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Biologically Active Isoquinoline Alkaloids covering 2014-2018

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Abstract

Isoquinoline alkaloids, an important class of *N*-based heterocyclic compounds, have attracted considerable attention from researchers worldwide since the early 19th century. Over the past 200 years, many compounds from this class were isolated, and most of them and their analogs possess various bioactivities. In this review, we survey the updated literature on bioactive alkaloids and highlight research achievements of this alkaloid class during the period of 2014–2018. We reviewed over 400 molecules with a broad range of bioactivities, including antitumor, antidiabetic and its complications, antibacterial, antifungal, antiviral, antiparasitic, insecticidal, anti-inflammatory, antioxidant, neuroprotective, and other activities. This review should provide new indications or directions for the discovery of new and better drugs from the original naturally occurring isoquinoline alkaloids.

Keywords

isoquinoline alkaloids; biological activities; berberine; antitumor

1. Introduction

Isoquinoline alkaloids, an important class of *N*-heterocyclic bioactive natural products, are common throughout the plant kingdom[1]. They are likely derived from tyrosine or phenylalanine building blocks and show a wide range of structural diversity[2]. Since the first

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bioactive isoquinoline alkaloid, morphine, was isolated from the opium plant in the early 19th century[3], this compound class has attracted considerable scientific attention. Increasing numbers of isoquinoline alkaloids have been isolated and identified from natural sources, and various studies have reported their antitumor, antimalarial, antibacterial, antifungal, antiparasitic and insecticidal, antiviral, anti-inflammatory, antiplatelet and other activities[4-12]. As lead compounds in the drug discovery and development process, isoquinoline alkaloids have high probabilities of success,[13] as reflected by several revolutionary drugs, such as the analgesic morphine, the antibacterial berberine, the antitussive codeine[14], the antirheumatic sinomenine[15], and the acetylcholinesterase inhibitor galanthamine[16] (Figure 1). Therefore, the search for novel isoquinolines as promising drug leads remains an active area of study in natural product chemistry.

In view of the importance and significant biological activities of isoquinoline alkaloid natural products, several thousand publications (journal articles, books and patents) on isoquinoline alkaloids have been recorded over the past 200 years. The increasing numbers of publications reflect the research intensity and importance of this field, as well as the bright prospect for drug development from these compounds. Some excellent earlier reviews on the chemical structures and biological properties of isolated isoquinoline alkaloids have contributed significantly to the general scientific understanding of this kind of compounds[5,6,8,9,10,11,12,17-21]. However, during the past five years, significant studies and novel technologies, such as metabolomics, were widely reported and used to identify alkaloids from plants. Many new compounds were isolated, and novel pharmacological activities and comprehensive mechanism of actions were investigated by researchers worldwide. Hence, a more comprehensive and up-to-date review is merited. Therefore, this review combines newer literature reports as well as presents the developments in this field particularly from the perspective of biological activities. It covers not only the chemical structures of isolated isoquinoline alkaloids (Table 1), but also their biological activities and mechanism of actions. We hope that this review will provide new indications or directions for the development of these compounds as new clinically useful therapeutic agents.

2. Structure and classification of isolated isoquinoline alkaloids

2.1 Simple isoquinoline alkaloids

The alkaloids in this classification have the simplest structures and are distributed mainly in the genera *Papaver, Corydalis, Thalictrum* and others. Eighteen isoquinoline alkaloids were identified and isolated from plants and animals between 2014 and 2018 (Figure 2).

In 2016, two new isoquinoline alkaloids 3,8-diolisoquinoline (**1**) and 1-methoxy-4,5-diolisoquinoline (**2**) were isolated from an ethanol extract of the Chinese redheaded centipede *Scolopendra subspinipes mutilans*[22]. In another study in the following year, the new isoquinoline alkaloid 1,5-dihydroxy-4-methoxyisoquinoline (**3**), also isolated from this centipede species, showed moderate cytotoxicity against five cancer cells[23].

Carnegine (**4**) and *N*-methylisosalsoline (**5**), isolated from the plant *Hammada scoparia*, exhibited antibacterial and antioxidant activities[24]. Also, in 2016, *N*-methylcorydaldine (**6**)

was isolated from *Fumaria officinalis*[25] and 6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid (**7**) from *Mucuna pruriens* seeds[26].

In 2018, the previously reported *N*-methylcorydaldine (**6**) together with two more isoquinoline alkaloids 7-methoxy-1,2,3,4-tetrahydroisoquinolin-1-one (**8**) and thalifoline (**9**) were isolated from *Michelia champaca*[27]. Other studies in same year described the isolation as well as hepatoprotective activities of the latter compound (**9**), *N*-methylisosalsoline (**5**), corydaldine (**10**), oxohydrastinine (**11**), 6,7-methylenedioxy-1(2*H*)-isoquinolinone (**12**) and oxyhydrastinine (**13**) from *Corydalis tomentella, C. hendersonii* and *Plumula nelumbinis*[28-30].

6,7-Dihydroxy-1-methyl-3,4-dihydroisoquinolone (**14**), (*S*)-(−)-salsolinol (**15**), 6,7-dihydroxy-3,4-dihydroisoquinolone (**16**) and (*R*)-(+)-1-isobutyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (**17**), were isolated from the medicinal plant *Portulaca oleracea*[31]. These four simple isoquinoline alkaloids contained 6,7-dihydroxy substitution but different saturation or substituents at C-1. Four “naphthalene-devoid” tetra- and dihydroisoquinolines, named ealaines A–D (**18-21**), were isolated from the Congolese plant *Ancistrocladus ealaensis*[32]. Akihisa *et al*.[33] isolated noroxyhydrastinine (**22**) from the bark of *Phellodendron amurense* (Figure 2).

2.2. Benzylisoquinoline alkaloids

2.2.1 Simple benzylisoquinoline alkaloids—Reticuline (**23**) exhibits significant pharmacological activities, leading to the search for and identification of alternate natural sources, such as *Litsea cubeba*, *Unonopsis* genus, *Cryptocarya densiflora, C. infectoria, C. griffithiana* and *Dehaasia longipedicellata*, over the past five years[34-39]. (+)-*N*-Methylisococlaurine (**24**) also was found in *Cryptocarya* species[37] and (−)-*N*-methylcoclaurine (**25**) was identified in the rhizomes of *Sinomenium acutum* in 2014[40]. Berbithine (**26**) and 6-([1,3]dioxolo[4,5-g]isoquinoline-5-carbonyl)-2,3-dimethoxybenzoic acid methyl ester (**27**) were isolated from the rhizome of *Coptis chinensis*[41].

