticosin | *K. fruticosa* aerial part                  | 3                     |
| 237 | N(4)-Oxide prunifoline D                      | *K. lancebacteolata* 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                    |
| 242 | Aspidospermine                                 | *K. pauciflora* leaf                        | 22                    |
| 243 | (+)-1,2-Dehydroaspidospermine                 | *K. pauciflora* leaf                        | 22                    |
| 244 | Eburenine                                     | *K. arborea* aerial part                    | 90                    |
| 245 | Kopsioficine G                                | *K. officinalis* stem                       | 11                    |
| 246 | Kopsiunnanine G                               | *K. arborea* aerial part                    | 90                    |
| 247 | Vincadiformine                                | *K. arborea* twig and stem bark, *K. officinalis* stem and fruit | 10, 11, 14 and 21   |
| 248 | Vincadiformine N(4)-oxide                     | *K. officinalis* stem                       | 11                    |

**Aspidospermines**

| No. | Compounds                                      | Species                                      | References            |
|-----|-----------------------------------------------|----------------------------------------------|-----------------------|
| 249 | Danuphyline                                   | *K. dasyrachis* leaf                         | 30 and 91             |
| 250 | Danuphyline B                                 | *K. arborea* leaf                           | 78                    |
| 251 | 11,12-De(methylenedioxy) danuphyline          | *K. officinalis* leaf                        | 13                    |
| No. | Compounds                  | Species                          | References |
|-----|----------------------------|----------------------------------|------------|
| 252 | Kopsihainin A              | *K. hainanensis* stem            | 65         |
| 253 | (−)-Demethyloropleiomutine |                                  |            |
| 254 | (+)-Eburnamenine           | *K. pauci* twig, *K. pauciflora* stem | 18 and 19 |
| 255 | (−)-Eburnamenine           | *K. arborea* twig and stem bark  | 19 and 22  |
| 256 | (+)-Eburnamine             | *K. hainanensis* stem            | 29         |
| 257 | (−)-Eburnamine             | *K. arborea* twig, *K. hainanensis* twig and stem bark, *K. pauciflora* stem and stem bark, *K. singapurensis* stem bark, *K. terengganensis* bark | 5, 9, 15, 19, 22, 23, 50, 51, 66, 68, 70, 77, 90 and 92 |
| 258 | (−)-Eburnaminol            | *K. larutensis* stem, *K. terengganensis* bark | 68 and 92 |
| 259 | (+)-Eburnamonine           | *K. arborea* parental, *K. dasyrachis* stem, *K. griffithii* leaf, *K. jasmini* leaf and stem bark, *K. officinalis* leaf and stem twig, *K. pauciflora* stem and stem bark, *K. officinalis leaf and twig, *K. officinalis root and stem bark, *K. officinalis stem and twig, *K. officinalis leaf* | 5, 13, 15, 17–19, 42, 51, 68, 70, 90 and 93 |
| 260 | (+)-Eburnamine (N(4)-oxide)| *K. larutensis* leaf and stem | 5 and 70   |
| 261 | (−)-Eburnamonine           | *K. jasminiflora* stem bark      | 24         |
| 262 | (−)-O-Ethyleburnamine      | *K. arborea* parental, *K. larutensis* stem | 70 and 90 |
| 263 | (+)-Ethylisoeburnamine      | *K. arborea* aerial part         | 77         |
| 264 | 16α-Hydroxy-19-o xoeburnamine | *K. officinalis* leaf            | 25         |
| 265 | 16β-Hydroxy-19-o xoeburnamine | *K. officinalis* leaf            | 25         |
| 266 | (+)-19(R)-Hydroxyeburnamine| *K. dasyrachis* stem             | 18 and 93  |
| 267 | 19-Hydroxy(−)-eburnaminol  | *K. arborea* twig, *K. larutensis* leaf, *K. officinalis* twig, *K. pauciflora* stem and stem bark, *K. officinalis leaf and stem twig, *K. officinalis stem and twig, *K. officinalis leaf and twig, *K. officinalis root and stem bark, *K. officinalis leaf* | 5, 7 and 42 |
| 268 | (+19R)-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-D14-vicamone  | *K. jasminiflora* stem bark      | 24         |
| 274 | (+)-Isoeburnamine           |                                  |            |
| 275 | (−)-Isoeburnamine           | *K. officinalis* root            | 28 and 69  |
| 276 | 16-Isoeburnamine [(+)-methylisoeburnamine)] | *K. arborea* aerial part, *K. officinalis* stem | 75 and 90 |
| 277 | (+)-Kopsoflavin            | *K. hainanensis, *K. officinalis* root | 28 and 29 |
| 278 | Kopsioflavine H             | *K. officinalis* stem            | 75         |
| 279 | Kopsioflavine I             | *K. officinalis* stem            | 75         |
| 280 | Kopsioflavine J             | *K. officinalis* stem            | 75         |
| 281 | Kopsioflavine K             | *K. officinalis* stem            | 75         |
| 282 | Kopsoflavin                | *K. dasyrachis* stem, *K. pauciflora* stem | 19 and 93 |
| 283 | (−)-Larutenin              | *K. larutensis* stem             | 68         |
| 284 | Larutenin                  | *K. larutensis* leaf and stem, *K. officinalis leaf, *K. pauciflora* leaf, *K. terengganensis* bark | 5, 13, 18, 19, 22, 23, 29, 51, 68, 70, 90, 92 and 93 |
| 285 | Larutenine A               | *K. pauciflora* stem and stem bark, *K. teoi* stem bark and leaf, *K. woodii* stem bark and leaf, *K. officinalis root, *K. officinalis leaf and twig, *K. officinalis stem and stem bark, *K. terengganensis* bark | 19 and 22 |
| 286 | Larutenine B               | *K. pauciflora* stem and stem bark | 19 and 22 |
| 287 | Melohonine B               | *K. hainanensis* twig and leaf | 9         |
| 288 | (−)-Methyleneburnamine     | *K. arborea* aerial part         | 90         |
| 289 | (−)-Norpleiomutine         | *K. dasyrachis* stem, *K. macrophylla* bark, *K. pauciflora* stem and stem bark, *K. terengganensis* bark | 18, 19, 22, 27 and 51 |
| 290 | (+)-O-Methyleneburnamine   | *K. officinalis* stem            | 75         |
| 291 | (−)-O-Methylisoeburnamine [(O-methylvincol)] | *K. hainanensis* twig and leaf, *K. officinalis* stem | 9 and 75 |
| 292 | (−)-19-Oxoeburnamine       | *K. pauciflora* stem and stem bark, *K. officinalis* twig | 19 and 22 |
| 293 | 19-Oxo-(−)-eburnamine      | *K. jasminiflora* stem bark, *K. officinalis* twig | 24 and 42 |
| 294 | (−)-19-Oxoeburnamine       | *K. pauciflora* stem             | 19         |
| 295 | 1-Methyl-16-epi-vicamol    | *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 | Δ14-Vicamone               | *K. jasminiflora* stem bark      | 24         |
| 301 | Yunnanoffine C             | *K. officinalis* leaf            | 25         |
| No. | Compounds                      | Species                                   | References            |
|-----|-------------------------------|-------------------------------------------|-----------------------|
| 302 | Akoummidine                   | K. arborea stem bark, K. singapurensis root, stem bark and leaf | 10, 23, 32, 48 and 49 |
| 303 | Akoummiline                   | K. macrophylla bark, K. teoi stem and stem bark | 27, 34, 43, 45 and 47 |
| 304 | Akoummiline N(4)-oxide        | K. griffithii stem bark                   | 15                    |
| 305 | ψ-Akoummigine                 | K. fruticosa stem bark                   | 31                    |
| 306 | Deacetylakoummiline (rhazimol) | K. deverrei stem bark, K. griffithii leaf and stem bark, K. macrophylla | 15, 17, 23, 27, 34, 45, 47 and 94 |
| 307 | Dregamine                     | K. macrophylla bark                      | 27                    |
| 308 | 16-epi-akoummiline            | K. singapurensis leaf, stem bark and root, K. teoi stem bark | 23, 32, 36, 43 and 48 |
| 309 | 16-epi-deacetylakoummiline    | K. deverrei stem bark, K. griffithii stem bark, K. fruticosa stem bark, K. singapurensis stem bark, K. teoi stem and stem bark | 15, 23, 31, 34, 48, 49, 94 |
| 310 | 16-epi-deacetylakoummiline-N(4)-oxide | K. griffithii stem bark, K. singapurensis stem bark | 15 and 36 |
| 311 | 16-Hydroxyethyl-pleiocarpamine| K. deverrei stem bark, K. fruticosa stem bark, K. singapurensis stem bark and K. teoi stem bark | 23, 31, 43, 36 and 94 |
| 312 | N-Methylpleiocarpamine        | K. singapurensis root                     | 36                    |
| 313 | 5-Methoxystictamine           | K. hainanensis twig and leaf             | 9                     |
| 314 | Rhazimal                      | K. arborea stem bark                     | 10                    |
| 315 | Rhazinaline N(4)-oxide        | K. griffithii stem bark                   | 10                    |
| 316 | Rhazinoline                   | K. arborea stem bark                     | 15                    |
| 317 | Picralinal                    | K. hainanensis twig and leaf             | 9                     |
| 318 | Picramicine                   | K. fruticosa stem bark, K. singapurensis stem bark | 23 and 31 |
| 319 | Pleiocarpamine                | K. dasyrychis stem, K. deverrei stem bark, K. fruticosa stem bark, K. singapurensis stem bark, K. teoi stem bark | 18, 31, 36, 43 and 94 |
| 320 | Pleiocarpamine methochloride  | K. officinalis leaf and twig             | 16                    |
| 321 | Pleiomalicicine               | K. hainanensis twig and leaf             | 9                     |
| 322 | Singoparentinidine            | K. singapurensis root                    | 35 and 36             |
| 323 | 10-Hydroxy-vincaffine         | K. hainanensis twig and leaf             | 9                     |
| 324 | Perivine                      | K. officinalis root and stem             | 50                    |
| 325 | Tabernaemontanine             | K. macrophylla bark                      | 27                    |
| 326 | Vincadifline                  | K. hainanensis twig and leaf             | 9                     |
| 327 | Aspidodyasycarpiene           | 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 stem bark and K. teoi stem and stem bark | 23, 31–34, 36, 43 and 48 |
| 331 | Vincophylline                 | K. singapurensis leaf                    | 32                    |
| 332 | Akoummicine                   | K. pauciflora leaf                       | 22                    |
| 333 | Arbolodinine B                | K. arborea stem bark                     | 8                     |
| 334 | Arbolodinine C                | K. arborea stem bark                     | 8                     |
| 335 | (E)-Condylcarpine             | K. arborea aerial part, K. pauciflora leaf | 22 and 95            |
| 336 | (E)-Condylcarpine N-oxide     | K. arborea aerial part                   | 95                    |
| 337 | 14z-Hydroxycondylcarpine      | K. deverrei stem bark, K. singapurensis stem bark | 23 and 94 |
| 338 | 14z-Hydroxy-N(4)-methylcondylcarpine | K. singapurensis root                 | 35 and 36             |
| 339 | 14(S)-Hydroxy-19(R)-methoxytubotaiwine | K. jasminiflora stem bark             | 24                    |
| 340 | Isocondylcarpine              | K. arborea aerial part                   | 95                    |
| 341 | Isocondylcarpine 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                   | 95                    |
| 348 | Kopsiyunnanine F1             | K. arborea aerial part                   | 101 and 102           |
| 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(β)-Methoxytubotaiwine         | K. arborea aerial part and stem bark, K. jasminiflora stem bark | 10, 24 and 95 |
| 353 | 19(β)-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 bark | 29, 64 and 95 |