In 2018, several benzylisoquinoline alkaloids, including **24**, **25**, norcolaurine-4′-*O*-glucoside (**28**), *N*-methylhigenamine (**29**), norcoclaurine-6-*O*-glucoside (**30**), norcoclaurine (**31**), argemexirine (**32**), lotusine (**33**), isococlaurine (**34**), armepavine (**35**), 6-demethy-4′-methyl-*N*-methylcoclaurine (**36**), coclaurine (**37**), *N*-nor-*O*-methylarmepavine (**38**), isococlaurine-5′-*O*-pentoside (**39**), and coclaurine-5′-*O*-pentoside (**40**) were identified from *Plumula nelumbinis* through UPLC-ESI-QTOF-MS[30]. Subsequently, juzirine (**41**) was identified from the aerial parts of *Leonurus japonicus*[42]. (*R*)-(+)-1-Benzyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (**42**) from *Portulaca oleracea* showed anti-inflammatory and β2-adrenergic receptor agonist activities[26]. Laudanosine (**43**), pseudolaudanine (**44**) and rugosinone (**45**)were isolated from the whole herb of *Thalictrum cirrhosum*[43] (Figure 3). Hendersine B methyl ester (**46**), bicucullinine (**47**) and hendersine B (**48**) were isolated from *Corydalis tomentella*[28].

2.2.2. Bisbenzylisoquinoline alkaloids—Bisbenzyl isoquinoline alkaloids are one of the major phytochemicals reported from members of the plant families *Menispermacea,*

Berberidaceae, Lauraceae, and *Ranunculaceae,* which grow in tropical and subtropical regions. They contain two benzylisoquinolines linked through diphenyl ether, benzyl phenyl ether, or biphenyl bonds[5,19]. In 2016, two new bisbenzylisoquinolines, 6,6′,7′,12-tetramethoxy-5′-hydroxy-2,2′-dimethyloxycanthan (**49**) and 6,5′,6′,7′,12-pentamethoxy-2,2′-dimethoxyethane (**50**), were isolated from the stems of *Thalictrum foliolosum*[44]. Meanwhile, hernandezine (**51**), a known alkaloid, was identified from *T. flavum*[45]. In 2018, two *seco*-bisbenzylisoquinolines, 6,7,12-trimethoxy-2-methyl-13-hydroxy-11-(4′-formylphenoxy)benzylisoquinoline (**52**) and 5,6-(methylenedioxy)-7,12-dimethoxy-2-methyl-10-(4′-formylphenoxy)benzylisoquinoline (**53**), were isolated from *T. wangii*[46]. Tiliamosine (**54**) was found from *T. racemosa*[47] (Figure 3).

Bisbenzylisoquinoline alkaloids are also found in the genus *Stephania*. In 2014, two new compounds, (−)-pseudocurine (**55**) and (−)-pseudoisocurine (**56**), were isolated from a leaf extract of *Stephania abyssinica*[48]. Tetrandrine (**57**) and fangchinoline (**58**) were isolated from *S. tetrandra,* which has been used for 2,000 years as an antirheumatic herbal medicine in China[49]. In addition, (−)-*O*-*O*-dimethylgrisabine (**59**) from *Dehaasia longipedicellata* exhibited significant antiparasitic and antioxidant activities[38]. Using a ^{1}H NMR-based metabolomics approach, berbamine (**60**), a bisbenzylisoquinoline-type compound, was identified from *Mahonia aquifolium*[50] (Figure 4).

Neferine (**61**) is a well-known bisbenzylisoquinoline-type alkaloid due to its wide range of pharmacological activities, including antiarrhythmic, antihypertensive[51,52], relaxant[53], antidiabetic[54], cholinesterase inhibitory[55], antioxidant, anti-inflammatory, anti-amnesic[56] and sedative[57,58] effects. In addition to *M. aquifolium*, it is found in lotus (*Nelumbo nucifera*) seed embryos[59]. In 2018, compound **61** as well as four other bisbenzylisoquinoline alkaloids, liensinine (**62**), isoliensinine (**63**), norisoliensinine (**64**) and 6-hydroxynorisoliensinine (**65**) were found in *Plumula nelumbinis*[30]. Five alkaloids also were isolated from *Alseodaphne corneri*, including (−)-gyrolidine (**66**), (+)-*O*-methyllimacusine (**67**), (+)-2-norobaberine (**68**), (+)-norstephasubine (**69**) and (+)-stephasubine (**70**)[60] (Figure 4).

2.2.3. *Spiro*benzylisoquinoline alkaloids—Spirobenzylisoquinoline alkaloids are isoquinoline alkaloids with a unique '*spiro*' structure as shown in Figure 6. They have been found only within the plant family Fumariaceae, and more specifically within the genera *Fumaria* and *Corydalis.* In 2014, coptichic aldehyde (**71**) was isolated from the traditional Chinese medicine preparation *Coptidis Rhizoma–Euodiae Fructus* couple; it showed growth inhibitory activity against NCI-N87 cells with an IC_{50} value of 8.92 μM[61]. In 2016, the new isoquinoline alkaloid fumaranine (**72**) together with seven other alkaloids, (−)-fumaricine (**73**), (+)-dihydrofumariline (**74**), (−)-fumaritine (**75**), (−)-*O*-methylfumarophycine (**76**), (−)-fumarophycine (**77**), (+)-fumariline (**78**), (+)-parfumidine (**79**), and (+)-parfumine (**80**) were found from the aerial parts of *F. officinalis*[24]. Also, four new spirobenzylisoquinoline *N*-oxide alkaloids hendersines C-F (**81-84**) were identified from *Corydalis hendersonii*[27] (Figure 4).

2.3. Aporphine isoquinoline alkaloids

Aporphine alkaloids are a large group of isoquinolines that generally possess a characteristic tetracyclic ring system (rings A-D) with a nitrogen in ring B[62]. The structures of the aporphine alkaloids can be classified into subtypes, including simple aporphines, their dehydro derivatives, oxoaporphines, miscellaneous aporphinoids, and dimeric aporphinoid alkaloids[63-66].

2.3.1. Simple aporphines—Simple aporphines have a 5,6,6a,7-tetrahydro-4*H*-dibenzo[*de,g*]quinoline core substituted primarily with different numbers of hydroxy, methoxy, and methylenedioxy groups at various positions. The nitrogen is substituted most frequently with hydrogen or methyl, although other groups (e.g., formyl, acetyl, and others) are sometimes present. They are 1-benzylisoquinolines with one additional ring closure between the 2′-carbon in the pendant phenyl ring and the 1a-carbon in the isoquinoline ring junction, forming a non-linear tetracyclic (6-6-6-6) system.

Boldine (**85**), isolated from *Litsea cubeba* and *Dehaasia longipedicellata*, showed anti-inflammatory activity and potential synergistic effects *in vivo*[67,60]. Compound **85** and (−)-norboldine (**86**), also found in *D. longipedicellata*,[38] showed moderate antioxidant and antiplasmodial activities[38]. In 2016, (+)-laurotetanine (**87**), isolated from *Alseodaphne corneri*[68] and *Bocageopsis pleiosperma*[39], was found to exhibit strong antiplasmodial activity (Figure 5).

Compound **87**, (+)-nornantenine (**88**) and (+)-*N*-methyllaurotetanine (**89**) were isolated from *Cryptocarya densiflora*, *C. infectoria* and *C. griffithiana*[37]. Corydine (**90**) and norisoboldine (**91**) were isolated from *Croton echinocarpus* leaves[69], while isocorydine (**92**) and norisocorydine (**93**) were identified from *Alseodaphne corneri*[60] (Figure 5).

The aporphine stephalagine (1,2-methylenedioxy-3-methoxyaporphine) (**94**) was isolated from the fruit peel of *Annona crassiflora*[70]. In 2017, *N*-formyl-asimilobine-2-*O*-β-D-glucoside (**95**), an amidic aporphine, was obtained from the tubers of *Stephania succifera*[71]. Four aporphine alkaloids, isoboldine (**96**), anonaine (**97**), nornuciferine (**98**) and actinodaphnine (**99**), were isolated from *Annona hypoglauca*[72]. Magnoflorine (**100**) was found in the rhizomes of *Mahonia aquifolium, Coptis japonica* and *Sinomenium acutum*[40,50,73] (Figure 5).

Both norpurpureine (**101**) and purpureine (**102**) were isolated from *Annona purpurea* leaves[74]. In 2018, eight aporphine alkaloids [anonaine (**97**), *N*-nornuciferine (**98**), nornuciferidine (**103**), zenkerine (**104**), *O*-nornuciferine (**105**), nuciferine (**106**), roemerine (**107**) and oxidation-nuciferine (5-hydroxynuciferine) (**108**)] were identified from *Plumula nelumbinis*[30]. Compounds **93**, **97** and **98** as well as asimilobine (**109**), isopiline (**110**), *O*-methylisopiline (**111**), glaucine (**112**), and norglaucine (**113**) were reported for the first time from *Unonopsis floribunda*[35,36] (Figure 5). Compounds **97**, **98**, **109** and **112** also were found from *Unonopsis duckei*[75], and compounds **89**, **96**, **97** and **109** also were reported from *Bocageopsis pleiosperma*[40]. (+)-*N*-Formylnorglaucine (**114**) was reported from *Unonopsis stipitata*[76].

Four new phenyl-C_1 substituted aporphine alkaloids, 6a*R*-2′-methoxycarbonylthaliadine (**115**), 6a*R*-2′-carboxylthaliadine (**116**), 6a*R*-3-methoxyhernandalinol (**117**), 6a*S*-1,3,10-trimethoxynatalamine (**118**), together with three known isoquinoline alkaloids **89**, predicentrine (**119**), and thaliadine (**120**) were isolated from the whole herb of *Thalictrum cirrhosum*[43].

Glaucine (**121**) from *Corydalis turtschaninovii*[77], as well as three new analogs, (+)-8-(4′-formylphenoxy)glaucine (**122**), (+)-8-(4′-hydroxymethylphenoxy)glaucine (**123**), (+)-3-methoxy-8-(4′-formylphenoxy)glaucine (**124**), and two known alkaloids, **120** and its oxidized derivative **125**, were isolated from the whole plant of *Thalictrum wangii*[46] (Figure 5).

An unprecedented alkaloid, dactyllactone A (**126**), which contains a rearranged benzofuran lactone with a gemdimethoxycarbonyl unit and is derived from an 8,9;11,11a-*bis*-seco-aporphine skeleton, was isolated from *Dactylicapnos scandens*. It exhibited anti-inflammatory activity[78] (Figure 5).

2.3.2. 7-Substituted Aporphines and Oxoaporphines—7-Oxygenated aporphines have a hydroxyl or methoxy group at C-7 or two such groups at C-4 and C-7[66,79]. The oxoaporphines (7*H*-dibenzo[*de,g*]quinoline-7-one skeleton) and oxoisoaporphines (7*H*-dibenzo[*de,h*]quinoline-7-one skeleton) have an aromatic isoquinoline (aromatic ring B in the tetracyclic structure) and a carbonyl group at C-7[80].

Two oxoisoaporphines sallisonine E (**127**) and dauriporphine (**128**) were isolated from the rhizomes of *Sinomenium acutum*, in 2014 and 2016, respectively[40,81]. Five oxoaporphines isomoschatoline (**129**), O-methylmoschatoline (**130**), liriodenine (**131**), subsessiline (**132**) and lysicamine (**133**) were identified from *Guatteria blepharophylla* also in 2016[74] and compounds **131**, **133** were reported from *Unonopsis duckei* in 2014[75].