**Stemmadenine**

| 357 | Stemmadenine                    | K. pauciflora leaf                       | 22         |

**Mersinines**

| 358 | Mersidasesine A                 | K. singapurensis leaf                   | 103        |
| 359 | Mersidasesine B                 | K. singapurensis leaf                   | 103        |
| 360 | Mersidasesine C                 | K. singapurensis leaf                   | 103        |
| 361 | Mersidasesine D                 | K. singapurensis leaf                   | 103        |
| 362 | Mersidasesine E                 | K. singapurensis leaf                   | 103        |
| 363 | Mersidasesine F                 | K. singapurensis leaf                   | 103        |
| 364 | Mersidasesine 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 | Mersilosine                     | K. singapurensis leaf                   | 103 and 105|
| 370 | Mersilosine A                   | K. singapurensis leaf                   | 103        |
| 371 | Mersilosine 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 | Mersiphylines A                 | K. singapurensis leaf                   | 108        |
| 377 | Mersiphylines 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-Deoxypopiasminilam            | K. jasminiflora leaf             | 40  |
| 381 | Kopsiarborines C                 | K. arborea aerial part           | 56  |
| 382 | Kopsiasminilam                   | K. jasminiflora leaf             | 40  |
| 383 | Δ⁴-Kopsiasminilam                | K. jasminiflora leaf             | 40  |
| 384 | Kopsiofine A                     | K. officinalis stem and leaf      | 109 |
| 385 | Kopsiofine B                     | K. officinalis stem and leaf      | 109 |
| 386 | Kopsiofine 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 | Pauciflorine                     | 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. dasycrachis leaf               | 30         |
| 398 | Kopsilactone                     | K. macrophylla bark               | 27         |
| 399 | Kopsirachine                    | K. dasycrachis 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 C                | 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-Methyleuconolam | *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 | 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 Isolapidilectin 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 Catharinenine | 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 Arbolocrine | *K. arborea* stem bark | 10 and 118 |
| 438 Arboloscline 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 |

### Percines

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

### Alstonines

| No. Compounds | Species | References |
|---------------|---------|------------|
| 447 Oxyohimban-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. 32, 42, 43, 66 and 69 | 10, 15, 17–19, 23, 25, 65, 66, 67, 68 and 69 |
Kopsamidines A–B (37–38) were separated from the acidic EtOH extract of *K. arborea* stem bark. 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. Eleven new analogs, kopsiahainains A–F (48–53) and kopsiahainains A–E (54–58) were among the new compounds found in the 80% EtOH extract of *K. hainanensis* twigs and leaves. 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 kopsiyunnanine D (450) and kopsiyunnanine H (451) from the 80% EtOH extract of *K. arborea* aerial part, the new compound kopsiarborines A (62) was isolated. 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. Thirteen previously undescribed metabolites kopsamidines A–D (67–70), kopsinitarines B–D (132–134), mersingines A–B (150–151), 11-methoxykopsingine (160), 11-methoxy-12-hydroxy-kopsinol (163), 11,12-...
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), kopsinarine (74), kopsinarine (75), and kopsonoline (146). 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). In two years 2007 and 2008, primarily based on CC approach, Subramaniam et al. successfully isolated nineteen new aspidofractinines, including kopsilongine-N-oxide (92), kopsilosines A–J (93–102), kopsinalines A–F (103–108), kopsinicline (118), and kopsofoline (145) from K. singapurensis leaf or stem bark (Table 1 and Fig. 1). 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. 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. Kopsifoline G (82) and kopsihainains B–F (83–87) were purified as new alkaloids from the stem or twig extracts of *K. hainanensis*. Among the isolated compounds, kopsijasminine (88) and kopsilartensine (90) were also identified to be two new aspidofractinines derived from the stem bark of *K. teei* and *K. larutensis*, respectively. The earliest report by Guggisberg *et al.* (1963) identified that kopside (110) was a new and major component of *K. fruticosa* leaves, and it was then isolated frequently. 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. 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-methoxynedioxycopsideinoline (153), N(1)-methoxycarbonyl-12-methoxycopsideinoline (156), N(4)-methylkopsininate (170), (−)-11,12-methoxynedioxycopsideinoline (172), and 5-oxokopsinic acid (176), in addition to seven known compounds kopsilamin (124), kopsinine (126), kopsinine methochloride (128), kopsinine B (129), (−)-kopsinine (137), (−)-12-methoxycopsideinoline (165), and 11,12-methoxynedioxycopsideinoline N(4)-oxide (173). 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 (δ_C 181.6 ppm in CD3OD). 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 kopsioflavismines 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. Aspidofractinines were further observed in other *Kopsia* plants. For instance, apart from known compounds, five new derivatives N(1)-methoxycarbonyl-11,12-methylenedioxy-Δ₁₆,₁₇-kopsinine (154), N(1)-methoxycarbonyl-12-methoxy-Δ₁₆,₁₇-kopsinine (155), N(1)-methoxycarbonyl-11,12-methylenedioxy-Δ₁₆,₁₇-kopsinine N(4) oxide (157), N(1)-methoxycarbonyl-12-hydroxy-Δ₁₆,₁₇-kopsinine (158), and N(1)-methoxycarbonyl-12-methoxy-Δ₁₆,₁₇-kopsinine N(4) oxide (159) were characteristics of *K. profunda*, or lahadinines A–B (143–146), 12-methoxy-10-demethoxycopsideinane (167), paucidactine D-E (180–181), paucidactinine (182), paucidactinine (183), paucidactinine (184), paucidactinine (185), paucidactinine (186), paucidactinine (187), and paucifinone-N-oxide (188) were new metabolites isolated from the parts of *K. pauciflora*. 

### 2.2. Chanofruticosinates, aspidospermines, and danuphyllines

In general, *Kopsia* chanofruticosinate derivatives 205–241 have in general 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 often occurred in *K. arborea*, *K. dasyrachis*, *K. fruticosa*, *K. flavida*, *K. hainanensis*, *K. lancibracteolata*, *K. officinalis*, and *K. pauciflora*. In 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-Δ₁₄,₁₅-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,19ız)-6,7-didehydro-8,21-dioxo-11,21-cycloaspidospermidine-2-carboxylate (231). 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. 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-N₁-decarbomethoxy-14,15-didehydrochanofruticosinate (236). The MeOH extract of *K. flavida* leaf consisted of serial new alkaloids type chanofruticosinates flavisiamines A–F (208–213). 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, 210, and 238–241). 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. 

Regarding aspidospermines, the acidic EtOH extract of *K. pauciflora* leaf contained aspidospermine (242), and its (+)-1,2-dehydro derivatives (243). 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 eburneine (244). Similarly, new compound kopsioflavicine G (245), together with two known ones, vincadifformine (247) and vincadifformine N(4)-oxide (248) represented for *K. officinalis* stem. 