One new 4,7-dihydroxy-7-methylaporphine alkaloid (7-hydroxyguatteriopsiscine (**134**)) and three new 7,7-dimethylaporphinoids [(*R*)-dihydroguatteriscine (**135**), guatterfriesidine (**136**), and iso-9-methoxyguatterfriesine (**137**)] were isolated from the stem bark of *G. friesiana* in 2018.[75] Compound **136** exhibited antiglycation activity as determined by inhibiting the formation of advanced glycation end-products in both bovine serum albumin (BSA)/methylglyoxal and BSA/fructose assay systems[82]. In 2018, one 7-hydroxyaporphine [norushinsunine (**138**)] and four oxoaporphines [**131**, **133**, oxoglaucine (**139**), and lanuginosine (**140**)] were reported for the first time from *Unonopsis floribunda*[35] (Figure 6).

Another new oxoaporphine alkaloid 3-methoxy-2′-methoxycarbonyl-oxohernandalincin (**141**) as well as the known 3-methoxy-oxohernandaline (**142**), oxopurpureine (**143**), and oxophoebine (**144**) were isolated from the whole herb of *Thalictrum cirrhosum*[43]. 1,2,3,9,10-Pentamethoxy-11-(4′-formylphenoxy)-7-oxoaporphine (**145**) and 1,2,9,10-tetramethoxy-11-(4′-formylphenoxy)-7-oxoaporphine (**146**), two new oxoaporphines that, like **142**, contain an ether-linked formylphenyl moiety were identified from *T. wangii*[46] (Figure 6).

2.3.3. Dehydroaporphines—Dehydroaporphines are 5,6-dihydro-4H-dibenzo[de,g]quinolines with a double, rather than single, between C-6a and C-7. In the preceding subtypes, this bond is saturated or C-7 is substituted with hydroxy, methoxy, or methyl groups or part of a carbonyl unit[19,83,84]. Based on bioassay-guided fractionation against numerous cancer cells, Le *et al.*[85] isolated one dehydroaporphine [dehydrocrebanine (**147**)] and three simple aporphines [crebanine (**148**), stephanine (**149**) and *O*-methylbulbocapnine (**150**)] from the tubers of *Stephania venosa* growing in Vietnam. Compound **149** was the most active among the four compounds with IC_{50} values of 3.33 μM, 5.66 μM and 6.49 μM against HeLa, MDA-MB231 and MCF-7 cells, respectively. In 2017, an amidic dehydroapophine (**151**, 6-formyl-1,2,9,10-tetramethoxy-6α,7-dehydroaporphine) was isolated from the aerial parts of *Aconitum carmichaelii*[70] (Figure 6).

2.3.4. Proaporphine alkaloids—Proaporphine alkaloids are biogenetic precursors to certain aporphine alkaloids. The tetracyclic system (2',3',8',8a'-tetrahydro-1'H-spiro[cyclohexane-1,7'-cyclopenta[ij]isoquinoline) is composed of a bicyclic isoquinoline fused to a five-membered ring that is also connected to a six-membered ring through a spiro carbon.

In 2014, glaziovine (**152**) was reported from *Unonopsis duckei*[75]. In 2016, the proaporpine (+)-oridine (**153**) was obtained from leaves of *Cryptocarya densiflora*[37]. In 2018, several proaporphines were identified from various plant species: two new [(−)-10-*O*-acetylprodensiflorins A (**154**) and B (**155**)] and one known [prodensiflorin B (**156**)] and from the whole plant of *Thalictrum wangii*[46], dihydroglaziovine (**157**) and linearisine (**158**) from *T. cirrhosum*,[43] pronuciferine (**159**) from *Plumula nelumbinis*[30] and stepharine (**160**) from *Unonopsis floribunda* for the first time[35,36], and compound **160** also was found *Bocageopsis pleiosperma*[39]. (Figure 6).

2.4. Berberine and protoberberine isoquinoline alkaloids

2.4.1. Berberine (quaternary protoberberine) alkaloids—Berberine (**161**) is a famous isoquinoline alkaloid from the rhizome, roots and stem bark of *Berberis sp.*; it exhibits various pharmacological effects, such as antitumor, antibacterial, antiviral, antiinflammatory, antidiabetic and myocardial protective activities. Berberine is a quaternary protoberberine alkaloid with a tetracyclic skeleton [5,6-dihydrobenzo[a,g]quinolizinium ($C_{17}H_{14}N^+$) salt] with the nitrogen at the junction of the two middle rings (position 7). Structurally, it is a benzylisoquinoline with an additional ring formed between the 2′-carbon of the pendant phenyl ring and a methyl on the isoquinoline nitrogen. Various oxygenated substituents (hydroxy, methoxy, methylenedioxy) are present on the two outer rings, most often, although not exclusively, at positions 2,3,9,10 or 2,3,10,11, which is often designated as 'pseudo'. Methylation at position 13 is commonly seen as well. Besides the genus *Berberis*, it has also been isolated from plants of the genera *Coptis*, *Corydalis* and *Mahonia* together with other known structurally related alkaloids, including jatrorrhizine (**162**), epiberberine (**163**), demethyleneberberine (**164**), coptisine (**165**) and palmatine (**166**)[50,73,86-88].

Compounds **161, 162, 165, 166,** pseudodehydrocorydaline (**167**), dehydrocorybulbine (**168**) and pseudocoptisine (**169**) were isolated from the roots of *Corydalis turtschaninovii*. They showed strong neuraminidase inhibitory activity (IC_{50}, 12.8–65.2 μM)[77]. Dehydroisoapocavidine (**170**), dehydrocheilanthifoline (**171**), isolated from the related species *C. tomentella*, showed hepatoprotective activity[28]. Corydamine (**172**), a B-ring opened 3-phenyl isoquinoline analog of **159**, was isolated from the aerial parts of *Fumaria officinalis*[19] (Figure 7).