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). All these isolates were new in nature. Similar to aspidofractinine derivatives, chanofruticosinates, aspidospermines, and danuphyllines were
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. jararacophora*, *K. larutensis*, *K. macrophylla*, *K. officinalis*, *K. pauciflora*, *K. singapuresensis*, *K. teoi*, and *K. terengganensis*.5,13,18,19,22,29,33,51,68,70,90,92,93 *Kopsia* eburnamines appeared in both monomer and dimer forms, but not to have connected with sugar units. (−)-Eburnamenine (255), (−)-eburnamine (257), (+)-eburnamone (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-(−)-eburnamone (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-(−)-eburnamone (293) were found in two or three *Kopsia* plants (Table 1). (−)-Eburnamenine (254), (+)-eburnamine (256),

Fig. 2  Chanofruticosinates, aspidospermines and danuphylines from genus *Kopsia*. © 2022 The Author(s). Published by the Royal Society of Chemistry RSC Advances, 2022, 12, 19171–19208 | 19185
(-)-eburnamine (261), (+)-ethylisoeburnamine (263), 16α-hydroxy-19-oxoeburnamine (264), 16β-hydroxy-19-oxoeburnamine (265), melohenenine B (287), (-)-methyleburnamine (288), (+)-O-methyleburnamine (290), and O-methyl-16-epi-vincanol (295), and Δ\(^{14}\)-vicamone (300) have never been observed in genus Kopsia before. Especially, (-)-eburnaminol (258), (+)-eburnamine N(4)-oxide (260), (+)-(19R)-hydroxyeburnamine (266), (-)-(19R)-hydroxyisoeburnamine (268), (−)-(19R)-hydroxyeburnamenine (270), (−)-(19R)-hydroxyisoeburnamenine (271), (−)-(19R)-hydroxy-O-ethylisoeburnamine (272), (−)-isoeburnamine (275), kopsofficines H–K (278–281), (+)-larutensine (283), larutenine (284), larutenines A–B (285–286), (−)-norploiomutine (289), (+)-19-oxoeburnamine (292), (−)-19-oxoisoeburnamine (294), 20-oxo-eburnamenine (296), phutdonginin (297), terengganensines A–B (298–299), and yunnanonine 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.
offficinalis, K. singapurensis, and K. teoi were main resource of these phyto-constituents.\textsuperscript{9,10,15–17,23,27,32,34–36,43,45,47–49} 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 \textit{Kopsia}.

The first compound akuammidine (302) was originated from \textit{K. arborea} stem bark, \textit{K. singapurensis} root, stem bark, and leaves, while akuammiline (303) presented in the aerial part of \textit{K. macrophylla} and \textit{K. teoi}.\textsuperscript{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 \textit{K. griffithii} stem bark.\textsuperscript{15} \textit{ψ}-Akuammigine (305), dregamine (307), \textit{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 \textit{Kopsia} for the first time.\textsuperscript{9,10,15,16,27,31,36} Lastly, two new metabolites, rhazinoline (316) and singaporentinidine (322), were purified from the extracts of \textit{K. arborea} stem bark, \textit{K. singapurensis} root, respectively.\textsuperscript{10,35}

A list of four alkaloidal sarapgines 323–326 has been updated in Table 1 and Fig. 4.\textsuperscript{9,27,50} Vincadiffline (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 \textit{K. hainanensis}.\textsuperscript{9} Perivine (324) and tabernaemontanine (325) were two known sarapgines derived from \textit{K. offficinalis} root and stem and \textit{K. macrophylla} bark, respectively.\textsuperscript{27,50}

Resemble sarapgines, aspidophylline derivatives are not available in genus \textit{Kopsia}. A total of five isolates 327–331 were summarized in Table 1 and Fig. 4.\textsuperscript{2,3,31–34,36,43,48,49}
Aspidodascarpine (327) was recorded by various authors and was detected in *K. singapurensis* root and stem bark, *K. teoi* stem, and stem bark. 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. 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.

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

Compounds 332–357 have been fallen into the group of alka-
loidal 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. offici-
cinalis, K. pauciflora, K. singapurensis, especially K. arborea.8,10,12,22–24,29,35,36,64,94–102 Significantly, except for akuam-
icine (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 eluci-
dated as bulk novel strychnoses, which were derived from K. arborea stem bark.8 Compound 335 is a known compound,23,95
but its 14α-hydroxy and 14(5)-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. sin-
gapurensis stem bark.23 K. arborea aerial part has so far
distributed thirteen new compounds, isocondylocarpine (340),
isocondylocarpine N-oxide (341), kopsiyunnanes A, I, J1–J2, I, M, and F1–F3 (342–350), 19(5)-methoxytubotaiwine (352),
and 19(5)-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(5)-
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 (337) from K. pauci-
flora 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).23,103–106 Of particular
interest, all these isolates were novel compounds in literature.
Searching for cytotoxic agents from plants, sixteen novel mer-
inines, comprising of mersidasines A-G (358–364), mersifo-
lines A-C (365–367), mersilosine (369), mersilosines A-B (370–371), and mersinines A-C (373–375) were isolated from the
acidic EtOH extract of K. singapurensis leaf.103 Their stereo-
chemistry was confirmed by NMR, IR, UV, and X-ray analysis. K. singapurensis leaf has further been shown to contain five novel
congener, mersilongine (368), mersinaline (372), mersiphyl-
lines 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 pau-ciflorines 20-deoxykopsijasminilam (380), kopsijasminilam (382), and Δ^{14}kopsijasminilam (383). In addition to known compound 379, three novel derivatives, kopsiofines A–C (384–386) were arisen from the 95% EtOH extract of *K. officinalis* dried stem and leaves. Pauciflorines A–B (387–388) reached 0.22 and 0.03 g kg^{-1} in *K. pauciflora* leaf. 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. 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. 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. Two publications in 1996 and 1997 by Kam and partners successfully reported the structures of serial new skytanthines kinabalurines (Serious) and other genera of the family Apocynaceae.
A–F (391–396) from *K. pauciflora* leaves,\(^{111,112}\) while their following congener *kinabalurine* G (397) was derived from *K. dasyrachis* leaf.\(^{109}\) 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.\(^{111}\) 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.
griffithii leaves and stem bark, K. hainanensis twig, stem and leaf, K. officinalis leaf, K. pauciflora leaves, and K. singapurensis stem bark. As shown in Table 1, known compound 5,21-dihydrorhizainilam (401) existed in K. arborea stem bark and K. singapurensis stem bark and leaves. From Fig. 7, three new compounds, kopsiunnannines C1–C3 (402–404), which were isolated from the aerial part of K. arborea and K. officinalis, established the same backbone with rhizainilam (409). O-Methylleuconolam (406) and rhazinal (407) were two well-known compounds, but their congener rhizainine (408) separated from K. arborea stem bark, K. dasyrrhachis stem, and K. singapurensis root was a new derivative. To the best of our knowledge, rhazinalms 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), lapidilectan (415), lapidilectines A-B (416–417), and lapidilectinol (418) from aerial part of K. lapidilecta. Three novel indole alkaloids, grandilodies 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. 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. In which compounds 423–425 were unprecedented dimers, while compound 426 is unique due to the incorporation between aspidofractinilte 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, perincines, alstonines, and quebrachamines

Alkaloid type aspidospermas were named following the name of the genus Aspidosperma (family Apocynaceae). With regard to genus Kopsia, five known isolates 427–431 were summarized in Table 1 and Fig. 8. It turns out that buchtilin (427) was presented in either the leaf or stem of K. griffithii. The MeOH extract of K. hainanensis twig and leaf consisted of two aspidospermas, corynantheol (428) and dihydrocorynantheol (430). Only K. officinalis stem was found to contain 19,20-dihydroisoretinosidine (429), while its congener 16(R)-19,20-E-isoretinosidine (431) has been observed in the leaf of both K. griffithii and K. pauciflora. 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. 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 CHCl3–MeOH is appropriate to isolate alkaloidal catharinensines. By this approach, three new compounds, kopsiresines A–C (433–435), together with known analog catharinensine (432), have been successfully purified from the acidic EtOH extract of K. pauciflora leaves. New catharinensine kopsiunnannine 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.

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. Arbolocide (437) was one of the new compounds in K. arborea stem bark, while melodinine E (442) was a known metabolite extracted from its twigs.

To find bioactive molecules from medicinal plants, four alkaloids type perincines, 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.

To the best of our knowledge, only three compounds 447–449 were classified as alkaloid alstonines (Table 1 and Fig. 8). Oxoyohimban-16-carboxy acid (447) derived from K. officinalis stem has never been isolated from the genus Kopsia before. The major component (−)-tetrahydroalstonine (448) appeared in K. arborea stem bark, K. dasyrrhachis 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. Compound 449, a pseudiodoindoxyl derivative of compound 448, was identified to be a new constituent from the acidic EtOH extract of K. pauciflora leaves.

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. However, kopsiunnannines D and H (450–451) from K. arborea aerial part were confirmed to be two new analogs.

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, arbophyllines A–B (453–454) and arbophyllidine (463). Arboflorine (453) 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.\textsuperscript{10,96,99,121} Besides the main constituents, the EtOH extract of K. paciflora leaves has composed of a new component, andransinine A (458), along with a known one andransinine (457).\textsuperscript{22} New corynane theines arboricine (459) and arboricine (460) were found in both the leaves and stem of K. arborea.\textsuperscript{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.\textsuperscript{15,17} To find bioactive compounds from plants, mersicarpine (464) was first isolated from K. arborea stem bark.\textsuperscript{10} It was then further found in K. pauciflora leaves and K. singapurensis stem bark.\textsuperscript{8,22} Two final alkaloids, a new alkaloid type, azepane-fused tetrahydro-b-carboline kopsiyunnanine K (463) and a known alkaloid type andranginine (466), were constituents of K. arborea aerial part.\textsuperscript{182}

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).\textsuperscript{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,\textsuperscript{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 Kopsia 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.
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. Among them, kopsiline (73) induced the lowest CD50 value of 0.9 μg mL⁻¹ against HL-60 cells in referencing with the positive control vincristine (CD50 1.8 μg mL⁻¹).

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 IC50 values of 7.3–9.5 μM. Meanwhile, its congeners kopsiafrutinines C–D (45–46) containing a hydroxyl group at carbon C-15 have shown to associate with the respective IC50 values of 10.3–12.5 and 11.8–13.8 μM, but kopsiafrutinines A–B (43–44) and kopsifoline A (76) did not inhibit cancer cell growth (IC50 > 20 μM). In the same way, the following new aspidofractinines kopsiahainanins A–B (48–49) with a lactone bridge have induced the respective IC50 values of 9.4–11.7 and 12.2–15.9 μM against A-549, BGC-823, HepG-2, HL-60, MCF-7, SMCC-7721, and W-480 cells. However, four new analogous kopsiahainanins C–F (50–53) accompanied by the IC50 values of >20 μM.