2.4.2. Protoberberine isoquinoline alkaloids—Other protoberberines include tetrahydroprotoberberines and dihydroprotoberberines. In 2014, several 8-oxo-protoberberines, including a pair of new enantiomeric isoquinoline alkaloids, (+)- and (−)-5-hydroxyl-8-oxyberberine (**173**), 8,13-dioxocoptisine hydroxide (**174**), 8-oxyberberine (**175**), 8-oxo-epiberberine (**176**), 8-oxocoptisine (**177**), and 8-oxoberberrubine (**178**), together with tetrahydroberberine (**179**) and corydaline (**180**) as well as the benzylisoquinoline alkaloid **26** were isolated from the rhizoma of *Coptis chinensis*. C2C12 cells exposed to **176** and **178** showed reduced glucose uptake[41,89]. The whole plant of *Corydalis pallida* also yielded **177** together with four tetrahydroprotoberberines, (−)-corydalidzine (**181**), (−)-corybulbine (**182**), (−)-yuanhunine (**183**) and (−)-ophiocarpine (**184**), as well as the quaternary protoberberine alkaloid dehydrocorydaline (**185**)[90]. Dihydrocoptisine (**186**), *trans*-protopinium (**187**), *cis*-protopinium (**188**), and thalictrifoline (**189**) from *Corydalis tomentella* displayed moderate hepatoprotective activities; the values of relative survival rates were 34.25–47.51% at a concentration of 10 μM[28]. The isomeric **187** and **188** obtained from roots of *Fumaria parviflora* also showed nematocidal activity[91] (Figure 7).

In 2014, compound **180** and tetrahydrocoptisine (**190**) were isolated from the roots of *Corydalis turtschaninovii*[77]. A new compound 13-carboxaldehyde-8-oxocoptisine (**191**) together with **177** were isolated from the traditional Chinese preparation *Coptidis Rhizoma-Euodiae Fructus* couple, used to treat gastrointestinal disorders[61]. *Corydalis hendersonii* and *Coptis japonica* were found to contain tetrahydropalmatine (**192**) and 8-hydroxy-7,8-dihydrocoptisine (**1 93**), respectively[27,73]. Cavidine (**194**) was isolated from *Corydalis impatiens*[92]. In 2016, (−)-stylopine (**195**), (−)-sinactine (**196**) and (−)-cheilanthifoline (**197**) were isolated from aerial parts of *Fumaria officinalis*[24]. The latter compound also was found in *Sinomenium acutum*[81]. Phellodendrine (**198**) was identified from *Phellodendri chinensis* cortex[93]. In 2017, a new glycoalkaloid, (−)-1-*O*-β-D-glucoside-8-oxotetrahydropalmatine (**199**), isolated from tubers of *Stephania succifera*, exhibited antimicrobial activity against *Staphylococcus aureus*[71]. *N*-Methylcanadine (**200**) was isolated from *Zanthoxylum tingoassuiba*[94], and demethylalangiside (**201**), alangiside (**202**) and isoalangiside (**203**) were identified and isolated from *Ophiorrhiza nutans*[95]. Subsequently, in 2018, it was shown that scoulerine (**204**) from *Corydalis dubia* exhibited promising suppression of cancer cell growth[96]. (Figure 8).

2′-*O*-*trans*-Sinapoylisoalangiside (**205**) was identified from *Alangium longiflorum*[97]. Four new isoquinoline alkaloids rupestrines A-D (**206-209**) and the known **195** were identified from *Corydalis rupestris*[98] (Figure 8).

2.5. Protopine isoquinoline alkaloids

Compounds from this classification have a 5,6,7,8,13,14-hexahydrodibenzo[c,g]azecine skeleton. They lack the B/C bond and, thus, are tricyclic (6-10-6) with a 10-membered ring between two phenyl rings. Only two compounds of this type were identified during the past five years. Protopine (**210**) and cryptopine (**211**) were isolated from *Fumaria officinalis*[24], and the former compound also was found in *Corydalis mucronifera*[99] (Figure 9).

2.6. Naphthylisoquinoline alkaloids

Naphthylisoquinolines are a group of structurally diverse secondary metabolites containing both naphthalene and isoquinoline bicyclic systems connected by a *C,C* or *C,N* biaryl axis. These chiral compounds are mostly found only in two palaeotropic families, Dioncophyllaceae and Ancistrocladaceae. Dioncophyllaceae-type alkaloids have a R-configuration at C-3 and always lack an oxygen function at C-6. The structurally similar Ancistrocladaceae-type alkaloids are found in the closely related Ancistrocladaceae plant family. Among the studies over the past two decades on the isolation and bioactivity evaluation of naphthylisoquinoline alkaloids, extensive work has been published by Bringmann *et al.*[21, 100-113].

From 2014 to the present, numerous new compounds were isolated in investigations by several research groups on Asian lianas. The approximately 60 structurally divergent monomeric and dimeric naphthylisoquinoline alkaloids exhibit all seven known C,C-coupling types (5,1′, 5,3′, 5,8′, 7,1′, 7,3′, 7,6′, and 7,8′). The twigs and stems of the Chinese liana *Ancistrocladus tectorius* contained five new 5,8′-coupled naphthylisoquinolines, ancistectorine D (**212**), its 6-*O*-demethyl derivative (**213**), ancistrotectoriline A (**214**), ancistrotanzanine B (**215**), and ancistroealaine A (**216**), three new 7,1′-linked alkaloids, 6-*O*-methylancistectorine B_1 (**217**), ancistectorine B_2 (**218**), and 6-*O*-demethyl-8-*O*-methyl-7-epi-ancistrobrevine D (**219**), and twenty 5,1′-linked naphthylisoquinoline alkaloids ancistrobenomines B (**220**) and C (**221**), 6-*O*-methylancistectorine A_3 (**222**), 4′-*O*-demethylancistectorine A_2 (**223**), ancistectorine A_3 (**224**), ancistrocladine (**225**), hamatine (**226**), 5′-*O*-demethylhamatine (**227**), ancistrocline (**228**), ancistrocladinine (**229**), hamatinine (**230**), ancistectorine A_2 (**231**) and its atropo-diastereomer 5-*epi*-ancistectorine A_2 (**232**), ancistrobenomine A (**233**), 6-*O*-methylancistrocladine (**234**), 6-*O*-methylhamatine (**235**), 4′-*O*-demethylancistrocladine (**236**), 5′-*O*-demethylhamatine (**237**), 6-*O*-methylhamatinine (**238**) and 5′-*O*-demethylhamatinine (**239**)[105,106]. Although some compounds were already known from related Asian and African Ancistrocladus species, they were discovered from *A. tectorius* for the first time, such as a monomeric alkaloid, korupensamine D (**240**)[110]. From this species, two unique pentacyclic *N,C*-coupled naphthylisoquinolines, ancistrocyclinones A (**241**) and B (**242**), also were discovered, as well as six known *N,C*-coupled alkaloids, viz., ancistrocladinium A (a/b) (**243**), 4′-*O*-demethylancistrocladinium A (a/b) (**244**), 6,4′-*O,O*-didemethylancistrocladinium A (a/b) (**245**), ancistrotectorine B_1 (**246**), shuangancistrotectorine C (**247**), ancistrotectoquinone B (a/b) (**248**) and compounds **161** and **222**[107] (Figures 10, 11).