From Table 2, new aspidofractinines kopsiahainanins 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 IC50 values of ≤10 μM. Similarly, in the N(4)-oxide group, new alkaloid 237 possessed the IC50 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 (IC50 > 20 μM).

The new metabolite kopsiaofficines C (61) showed the IC50 values of <10 μM towards cancer cell lines 95-D, A-549, ATCC, H-464, H-460, H-292, and SPCA-1, and was better than its analogs 59 (10 < IC50 ≤ 20 μM) and 60 (IC50 > 20 μM). The bulk dimeric molecule arbolodinidine 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 IC50 values ranging from 1.3 to 9.6 μg mL⁻¹, while arbolodinines A and C (1 and 334) failed to do so.

Rhazinilam (409) itself displayed the potential application in cancer treatments because its strong inhibitory capacity to A-549 and HT-29 cells (IC50 0.35 μM), kopsiyunnanines A–C (402–404) indicated moderate activities (IC50 4.67–8.89 μM), but both kopsiyunnanine D (450) and (−)-quebrachamine (452) were inactive (≥30 μM). Novel alkaloidal arbophyllidine (463) suppressed HT-29 cell growth with the IC50 value of 6.2 μM, but the novel metabolite arbophyllinine A (453) failed to inhibit. Six non-alkaloidal constituents 467–472 were also subjected to cytotoxic assay, in which their IC50 values ranged from 14.5 to 22.5 μg mL⁻¹.

Vincristine, a renowned chemotherapy medication, is usually used in combining with other drugs to treat many types of cancers. 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 (MDR) by suppressing the bound of [3H]azidopine to P-glycoprotein. Alkaloidal compounds 88, 102–107, 411, 413, 417, 434, and 438 exhibited no appreciable cytotoxic activity against KB (VJ300) cells. However, they possessed IC50 values of 0.39–38.7
| Compounds | Models Effect | Positive control Effect | References |
|-----------|---------------|-------------------------|------------|
| **Anti-cancer activity** | | | |
| 39 | *In vitro* CD<sub>50</sub> > 60 µg mL<sup>-1</sup>/NIH/3T3 and HeLa cells CD<sub>50</sub> = 6.9 µg mL<sup>-1</sup>/HL-60 cells | Vincristine CD<sub>50</sub> > 60 µg mL<sup>-1</sup>/NIH/3T3 cells CD<sub>50</sub> = 1.8 µg mL<sup>-1</sup>/HL-60 cells CD<sub>50</sub> = 0.4 µg mL<sup>-1</sup>/HeLa cells | 49 |
| 40 | *In vitro* CD<sub>50</sub> > 60 µg mL<sup>-1</sup>/NIH/3T3, HL-60 and HeLa cells Vincristine | | 49 |
| 43 | *In vitro* IC<sub>50</sub> = 33.7 µM/HS-1 cells IC<sub>50</sub> = 28.4 µM/HS-4 cells IC<sub>50</sub> = 32.4 µM/SCL-1 cells IC<sub>50</sub> = 29.7 µM/A-431 cells IC<sub>50</sub> = 30.9 µM/BGC-823 cells IC<sub>50</sub> = 27.1 µM/MCF-7 cells IC<sub>50</sub> = 31.2 µM/W-480 cells | Adiamycin IC<sub>50</sub> = 17.8 µM/HS-1 cells IC<sub>50</sub> = 24.7 µM/HS-4 cells IC<sub>50</sub> = 21.8 µM/SCL-1 cells IC<sub>50</sub> = 33.7 µM/A-431 cells IC<sub>50</sub> = 28.4 µM/BGC-823 cells IC<sub>50</sub> = 37.6 µM/MCF-7 cells IC<sub>50</sub> = 14.1 µM/W-480 cells | 52 |
| 44 | *In vitro* IC<sub>50</sub> = 34.9 µM/HS-1 cells IC<sub>50</sub> = 29.9 µM/HS-4 cells IC<sub>50</sub> = 33.1 µM/SCL-1 cells IC<sub>50</sub> = 30.1 µM/A-431 cells IC<sub>50</sub> = 35.5 µM/BGC-823 cells IC<sub>50</sub> = 31.2 µM/MCF-7 cells IC<sub>50</sub> = 32.6 µM/W-480 cells | Adiamycin IC<sub>50</sub> = 17.8 µM/HS-1 cells IC<sub>50</sub> = 24.7 µM/HS-4 cells IC<sub>50</sub> = 21.8 µM/SCL-1 cells IC<sub>50</sub> = 33.7 µM/A-431 cells IC<sub>50</sub> = 28.4 µM/BGC-823 cells IC<sub>50</sub> = 37.6 µM/MCF-7 cells IC<sub>50</sub> = 14.1 µM/W-480 cells | 52 |
| 45 | *In vitro* IC<sub>50</sub> = 12.4 µM/HS-1 cells IC<sub>50</sub> = 12.3 µM/HS-4 and BGC-823 cells IC<sub>50</sub> = 12.9 µM/SCL-1 cells IC<sub>50</sub> = 11.8 µM/A-431 cells IC<sub>50</sub> = 12.6 µM/MCF-7 cells IC<sub>50</sub> = 13.8 µM/W-480 cells | Adiamycin IC<sub>50</sub> = 17.8 µM/HS-1 cells IC<sub>50</sub> = 24.7 µM/HS-4 cells IC<sub>50</sub> = 21.8 µM/SCL-1 cells IC<sub>50</sub> = 33.7 µM/A-431 cells IC<sub>50</sub> = 28.4 µM/BGC-823 cells IC<sub>50</sub> = 37.6 µM/MCF-7 cells IC<sub>50</sub> = 14.1 µM/W-480 cells | 52 |
| 46 | *In vitro* IC<sub>50</sub> = 11.6 µM/HS-1 cells IC<sub>50</sub> = 11.4 µM/HS-4 cells IC<sub>50</sub> = 12.1 µM/SCL-1 cells IC<sub>50</sub> = 10.3 µM/A-431 cells IC<sub>50</sub> = 11.7 µM/BGC-823 cells IC<sub>50</sub> = 10.4 µM/MCF-7 cells IC<sub>50</sub> = 12.5 µM/W-480 cells | Adiamycin IC<sub>50</sub> = 17.8 µM/HS-1 cells IC<sub>50</sub> = 24.7 µM/HS-4 cells IC<sub>50</sub> = 21.8 µM/SCL-1 cells IC<sub>50</sub> = 33.7 µM/A-431 cells IC<sub>50</sub> = 28.4 µM/BGC-823 cells IC<sub>50</sub> = 37.6 µM/MCF-7 cells IC<sub>50</sub> = 14.1 µM/W-480 cells | 52 |
| 47 | *In vitro* IC<sub>50</sub> = 7.3 µM/HS-1 cells IC<sub>50</sub> = 8.6 µM/HS-4 and MCF-7 cells IC<sub>50</sub> = 8.2 µM/SCL-1 cells IC<sub>50</sub> = 9.5 µM/A431 cells IC<sub>50</sub> = 8.9 µM/BGC-823 cells IC<sub>50</sub> = 9.2 µM/W-480 cells | Adiamycin IC<sub>50</sub> = 17.8 µM/HS-1 cells IC<sub>50</sub> = 24.7 µM/HS-4 cells IC<sub>50</sub> = 21.8 µM/SCL-1 cells IC<sub>50</sub> = 33.7 µM/A-431 cells IC<sub>50</sub> = 28.4 µM/BGC-823 cells IC<sub>50</sub> = 37.6 µM/MCF-7 cells IC<sub>50</sub> = 14.1 µM/W-480 cells | 52 |
| 48 | *In vitro* IC<sub>50</sub> = 11.3 µM/A-549 cells IC<sub>50</sub> = 9.4 µM/BGC-823 cells IC<sub>50</sub> = 10.1 µM/HepG-2 cells IC<sub>50</sub> = 11.1 µM/HL-60 cells IC<sub>50</sub> = 10.4 µM/MCF-7 cells IC<sub>50</sub> = 9.7 µM/SMMC-7721 cells IC<sub>50</sub> = 11.7 µM/W-480 cells | Doxorubicin IC<sub>50</sub> = 0.02 µM/A-549, HepG-2 and W-53 480 cells IC<sub>50</sub> = 0.01 µM/BGC-823 cells IC<sub>50</sub> = 0.03 µM/HL-60 cells IC<sub>50</sub> = 0.04 µM/SMMC-7721 cells | 53 |
| 49 | *In vitro* IC<sub>50</sub> = 12.7 µM/A-549 cells IC<sub>50</sub> = 12.2 µM/BGC-823 cells IC<sub>50</sub> = 12.8 µM/HepG-2 cells IC<sub>50</sub> = 13.8 µM/HL-60 cells IC<sub>50</sub> = 14.3 µM/MCF-7 and SMMC-7721 cells IC<sub>50</sub> = 15.9 µM/W-480 cells | Doxorubicin IC<sub>50</sub> = 0.02 µM/A-549, HepG-2 and W-53 480 cells IC<sub>50</sub> = 0.01 µM/BGC-823 cells IC<sub>50</sub> = 0.03 µM/HL-60 cells IC<sub>50</sub> = 0.04 µM/SMMC-7721 cells | 53 |
| 50 | *In vitro* IC<sub>50</sub> = 31.9 µM/A-549 cells IC<sub>50</sub> = 31.2 µM/BGC-823 cells IC<sub>50</sub> = 30.7 µM/HepG-2 cells IC<sub>50</sub> = 32.2 µM/HL-60 cells IC<sub>50</sub> = 28.1 µM/MCF-7 cells | Doxorubicin IC<sub>50</sub> = 0.02 µM/A-549, HepG-2 and W-53 480 cells IC<sub>50</sub> = 0.01 µM/BGC-823 cells IC<sub>50</sub> = 0.03 µM/HL-60 cells IC<sub>50</sub> = 0.04 µM/SMMC-7721 cells | 53 |
| Compounds | Models | Effect |
|-----------|--------|--------|
| In vitro | IC$_{50}$ = 29.9 μM/SMMC-7721 cells |
|          | IC$_{50}$ = 27.6 μM/W-480 cells |
| 51       | Doxorubicin | IC$_{50}$ = 0.02 μM/A-549, HepG-2 and W- |
|          | 480 cells |
|          | IC$_{50}$ = 0.01 μM/BGC-823 cells |
|          | IC$_{50}$ = 0.03 μM/HL-60 cells |
|          | IC$_{50}$ = 0.04 μM/SMMC-7721 cells |
| 52       | Doxorubicin | IC$_{50}$ = 0.02 μM/A-549, HepG-2 and W- |
|          | 480 cells |
|          | IC$_{50}$ = 0.01 μM/BGC-823 cells |
|          | IC$_{50}$ = 0.03 μM/HL-60 cells |
|          | IC$_{50}$ = 0.04 μM/SMMC-7721 cells |
| 53       | Doxorubicin | IC$_{50}$ = 0.02 μM/A-549, HepG-2 and W- |
|          | 480 cells |
|          | IC$_{50}$ = 0.01 μM/BGC-823 cells |
|          | IC$_{50}$ = 0.03 μM/HL-60 cells |
|          | IC$_{50}$ = 0.04 μM/SMMC-7721 cells |
| 54       | Doxorubicin | IC$_{50}$ = 0.02 μM/BGC-823 cells |
|          | 54 |
|          | IC$_{50}$ = 0.01 μM/HepG-2 and SK-OV-3 cells |
|          | IC$_{50}$ = 0.06 μM/MCF-7 cells |
|          | IC$_{50}$ = 0.05 μM/SGC-7901 cells |
|          | IC$_{50}$ = 0.03 μM/SK-MEL-2 cells |
| 55       | Doxorubicin | IC$_{50}$ = 0.02 μM/BGC-823 cells |
|          | 54 |
|          | IC$_{50}$ = 0.01 μM/HepG-2 and SK-OV-3 cells |
|          | IC$_{50}$ = 0.06 μM/MCF-7 cells |
|          | IC$_{50}$ = 0.05 μM/SGC-7901 cells |
|          | IC$_{50}$ = 0.03 μM/SK-MEL-2 cells |
| 56       | Doxorubicin | IC$_{50}$ = 0.02 μM/BGC-823 cells |
|          | 54 |
|          | IC$_{50}$ = 0.01 μM/HepG-2 and SK-OV-3 cells |
|          | IC$_{50}$ = 0.06 μM/MCF-7 cells |
|          | IC$_{50}$ = 0.05 μM/SGC-7901 cells |
|          | IC$_{50}$ = 0.03 μM/SK-MEL-2 cells |
| 57       | Doxorubicin | IC$_{50}$ = 0.02 μM/BGC-823 cells |
|          | 54 |
|          | IC$_{50}$ = 0.01 μM/HepG-2 and SK-OV-3 cells |
|          | IC$_{50}$ = 0.06 μM/MCF-7 cells |
|          | IC$_{50}$ = 0.05 μM/SGC-7901 cells |
|          | IC$_{50}$ = 0.03 μM/SK-MEL-2 cells |
| 58       | Doxorubicin | IC$_{50}$ = 0.02 μM/BGC-823 cells |
|          | 54 |
|          | IC$_{50}$ = 0.01 μM/HepG-2 and SK-OV-3 cells |
|          | IC$_{50}$ = 0.06 μM/MCF-7 cells |
|          | IC$_{50}$ = 0.05 μM/SGC-7901 cells |
|          | IC$_{50}$ = 0.03 μM/SK-MEL-2 cells |
| 59       | Doxorubicin | IC$_{50}$ = 24.7 μM/95-D cells |
|          | 55 |
|          | IC$_{50}$ = 21.8 μM/A-549 cells |
|          | IC$_{50}$ = 33.7 μM/ATCC cells |
|          | IC$_{50}$ = 22.3 μM/H-446 cells |
Table 2 (Contd.)