In 2017, the first 5,8′-coupled Dioncophyllaceous alkaloid, dioncophylline F (**249**), together with dioncophyllines C_2 (**250**), D_2 (**251**), and three known compounds, 5′-*O*-methyldioncophylline D (**252**), dioncophylline A (**253**) and 4′-*O*-demethyldioncophylline A (**254**) were isolated from the Congolese liana *Ancistrocladus ileboensis*[108]. Moreover, the Ancistrocladaceae-type compound ancistrocladisine B (**255**) (oxygenated at C-6 and *S*-configured at C-3), together with four known alkaloids, **225**, ancistrobrevine C (**256**), ancistrocladisine A (**257**) and ancistrobertsonine D (**258**) also were identified. Four new C,C-coupled compounds, ancistroyafungines A-D (**259**-**262**), and eleven known *C,C*- and *N,C*-linked analogs, including compounds **214, 235, 236** and **243**, ancistroguineine A (**263**), ancistrobertsonine A (**264**), ancistrobrevine B (**265**), 6,5′-*O,O*-didemethylancistroealaine A (**266**), 6-*O*-demethylancistroealaine A (**267**), 7-*epi*-ancistrobrevine D (**268**) and ancistrocladinium B (**269**), were isolated from an unidentified *Ancistrocladus* plant[109] (Figure 12).

In 2016, five new michellamine-type dimeric naphthylisoquinoline alkaloids, named michellamines A_2, A_3, A_4, B_2, and B_3 (**270**-**274**), were isolated from the root bark of the Central African liana *Ancistrocladus congolensis*, along with their two known parent compounds, michellamines A (**275**) and B (**276**)[110]. More recently in 2018, michellamines A_6 (**277**) and A_7 (**278**), the first dimeric 5,8′-coupled naphthylisoquinoline alkaloids with cis-configured stereocenters in both tetrahydroisoquinoline subunits, were isolated from the leaves of an unidentified Congolese *Ancistrocladus* liana together with two new dimeric analogs, michellamines B_4 (**279**) and B_5 (**280**)[111] (Figure 13). In addition, ancistrobonsolines A_1 (**281**) and A_2 (**282**), unique naphthyldihydroisoquinolines with an M-configured biaryl axis and R-configuration at C-3, together with five known compounds, ancistroealaine C (**283**), korupensamines A (**284**) and B (**285**), **270** and michellamine E (**286**) were reported[111] (Figure 14).

In 2017, ealapasamines A-C (**287**-**289**), three unusual new heterodimeric naphthylisoquinoline alkaloids, were obtained from the leaves of the Congolese *Ancistrocladus ealaensis*[112] (Figure 14). These ‘mixed’, constitutionally unsymmetrical dimers are the first cross-coupled products of a 5,8′- and a 7,8′-coupled naphthylisoquinoline linked via C-6′ in both naphthalene segments. Previously, dimers with a central 6,6″-axis were found only from two African Ancistrocladus species[112]. The following year, four new [(michellamine A_5 (**290**), mbandakamines C-E (**291**-**293**)] and one known [mbandakamine A (**294**)] dimeric naphthylisoquinoline alkaloids were isolated in another study on *A. ealaensis*[32,113]. Four new 5,8′-coupled monomeric naphthylisoquinolines, ancistroealaines C-F (**283, 295**-**297**) as well as five known compounds **214, 243, 245, 284** and ancistrolikokine B (**298**) were isolated from the same plant[113] (Figure 14).

2.7. Phenanthridine alkaloid

2.7.1. Benzophenanthridine alkaloid—Benzophenanthridine isoquinoline compounds occur only in higher plants and show a wide spectrum of non-specific biological activities as well as multiple pharmacological properties. Sanguinarine (**299**) (Figure 15), the most extensively studied alkaloid of this group, exhibits many biological effects, such as

antibacterial[114], antifungal[115,116], anti-inflammatory[117], antioxidant[118], antiviral[119], nematicidal[120], antitumor[121], immunomodulatory[122], and insecticidal[123,124] activities.

Chelidonine (**300**) and homochelidonine (**301**), two B/C-*cis*-11-hydroxyhexahydrobenzo[*c*]phenanthridine alkaloids classified as partially hydrogenated-type congeners, were isolated and described as the main natural constituents of *Chelidonium majus*[125]. From the same plant, six pairs of 6-monosubstituted dihydrobenzophenanthridine alkaloids were separated as corresponding six scalemic mixtures from the aerial parts. Two scalemic mixtures were assigned as (1′*R*,6*R*/1′*S*,6*S*)- and (1′*S*,6*R*/ 1′*R*,6*S*)-1-(dihydrochelerythrine-6-yl) ethanol (**302, 303**), two as (1′*R*,6*R*)/(1′*S*,6*S*)- and (1′*S*,6*R*)/(1′*R*,6*S*)-1-(dihydrosanguinarine-6-yl)ethanol (**304, 305**), one as (±)-ethyl 2-(dihydrosanguinarine-6-yl) acetate (**306**), and one as (±)-ethyl dihydrosanguinarine-6-carboxylate (**307**) (Figure 15)[126].

Heitziquinone (**308**), a new benzophenanthridine alkaloid, together with dihydronitidine (**309**), isoarnottianamide (**310**), rhoifoline B (**311**) were found as minor compounds from a hexane extract of *Zanthoxylum heitzii* stem bark[127]. Furthermore, dihydrocheleryhtrine (**312**) was isolated from *Z. tingoassuiba*[94] and decarine (**313)** was identified from *Z. myriacanthum var. pubescens* bark[128].