| Compounds | Models | Effect | Positive control | References |
|-----------|--------|--------|------------------|------------|

- **IC₅₀** = 13.3 μM/H-460 cells
- **IC₅₀** = 12.6 μM/H-292 cells
- **IC₅₀** = 13.9 μM/SPCA-1 cells

**60** *In vitro*  
**IC₅₀** = 46.8 μM/95-D cells  
**IC₅₀** = 47.1 μM/ATCC cells  
**IC₅₀** = 46.6 μM/H-446 cells  
**IC₅₀** = 45.9 μM/H-292 cells

- Doxorubicin

**61** *In vitro*  
**IC₅₀** = 9.5 μM/95-D cells  
**IC₅₀** = 8.6 μM/A-549 cells  
**IC₅₀** = 9.3 μM/ATCC and H-292 cells  
**IC₅₀** = 9.4 μM/H-446 cells  
**IC₅₀** = 9.2 μM/H-460 cells  
**IC₅₀** = 9.7 μM/SPCA-1 cells

- Doxorubicin

**73** *In vitro*  
**CD₅₀** = 20.7 μg mL⁻¹/NIH/3T3 cells  
**CD₅₀** = 0.9 μg mL⁻¹/HL-60 cells  
**CD₅₀** = 36.5 μg mL⁻¹/HeLa cells

- Vincristine  
**CD₅₀** > 60 μg mL⁻¹/NIH/3T3 cells  
**CD₅₀** = 1.8 μg mL⁻¹/HL-60 cells  
**CD₅₀** = 0.4 μg mL⁻¹/HeLa cells

**74** *In vitro*  
To suppress the binding of β[3]azidopine to P-glycoprotein

**76** *In vitro*  
**IC₅₀** = 67.3 μM/HS-4 cells  
**IC₅₀** = 74.2 μM/A-431 cells  
**IC₅₀** = 66.2 μM/W-480 cells

- Adamycin

**88** *In vitro*  
**IC₅₀** = 38.7 μg mL⁻¹/KB (VJ300) + 0.1 μg mL⁻¹ vincristine

**93** *In vitro*  
**IC₅₀** = 19.5 μg mL⁻¹/KB cells  
**IC₅₀** = 18.0 μg mL⁻¹/KB (VJ300)  
**IC₅₀** = 3.80 μg mL⁻¹/KB (VJ300) + 0.1 μg mL⁻¹ vincristine

**102** *In vitro*  
**IC₅₀** = 15.0 μg mL⁻¹/KB (VJ300) + 0.1 μg mL⁻¹ vincristine

**103** *In vitro*  
**IC₅₀** = 3.9 μg mL⁻¹/KB (VJ300) + 0.1 μg mL⁻¹ vincristine

**104** *In vitro*  
**IC₅₀** = 13.0 μg mL⁻¹/KB (VJ300) + 0.1 μg mL⁻¹ vincristine

**105** *In vitro*  
**IC₅₀** = 18.2 μg mL⁻¹/KB (VJ300) + 0.1 μg mL⁻¹ vincristine

**106** *In vitro*  
**IC₅₀** = 9.2 μg mL⁻¹/KB (VJ300) + 0.1 μg mL⁻¹ vincristine

**107** *In vitro*  
**IC₅₀** = 18.0 μg mL⁻¹/KB (VJ300) + 0.1 μg mL⁻¹ vincristine

**214** *In vitro*  
**IC₅₀** = 29.7 μM/BGC-823 cells  
**IC₅₀** = 37.6 μM/HepG-2 cells  
**IC₅₀** = 35.8 μM/MCF-7 cells  
**IC₅₀** = 36.8 μM/SGC-7901 cells  
**IC₅₀** = 36.5 μM/SPCA-1 cells

- Doxorubicin

**215** *In vitro*  
**IC₅₀** = 32.1 μM/BGC-823 cells  
**IC₅₀** = 29.8 μM/HepG-2 cells  
**IC₅₀** = 31.9 μM/MCF-7 cells  
**IC₅₀** = 27.9 μM/SGC-7901 cells  
**IC₅₀** = 33.3 μM/SPCA-1 cells

- Doxorubicin

**CIS17** *In vitro*  
**IC₅₀** = 8.6 μM/BGC-823 cells  
**IC₅₀** = 7.2 μM/HepG-2 cells  
**IC₅₀** = 8.3 μM/MCF-7 cells  
**IC₅₀** = 8.2 μM/SGC-7901 cells  
**IC₅₀** = 8.9 μM/SPCA-1 cells

- Cisplatin

**282** *In vitro*  
**IC₅₀** = 9.7 μg mL⁻¹/PC-3 cells

- **IC₅₀** = 15.9 μg mL⁻¹/HCT-116 cells
- **IC₅₀** = 14.1 μg mL⁻¹/MCF-7 cells
- **IC₅₀** > 25 μg mL⁻¹/A-549 and KB (VJ300) cells
- **IC₅₀** = 8.6 μg mL⁻¹/KB (VJ300) + 0.1 μg mL⁻¹ vincristine