The genus *Corydalis* contains many benzophenanthridine alkaloids. Corynoline (**314**) from *Corydalis bungeana* possesses anti-inflammatory and antibacterial activities[129]. Ambinine (**315**), the major alkaloid of tuber *C. ambigua var. amurensis* tuber, produces protective effects on H9C2 myocardial cells[130]. Norsanguinarine (**316**), (−)-6-acetonyldihydrisanguinarine (**317**) and cavidilinine (**318**) were isolated from *C. tomentella*[28], and compound **317** also was found in the whole plant of *C. pallida*[90]. 8-Methoxydihydrosanguinarine (**319**) and dihydrosanguinarine (**320**) were obtained from *C. mucronifera*[99] (Figure 15).

2.7.2. Pyrrolophenanthridine alkaloids—The pyrrolephenanthridines have a non-linear tetracyclic structure (6-6-6-5) containing three six-membered rings (“phenanthridine”) and one five-membered ring (“pyrrole”). The *N*-atom and two carbons are common to the phenanthrene and pyrrole, while the points of fusion result in either a pyrrolo[3,2,1-de]phenanthridine (e.g., **321**) or a 5,10b-ethanophenanthridine (e.g., **326**, **328**).

Lycorine-type alkaloids, including lycorine (**321**), acetycaranine (**322**), caranine (**323**), galanthine (**324**), 9-*O*-demethylgalanthine (**325**), as well as α-crinane types, haemanthamine (**326**), haemanthidine (**327**), and β-crinane types, ambelline (**328**), 11-*O*-acetylambelline (**329**), 1-*O*-acetylbulbisine (**330**), undulatine (**331**), crinamidine (**332**), buphanamine (**333**) and srinine (**334**), were isolated from *Zephyranthes robusta*, *Chlidanthus fragrans*, *Nerine bowdenii* and *Narcissus poeticus* cv. Brackenhurst by Cahlíková and collegaues, these compounds show moderate antitumor activities[131-136]. In 2018, a novel lycorine-related iminium salt, 6,7,11b,11c-didehydrolycorinium salt (**335**), as well as the above compounds were isolated from bulbs of both *Crinum firmifolium* and *C. hardyi*[137]. Seco-isopowellaminone (**336**), **326** and incartine (**337**) also were isolated from *Narcissus poeticus* cv. Pink Parasol[138] (Figure 16).

2.8. Manzamine alkaloids

The isoquinoline ring in manzamine alkaloids is both attached to a β-carboline (9*H*-pyrido[3,4-*b*]indole) heterocycle and fused with two polycyclic *N*-containing systems. Since manzamine A hydrochloride (keramamine A, **338**) was initially isolated from an Okinawan sponge in 1986, almost 100 natural manzamines have been isolated from Indian and Pacific sponges[9,139-145]. In 2017, five new manzamine alkaloids, kepulauamine A (**339**), manzamine B *N*-oxide (**340**), 3,4-dihydromanzamine B *N*-oxide (**341**), 11-hydroxymanzamine J (**342**), and 31-hydroxymanzamine A (**343**), together with new hydrogen chloride salts of the known manzamine J *N*-oxide and 3,4-dihydromanzamine J *N*-oxide, as well as five known manzamine alkaloids, 32,33-dihydro-31-hydroxymanzamine A (**344**), **338**, 6-deoxymanzamine X (**345**), manzamine B (**346**), and *neo*-kauluamine (**347**), a manzamine dimer, were isolated from an Indonesian *Acanthostrongylophora sp.* sponge[146] (Figure 17).

2.9. Emetine isoquinoline alkaloids

Emetine (**348**) as well as its analogs are present in three plant families, *Alangiaceae, Icacinaceae*, and *Rubiaceae*. Structurally, **348** contains both pyridoisoquinoline and isoquinoline heterocycles linked through a methylene bridge. Another heterocycle found in compounds from this classification is a 2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole. Previous studies showed that **348** can be used as an emetic and expectorant,[147] and recently, its antiviral and anti-trypanosomes activities were proved[148,149]. In 2017, a new emetine isoquinoline alkaloid, 7′,10-dide-*O*-methylcephaeline (**349**), as well as the known 10-*O*-demethylprotoemetine (**350**) were identified and isolated from *Ophiorrhiza nutans*[95]. In 2018, two new alkaloids of this type, 8-hydroxytubulosine (**351**) and 9-demethyltubulosine (**352**), were isolated from *Alangium longiflorum*[97] (Figure 18).

2.10. Morphine isoquinoline alkaloids

Like aporphine alkaloids, morphine alkaloids have a 1-benzylisoquinoline skeleton with one additional ring closure. However, the added bond is between the 2′-carbon in the pendant phenyl ring and carbon 4a, rather than 1a, at the isoquinoline ring junction. Morphinan or 1,3,4,9,10,10a-hexahydro-2*H*-10,4a-(azanoethano)phenanthrene is the prototype chemical skeleton of this alkaloid classification. However, compounds with several structural variations, including rearranged (e.g., spiro) or additional rings, are found as well.

In 2014, two morphinandienones, (+)-sebiferine (**353**) and (−)-milonine (**354**), were isolated from *Dehaasia longipedicellata*[38]. Also, new bistetrahydroisoquinolines with morphinane-proaporphine and morphinane-benzyltetrahydroisoquinoline types, sinomacutines A–C (**355-357**), and cephalonine-2-*O*-β-D-glucopyranoside (**358**), together with sinomenine (**359**) and sinoacutine (**360**) were isolated from the rhizomes of *Sinomenium acutum*[40].

Subsequently, two new compounds, 8-demethoxycephatonine (**361**) and 7(*R*)-7,8-dihydrosinomenine (**362**), along with eight morphine alkaloids, **359**, 8-demethoxyrunanine (**363**), 14-episinomenine (**364**), sinomenine *N*-oxide (**365**), salutaridine (**366**), acutumine (**367**), acutumidine (**368**) and dauricumine (**369**) were isolated from a rhizome extract of *Sinomenium acutum*[81]. Then in 2018, the morphinadienone pallidine (**370**) was found for

the first time in *Unonopsis floribunda*[36] and *O*-methylflavinantine (**371**) was isolated from *Thalictrum cirrhosum*[43] (Figure 19).