**289** *In vitro*  
**IC₅₀** = 7.1 μg mL⁻¹/PC-3 cells  
**IC₅₀** = 7.6 μg mL⁻¹/HCT-116 cells

- Cisplatin

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RSC Adv., 2022, 12, 19171–19208 | 19197
| Compounds | Models Effect | Positive control Effect | References |
|-----------|---------------|-------------------------|------------|
| IC₅₀ = 9.7 µg mL⁻¹/MCF-7 cells | Vincristine IC₅₀ = 4.2 µg mL⁻¹/MCF-7 cells | Verapamil IC₅₀ = 4.7 µg mL⁻¹/KB (VJ300) + 0.1 µg mL⁻¹ vincristine | 302 |
| IC₅₀ = 20.4 µg mL⁻¹/A-549 cells | Vincristine IC₅₀ = 4.3 µg mL⁻¹/A-549 cells | 302 |
| IC₅₀ = 23 µg mL⁻¹/KB (VJ300) cells | Vincristine IC₅₀ = 6.3 µg mL⁻¹/KB (VJ300) + 0.1 µg mL⁻¹ vincristine | 302 |
| IC₅₀ = 4.80 µg mL⁻¹/KB (VJ300) + 0.1 µg mL⁻¹ vincristine | | 302 |
| | | | |
| CD₅₀ > 60 µg mL⁻¹/NIH/3T3 cells | | 327 |
| CD₅₀ = 30.2 µg mL⁻¹/HL-60 cells | | 327 |
| CD₅₀ = 2.8 µg mL⁻¹/HeLa cells | | 327 |
| | | | |
| CD₅₀ = 6.4 µg mL⁻¹/NIH/3T3 cells | Vincristine CD₅₀ = 60 µg mL⁻¹/NIH/3T3 cells | 49 |
| CD₅₀ > 60 µg mL⁻¹/NIH/3T3 cells | | 49 |
| CD₅₀ = 1.8 µg mL⁻¹/HL-60 cells | | 49 |
| CD₅₀ = 0.4 µg mL⁻¹/HeLa cells | | 49 |
| | | | |
| CD₅₀ = 7.5 µg mL⁻¹/HeLa cells | Vincristine CD₅₀ = 60 µg mL⁻¹/NIH/3T3 cells | 333 |
| CD₅₀ = 6.0 µg mL⁻¹/HL-60 cells | | 333 |
| CD₅₀ = 2.1 µg mL⁻¹/HeLa cells | | 333 |
| | | | |
| CD₅₀ = 1.3 µg mL⁻¹/HT-29 cells | Vincristine CD₅₀ = 6.6 µg mL⁻¹/HT-29 cells | 366 |
| IC₅₀ = 4.9 µg mL⁻¹/MCF-7 cells | | 366 |
| IC₅₀ = 4.7 µg mL⁻¹/PC-3 cells | | 366 |
| IC₅₀ = 7.0 µg mL⁻¹/MDA-MB-231 cells | Vincristine IC₅₀ = 8.8 µg mL⁻¹/HT-29 cells | 367 |
| IC₅₀ = 7.3 µg mL⁻¹/HCT-116 cells | | 367 |
| IC₅₀ = 9.6 µg mL⁻¹/A-549 cells | | 367 |
| IC₅₀ = 3.0 µg mL⁻¹/KB (VJ300) cells | Vincristine IC₅₀ = 1.0 µg mL⁻¹/KB (VJ300) | 366 |
| | | | |
| IC₅₀ = 3.70 µg mL⁻¹/KB (VJ300) + 0.1 µg mL⁻¹ vincristine | Vincristine IC₅₀ = 8.8 µg mL⁻¹/HT-29 cells | 367 |
| | | | |
| IC₅₀ = 7.0 µg mL⁻¹/KB (VJ300) + 0.1 µg mL⁻¹ vincristine | Vincristine IC₅₀ = 6.6 µg mL⁻¹/HT-29 cells | 373 |
| | | | |
| IC₅₀ = 4.1 µg mL⁻¹/KB (VJ300) + 0.1 µg mL⁻¹ vincristine | Vincristine IC₅₀ = 1.0 µg mL⁻¹/KB (VJ300) | 374 |
| | | | |
| IC₅₀ = 3.2 µg mL⁻¹/KB (VJ300) + 0.1 µg mL⁻¹ vincristine | Vincristine IC₅₀ = 1.0 µg mL⁻¹/KB (VJ300) | 375 |
| | | | |
| IC₅₀ = 11.2 µg mL⁻¹/KB (VJ300) + 0.1 µg mL⁻¹ vincristine | Vincristine IC₅₀ = 1.0 µg mL⁻¹/KB (VJ300) | 375 |
| | | | |
| IC₅₀ = 5.38 µM/A-549 cells | Docetaxel IC₅₀ = 4.95 × 10⁻⁴ µM/A-549 cells | 402 |
| IC₅₀ = 4.67 µM/HT-29 cells | | 402 |
| IC₅₀ = 7.44 µM/A-549 cells | | 403 |
| IC₅₀ = 6.39 µM/HT-29 cells | | 403 |
| IC₅₀ = 8.21 µM/A-549 cells | Docetaxel IC₅₀ = 4.95 × 10⁻⁴ µM/A-549 cells | 404 |
| IC₅₀ = 8.89 µM/HT-29 cells | | 404 |
| IC₅₀ = 0.24 µg mL⁻¹/KB cells | Vincristine IC₅₀ = 1.0 µg mL⁻¹/KB (VJ300) | 407 |
| IC₅₀ = 0.25 µg mL⁻¹/KB (VJ300) cells | | 407 |
| IC₅₀ = 0.30 µg mL⁻¹/KB (VJ300) + 0.1 µg mL⁻¹ vincristine | | 407 |
| | | | |
| CD₅₀ = 20.8 µg mL⁻¹/NIH/3T3 cells | Vincristine CD₅₀ > 60 µg mL⁻¹/NIH/3T3 cells | 408 |
| CD₅₀ > 60 µg mL⁻¹/HL-60 cells | | 408 |
| CD₅₀ = 2.9 µg mL⁻¹/HeLa cells | | 408 |
| IC₅₀ = 0.19 µg mL⁻¹/KB cells | Vincristine CD₅₀ = 1.0 µg mL⁻¹/KB (VJ300) | 408 |
| IC₅₀ = 0.25 µg mL⁻¹/KB (VJ300) cells | | 408 |
| IC₅₀ = 0.34 µg mL⁻¹/KB (VJ300) + 0.1 µg mL⁻¹ vincristine | | 408 |
| | | | |
| IC₅₀ = 0.35 µM/A-549 and HT-29 cells | Docetaxel IC₅₀ = 4.95 × 10⁻⁴ µM/A-549 cells | 409 |
| IC₅₀ = 1.25 µg mL⁻¹/KB cells | | 409 |
| IC₅₀ = 2.50 µg mL⁻¹/KB (VJ300) cells | | 409 |
| IC₅₀ = 1.85 µg mL⁻¹/KB (VJ300) + 0.1 µg mL⁻¹ vincristine | | 409 |
| | | | |
| IC₅₀ = 4.35 µg mL⁻¹/KB (VJ300) + 0.1 µg mL⁻¹ vincristine | Vincristine IC₅₀ = 1.0 µg mL⁻¹/KB (VJ300) | 411 |
| | | | |
| IC₅₀ = 4.11 µg mL⁻¹/KB (VJ300) + 0.1 µg mL⁻¹ vincristine | Vincristine IC₅₀ = 1.0 µg mL⁻¹/KB (VJ300) | 413 |
| | | | |
| IC₅₀ = 0.39 µg mL⁻¹/KB (VJ300) + 0.1 µg mL⁻¹ vincristine | Vincristine IC₅₀ = 1.0 µg mL⁻¹/KB (VJ300) | 417 |
| | | | |
| IC₅₀ = 21.8 µg mL⁻¹/KB (VJ300) + 0.1 µg mL⁻¹ vincristine | Vincristine IC₅₀ = 1.0 µg mL⁻¹/KB (VJ300) | 434 |
| | | | |
| IC₅₀ = 15.0 µg mL⁻¹/KB cells | Vincristine IC₅₀ = 1.0 µg mL⁻¹/KB (VJ300) | 437 |
| IC₅₀ = 11.0 µg mL⁻¹/KB (VJ300) cells | | 437 |
| IC₅₀ = 3.8 µg mL⁻¹/KB (VJ300) + 0.1 µg mL⁻¹ vincristine | | 437 |
### 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 | IC_{50} = 1.0 μg mL^{-1}/KB (VJ300) | 22 |
| 446       | In vitro | IC_{50} = 0.25 μg mL^{-1}, Jurkat cells | Vincadiflornine | IC_{50} = 21.8 μg mL^{-1}/Jurkat cells | 10 |
|           |        | IC_{50} = 3.6 μg mL^{-1}/KB cells | | IC_{50} = 10.2 μg mL^{-1}/KB cells | |
|           |        | IC_{50} = 0.75 μg mL^{-1}/KB (VJ300) cells | | IC_{50} = 6.3 μg mL^{-1}/KB (VJ300) cells | |
|           |        | IC_{50} = 0.46 μg mL^{-1}/KB (VJ300) + 0.1 μg mL^{-1} | | IC_{50} = 4.5 μg mL^{-1}/KB (VJ300) + 0.1 μg mL^{-1} | |
| 450 and 452 | In vitro | IC_{50} > 30 μM/A-549 cells | Docetaxel | IC_{50} = 4.95 × 10^{-4} μM/A-549 cells | 114 |
|           |        | IC_{50} = 30 μM/HT-29 cells | | IC_{50} = 3.34 × 10^{-4} μM/HT-29 cells | |
| 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**

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| IC_{50} = 31.3 μg mL^{-1}/E. coli, E. carotovra, B. subtilis, Ampicillin B. cereus, and S. aureus | Sanguinarine | MIC = 100 μg mL^{-1}/E. coli and E. carotovra |
| MIC = 15.5 μg mL^{-1}/E. carotovra | Netilmicin | MIC = 12.5 μg mL^{-1}/B. subtilis |
| EC_{50} = 33.3 μg mL^{-1}/R. solani | Mildothane | MIC = 25.0 μg mL^{-1}/B. cereus and S. aureus |
| EC_{50} = 29.2 μg mL^{-1}/P. italicum | | |
| EC_{50} = 16.3 μg mL^{-1}/F. oxysporum f. sp. Cubense | | |
| EC_{50} = 31.8 μg mL^{-1}/F. oxysporum f. sp. Niveum | | |

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| IC_{50} = 11 mm/K. pneumoniae | Sanguinarine | MIC = 10 mm/K. pneumoniae |
| IC = 9 mm/C. glabrata, E. cloacae and S. mutans | Netilmicin | IC = 8 mm/C. epidermidis and S. viridans |
| IC = 8 mm/S. epidermidis and S. dysenteriae | | IC = 24 mm/E. coli |
| IC = 7 mm/C. albicans, C. tropicalis and P. aeruginosa | | IC = 22 mm/E. cloacae |
| IC = 12 mm/P. aeruginosa and S. mutans | | IC = 23 mm/P. aeruginosa and S. dysenteriae |
| IC = 11 mm/E. coli | Sanguinarine | IC = 25 mm/S. mutans and S. viridans |
| IC = 10 mm/C. glabrata | Netilmicin | IC = 21 mm/S. aureus |
| IC = 9 mm/E. cloacae, S. aureus and S. dysenteriae | | IC = 8 mm/S. epidermidis and K. pneumoniae |
| IC = 8 mm/C. albicans, K. pneumoniae and S. epidermidis | | IC = 24 mm/E. coli |
| IC = 7 mm/C. tropicalis and S. viridans | | IC = 22 mm/E. cloacae |

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| IC_{50} = 0.77 mM/K. pneumoniae | Sanguinarine | IC_{50} = 0.87 mM/S. viridans |
| IC_{50} = 0.89 mM/E. coli | Netilmicin | IC_{50} = 0.97 mM/S. aureus and S. epidermidis |
| IC_{50} = 1.01 mM/P. aeruginosa | | IC_{50} = 0.97 mM/E. cloacae |
| IC_{50} = 0.97 mM/E. cloacae | | IC_{50} = 1.01 mM/P. aeruginosa |
| IC_{50} = 1.13 mM/S. mutans | | IC_{50} = 1.18 mM/C. tropicalis |
| IC_{50} = 1.18 mM/C. tropicalis | | IC_{50} = 2.68 mM/S. dysenteriae |
| IC_{50} = 2.87 mM/C. albicans | | IC_{50} = 3.09 mM/C. glabrata |
| IC_{50} = 23 mm/P. aeruginosa | | IC = 23 mm/P. aeruginosa and S. dysenteriae |
| IC_{50} = 0.27 mM/K. pneumoniae | | IC = 25 mm/S. mutans and S. viridans |

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| IC_{50} = 0.72 mM/E. coli | Sanguinarine | IC_{50} = 0.82 mM/S. mutans |
| IC = 20 mm and MIC = 0.72 mM/E. coli | | IC = 25 mm/S. mutans and S. viridans |
| Compounds | Models Effect | Positive control | References |
|-----------|---------------|------------------|------------|
| **In vitro** | IZ = 20 mm and MIC = 0.91 mM/S. epidermidis | Netilmicin | **RSC Advances Review 47 (Contd.)**, 2022, | 52 |
| | IZ = 20 mm and MIC = 1.03 mM/S. dysenteriae | | | |
| | IZ = 20 mm and MIC = 1.11 mM/S. viridans | | | |
| | IZ = 20 mm and MIC = 1.18 mM/P. aeruginosa | | | |
| | IZ = 19 mm and MIC = 1.20 mM/E. cloaca | | | |
| | IZ = 20 mm and MIC = 1.23 mM/C. tropicalis and S. aureus | | | |
| | IZ = 17 mm and MIC = 1.52 mM/C. glabrata | | | |
| | IZ = 21 mm and MIC = 1.37 mM/K. pneumoniae and C. albicans | | | |
| | IZ = 17 mm and MIC = 2.87 mM/C. albicans | | | |
| **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 | 52 |
| | IZ = 24 mm and MIC = 0.27 mM/E. cloaca | | | |
| | IZ = 24 mm and MIC = 0.32 mM/P. aeruginosa | | | |
| | IZ = 23 mm and MIC = 0.37 mM/K. pneumoniae | | | |
| | IZ = 23 mm and MIC = 0.87 mm/S. viridans | | | |
| **In vitro** | IZ = 24 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 = 24 mm and MIC = 0.13 mM/P. aeruginosa | | | |
| | IZ = 23 mm and MIC = 0.15 mM/E. cloaca | | | |
| | IZ = 23 mm and MIC = 0.16 mM/S. epidermidis | | | |
| | IZ = 24 mm and MIC = 0.18 mm/S. aureus | | | |
| | IZ = 24 mm and MIC = 0.23 mm/E. coli | | | |
| **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 = 24 mm and MIC = 0.17 mM/S. aureus | | | |
| | IZ = 22 mm and MIC = 0.18 mm/S. dysenteriae | | | |
| | IZ = 24 mm and MIC = 0.19 mm/E. cloaca | | | |
| | IZ = 23 mm and MIC = 0.19 mm/S. epidermidis | | | |
| | IZ = 24 mm and MIC = 0.26 mm/E. coli | | | |
| **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. cloaca | | | |
| | IZ = 17 mm and MIC = 1.12 mm/K. pneumoniae and S. dysenteriae | | | |
| | IZ = 18 mm and MIC = 1.20 mm/S. aureus | | | |
| | IZ = 19 mm and MIC = 1.23 mm/S. epidermidis | | | |

**Table 2**

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| 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 | 53 |
| **51** In vitro IZ = 17 mm and MIC = 0.92 mM/P. aeruginosa | Netilmicin | IZ = 23 mm and MIC = 0.015 mM/P. aeruginosa | 53 |
| IZ = 18 mm and MIC = 1.01 mM/E. cloacae | | IZ = 22 mm and MIC = 0.011 mM/E. cloacae | |
| IZ = 19 mm and MIC = 1.02 mM/S. dysenteriae | | IZ = 23 mm and MIC = 0.011 mM/S. dysenteriae | |
| IZ = 18 mm and MIC = 1.09 mM/K. pneumoniae | | IZ = 25 mm and MIC = 0.009 mM/K. pneumoniae | |
| IZ = 19 mm and MIC = 1.15 mM/S. epidermidis | | IZ = 25 mm and MIC = 0.004 mM/S. epidermidis | |
| IZ = 20 mm and MIC = 1.18 mM/S. aureus | | IZ = 21 mm and MIC = 0.005 mM/S. aureus | |
| IZ = 17 mm and MIC = 1.24 mM/E. coli | | IZ = 24 mm and MIC = 0.015 mM/E. coli | |
| **52** In vitro IZ = 17 mm and MIC = 1.19 mM/K. pneumoniae | Netilmicin | IZ = 25 mm and MIC = 0.009 mM/K. pneumoniae | 53 |
| IZ = 18 mm and MIC = 1.21 mM/E. coli | | IZ = 24 mm and MIC = 0.015 mM/E. coli | |
| IZ = 17 mm and MIC = 1.21 mM/P. aeruginosa | | IZ = 23 mm and MIC = 0.015 mM/P. aeruginosa | |
| IZ = 17 mm and MIC = 1.31 mM/E. cloacae | | IZ = 22 mm and MIC = 0.011 mM/E. cloacae | |
| IZ = 15 mm and MIC = 1.31 mM/S. dysenteriae | | IZ = 23 mm and MIC = 0.011 mM/S. dysenteriae | |
| **53** In vitro IZ = 16 mm and MIC = 0.99 mM/K. pneumoniae | Netilmicin | IZ = 25 mm and MIC = 0.009 mM/K. pneumoniae | 53 |
| IZ = 18 mm and MIC = 1.01 mM/S. dysenteriae | | IZ = 23 mm and MIC = 0.011 mM/S. dysenteriae | |
| IZ = 17 mm and MIC = 1.24 mM/P. aeruginosa | | IZ = 23 mm and MIC = 0.015 mM/P. aeruginosa | |
| IZ = 15 mm and MIC = 1.31 mM/E. coli | | IZ = 24 mm and MIC = 0.015 mM/E. coli | |
| IZ = 17 mm and MIC = 1.32 mM/E. cloacae | | IZ = 22 mm and MIC = 0.011 mM/E. cloacae | |
| **74** In vitro IZ = 9.7 mm/S. aureus | Kanamycin sulfate | IZ = 24.7 mm/S. aureus | 12 |
| **76** In vitro IZ = 13 mm/S. aureus | Kanamycin sulfate | IZ = 24.7 mm/S. aureus | 12 |
| IZ = 12 mm/S. epidermidis | | IZ = 24.7 mm/S. aureus | 12 |
| IZ = 9 mm/ C. albicans and C. glabrata | | IZ = 24.7 mm/S. aureus | 12 |
| IZ = 8 mm/C. tropicalis, S. mutans and S. dysenteriae | | IZ = 24.7 mm/S. aureus | 12 |
| IZ = 7 mm/E. coli and K. pneumoniae | | 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 subtillis, B. cereus, and S. aureus | Ampicillin | MIC = 100 μg mL⁻¹/E. coli and E. carotovra | 7 |
| MIC = 7.8 μg mL⁻¹/E. carotovra | Mildothane | MIC = 12.5 μg mL⁻¹/B. subtillis | |
| EC₅₀ = 21.9 μg mL⁻¹/R. solani | | MIC = 25.0 μg mL⁻¹/B. cereus and S. aureus | |
| EC₅₀ = 19.4 μg mL⁻¹/P. italicum | | EC₅₀ = 17.0 μg mL⁻¹/R. solani | |
| EC₅₀ = 15.2 μg mL⁻¹/F. oxysporum f. sp. Cubense | | EC₅₀ = 7.8 μg mL⁻¹/P. italicum | |
| EC₅₀ = 43.8 μg mL⁻¹/F. oxysporum f. sp. Niveum | | EC₅₀ = 57.0 μg mL⁻¹/F. oxysporum f. sp. Cubense | |
| | | EC₅₀ = 101.0 μg mL⁻¹/F. oxysporum f. sp. Niveum | |
| Compounds          | Models Effect                                                   | Positive control          | References |
|--------------------|----------------------------------------------------------------|---------------------------|------------|
| 267 and 297        | **In vitro** MIC = 32 µg mL⁻¹/E. coli                          |                           | 21         |
| **Anti-inflammatory activity** |                                                              |                           |            |
| 11                 | **In vitro** IC₅₀ = 25.4 µM/T cell inhibition                   | Ketotifen fumarate        | 16         |
| 170                | **In vitro** IC₅₀ = 21.6 µM/T cell inhibition                   | Ketotifen fumarate        | 16         |
| 222                | **In vitro** IC₅₀ = 27.8 µM/T cell inhibition                   | Ketotifen fumarate        | 16         |
| 409                | **In vitro** IC₅₀ = 1.0 µM/T cell inhibition                   | Ketotifen fumarate        | 16         |
| 219, 225, 228,      | The inhibitory effects on IL-1β and TNF-α, and                 | Ketotifen fumarate        | 75         |
| 279–280, 291, and   | PGE2 were comparable with positive control                     |                           |            |
| 439                | **In vitro**                                                   |                           |            |
|                    | **Anti-allergic activity**                                    |                           |            |
| 90                 | **In vitro** IC₅₀ = 3.73 µg mL⁻¹/histamine and β-hexosaminidase inhibition in RBL-2H3 cell | Ketotifen fumarate        | 66         |
| 126                | **In vitro** IC₅₀ = 7.06 µg mL⁻¹/histamine and β-hexosaminidase inhibition in RBL-2H3 cell | Ketotifen fumarate        | 66         |
| 257                | **In vitro** IC₅₀ = 5.51 µg mL⁻¹/histamine and β-hexosaminidase inhibition in RBL-2H3 cell | Ketotifen fumarate        | 129        |
| 448                | **In vitro** IC₅₀ = 11.78 µg mL⁻¹/histamine and β-hexosaminidase inhibition in RBL-2H3 cell | Ketotifen fumarate        | 66         |
|                    | **The MeOH extract in vitro**                                 |                           |            |
|                    | IC₅₀ = 2.17 µg mL⁻¹/histamine and β-hexosaminidase inhibition in RBL-2H3 cell | Ketotifen fumarate        | 66         |
|                    | The MeOH extract in vitro of K. larutensis bark                |                           |            |
|                    | IC₅₀ = 3.82 µg mL⁻¹/histamine and β-hexosaminidase inhibition in RBL-2H3 cell | Ketotifen fumarate        | 129        |
|                    | The MeOH extract in vitro of K. arborea bark                   |                           |            |
|                    | IC₅₀ = 3.01 µg mL⁻¹/histamine and β-hexosaminidase inhibition in RBL-2H3 cell | Ketotifen fumarate        | 66         |
|                    | The MeOH extract in vitro of K. larutensis leaf                |                           |            |
|                    | IC₅₀ = 2.58 µg mL⁻¹/histamine and β-hexosaminidase inhibition in RBL-2H3 cell | Ketotifen fumarate        | 129        |
|                    | The MeOH extract in vitro of K. arborea leaf                   |                           |            |
|                    | IC₅₀ = 1.61 µg mL⁻¹/histamine and β-hexosaminidase inhibition in RBL-2H3 cell | Ketotifen fumarate        | 66         |
|                    | The MeOH extract in vitro of K. arborea root                   |                           |            |
|                    | IC₅₀ = 4.32 µg mL⁻¹/histamine and β-hexosaminidase inhibition in RBL-2H3 cell | Ketotifen fumarate        | 129        |
|                    | **Anti-diabetic activity**                                    |                           |            |
| 29                 | **In vitro** EC₅₀ = 24.5 µM/glucose-evoked podocyte injury inhibition | Astragaloside IV EC₅₀ = 15.4 µM/glucose-evoked podocyte injury inhibition | 25         |
| 126                | **In vitro** EC₅₀ = 3.0 µM/glucose-evoked podocyte injury inhibition | Astragaloside IV EC₅₀ = 15.4 µM/glucose-evoked podocyte injury inhibition | 25         |
| 224                | **In vitro** EC₅₀ = 10.2 µM/glucose-evoked podocyte injury inhibition | Astragaloside IV EC₅₀ = 15.4 µM/glucose-evoked podocyte injury inhibition | 25         |
| 264                | **In vitro** EC₅₀ = 12.0 µM/glucose-evoked podocyte injury inhibition | Astragaloside IV EC₅₀ = 15.4 µM/glucose-evoked podocyte injury inhibition | 25         |
| 405                | **In vitro** EC₅₀ = 3.80 µM/glucose-evoked podocyte injury inhibition | Astragaloside IV EC₅₀ = 15.4 µM/glucose-evoked podocyte injury inhibition | 25         |
| 379 and 384–386     | **In vitro** IC₅₀ > 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** IC₅₀ = 12.5 µg/AChE inhibition                     |                           | 6          |
| 221                | **In vitro** IC₅₀ = 12.5 µg/AChE inhibition                     |                           | 6          |
### Cardiovascular and vasorelaxant activities

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

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

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 kopsofinol (289). 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\(^{-1}\). Valparicine (446) would be superior to the positive control vincadifformine in a cytotoxic assay against Jurkat cell growth. In addition, this compound and arboloscleine (437) showed positive signals to resist the growth of KB (VJ300) and KB (VJ300) + 0.1 μg mL\(^{-1}\) vincristine (Table 2).

### 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. 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. 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.

In another assessment, kopsiflorine (74) and kopsihainins D–F (85–87) showed suppression towards the Gram positive bacterium Staphylococcus aureus with IC50 values ranging from 9.7 to 11.2 mm, but compounds 3, 17, 73, 109, 124, 405, and 406 were inactive. In an antimicrobial assay against E. coli, Erwinia carotovora, Bacillus subtilis, B. cereus, and S. aureus, two best agents N-decarboxymethoxypsamine (14) and N_{1}-decarboxymethoxy chanofruticosic acid (206) were associated with the MIC values of 7.8–15.5 and 15.5–31.3 μg mL\(^{-1}\), respectively.

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). Lastly, two eburnamines 19-hydroxy-(−)-eburnonamine (267) and phutdongin (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.13–15 *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 decarbomethoxykopsin (11), N(4)-methylkopsininate (170), 12-methoxychanofruticosinic acid (222), and rhanzilam (409) inhibited T cell growth with the IC₅₀ 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 N₁-decarbomethoxychanofruticosinate (225), methyl 12-methoxychanofruticosin (228), kopsiicoficines I-J (279–280), (++)-O-methylubarnaminc (290), (−)-O-methylisobarnamine (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 antiadipic activities

Naturally occurring compounds have been recognized as potential antiallergic agents. In an experiment against histamine and β-hexosaminidase in RBL-2H3 cells, the IC₅₀ values of 3.73–11.78 μg mL⁻¹ were assigned to four alkaloids kopsilartensine (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).26,129

For antiadipic activity, among tested compounds for the high glucose-evoked podocyte injury inhibition, the EC₅₀ 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-oxoeburnaminc 264 (12.0 μM) > reference compound astragaloside IV (15.4 μM) > 11-hydroxykopsilonginc 29 (24.5 μM).25 However, four pauciflorine derivatives 11,12-demethoxy-16-deoxypaubiclin (379) and kopsiicofines A-C (384–386) failed to suppress enzyme α-glucosidase (IC₅₀ > 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, kopsiicofinanes A–B (220–221), displayed weak AChE inhibitory activity with the respective IC₅₀ values of 38.5 and 50.6 μM.66 (−)–12-Methoxykopsinamine (165) with the IC₅₀ value of 12.5 mg mL⁻¹, showed anti-manic activity in *Drosophila*.61

Kopsinine 126 (70 mg kg⁻¹, i.p.) and methyl N₁-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, anti-tussive 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.138

### 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 19th 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.135 However, kopsparine (42) was reasonable for blood pressure increase, and kopsidine A (67) with the deletion of the methoxy group did not alter the responsible hypotension.133

Vasodilators can be used for cerebral vasospasm and hypertension treatments, as well as to enhance peripheral circulation.138,139 Flavisanimines A, C, and D (208 and 210–211), kopreasin A (216), methyl 11,12-methylenedioxychanofruticosinate (219), methyl N₁-decarbomethoxychanofruticosinate (225), methyl 12-methoxy-N₁-decarbomethoxychanofruticosin (227), methyl 12-methoxychanofruticosinate (228), methyl 11,12-methylenedioxy-N₁-decarbomethoxychanofruticosinate (229), methyl 11,12-methylenedioxy-N₁-decarbomethoxy-A₁₄₁₅-chanofruticosinate (230), and prunifoline B (239) at the concentration of 3 × 10⁻³ 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, monoterpen alkaloids (466 compounds) accounted for 98.73%. *Kopsia* monoterpen 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, monoterpine 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**

| Abbreviation | Description |
|--------------|-------------|
| 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 | Dermatomas |
| 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 |
| PC-3         | Colorectal cancer cells |
| Jurkat       | Human prostate cancer cells |
| KB           | 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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