2.11. Phthalideisoquinoline alkaloids

As indicated by the classification's name, tetracyclic phthalideisoquinoline alkaloids contain both bicyclic isoquinoline and bicyclic phthalide (fused benzene and gamma-lactone ring) systems. From the basic structure of a 1-benzylisoquinoline, the ester functionality (O-C=O) forming the lactone is inserted between the benzyl linking carbon and an alpha-carbon on the pendant phenyl ring.

Two phthalideisoquinoline alkaloids, (+)-bicuculline (**372**) and (+)-corlumine (**373**), were isolated from *Fumaria officinalis* and *Viola tianschanica* in 2016 and 2017, respectively[24,150]. Three undescribed isoquinolines, (9*S*,7′*S*) tomentelline A (**374**), (9*S*,7′*R*) tomentelline A (**375**), (9*R*,7′*S*) tomentelline B (**376**) together with adlumidine (**377**) and (+)-capnoidine (**378**) were isolated for the first time from *Corydalis tomentella*[28]. Five pairs of isoquinoline alkaloid enantiomers, mucroniferanines A–E (**379**-**383**), two inseparable epimeric pairs, mucroniferanines F (**384**) and G (**385**), and five known isoquinoline alkaloids, **377**, (±)-hypecorinine (**386**), (−)-7′-*O*-methylegenine (**387**), sibiricine (**388**) and (+)-humosine A (**389**) were obtained from *C. mucronifera*[99]. Capnoidine (**390**) was isolated from a third related species, *C. dubia*[151] (Figure 20).

2.12. Benzopyrroloisoquinoline alkaloids

Seldom found in nature, the benzopyrroloisoquinolines have a linear tetracyclic structure (6-6-6-5) containing two aromatic six-membered rings, one non-aromatic six-membered heterocyclic ring and one five-membered heterocyclic ring. Thus, the alkaloid *N*-atom and one adjacent carbon are shared by benzopyrrole and isoquinoline systems. In 2017, a dimeric benzopyrroloisoquinoline alkaloid, tengerensine (**391**) with a rare unsymmetrical cyclobutane adduct was isolated from *Ficus fistulosa* var. *tengerensis*[152] (Figure 21).

2.13. Phenylethyltetrahydroisoquinoline alkaloids

The simplest compounds are 1-phenylethylisoquinolines ($-CH_2CH_2C_6H_5$) rather than 1-benzylisoquinolines ($-CH_2C_6H_5$). However, more complex rearranged compounds, including those with a tetracyclic 6-7-5-6 system, also belong to this classification. In 2016, the new compound fumarostrejdine (**392**) and its known oxo-derivative (±)-*O*-methylfumarofine (**393**) were isolated from *Fumaria officinalis*[24] (Figure 22).

2.14. Various isoquinoline alkaloids

In 2014, a new alkaloid, coptichine (**394**), from the *Coptidis Rhizoma-Euodiae Fructus* couple showed significant cytotoxicity against NCI-N87 cells[61]. Coptisonine (**395**) from *Coptis chinensis* showed significant stimulation of glucose uptake[89]. Sallisonine D (**396**) was isolated from the rhizomes of *Sinomenium acutum*[40].

A new compound, alternamine A (**397**) was isolated from the aerial parts of *Alternanthera littoralis*[153]. The phenethylisoquinoline alkaloid (±)-7-benzyloxy-1-(3-benzyloxy-4-methoxyphenethyl)-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline oxalate (**398**) was

targeted as a novel ABCB1 inhibitor based on high-throughput screening of a chemical library[154] (Figure 23).

Tomentelline C (**399**), tomentelline D (**400**), and 6,7-methylenedioxy-2-(6-acetyl-2,3-methylenedioxybenzyl)-1(2*H*)-isoquinolinone (**401**) were obtained for the first time from *Corydalis tomentella*. They exhibited hepatoprotective activities[28]. Oleracein E (**402**) was isolated from the medicinal plant *Portulaca oleracea*[31]. Two undescribed isoquinoline alkaloids, pipermullesines B (**403**) and C (**404**), were isolated from the aerial parts of *Piper mullesua*[155].

Zhang *et al*.[156] isolated a structurally unusual cyclopenta[*de*]isoquinoline alkaloid, delavatine A (**405**), from *Incarvillea delavayi*. It exhibited substantial cytotoxicity and anti-inflammatory activities[157]. A novel tropoloisoquinoline alkaloid, neotatarine (**406**), was isolated from a 95% ethanol extract of the rhizome parts of *Acorus calamus* L in 2017[158] (Figure 23).

3. Bioactivities

3.1. Antitumor activities

3.1.1. Cytotoxic activity—In the search to find potential antitumor agents from isoquinoline alkaloids, the most commonly studied bioactivity is the cytotoxicity of new isolated and known compounds from plants. In this review, we list in Table 2 the inhibitory rates and the IC_{50} values of compounds against various cancer cell lines corresponding to different human tumors, such as HL-60 (acute promyelocytic leukemia), Jurkat (acute T cell leukemia), MOLT-4 (acute lymphoblastic leukemia), A549 (lung carcinoma), H1299 (non-small cell lung cancer), COLO-201 (colorectal adenocarcinoma), AGS (gastric adenocarcinoma), PANC-1 (pancreas epithelioid carcinoma), A2780 (ovarian carcinoma), HeLa (cervix adenocarcinoma), MCF-7 (breast adenocarcinoma) and SAOS-2 (osteosarcoma). From this table, we found that most compounds exhibited moderate cytotoxicity with IC_{50} values ranging from 10 to 50 μM[22, 25, 26, 33, 38, 40, 45, 46, 61, 85, 97, 105-109, 111, 113, 125, 136, 146, 152,156,159].

Three Amaryllidaceae alkaloids, lycorine (**321**), haemanthamine (**326**) and haemanthidine (**327**), showed the best cytotoxicity against 17 human cell types with individual IC_{50} values in the range of 0.30-9.80 μM compared with other compounds listed in Table 2. Higher antiproliferative effects also were reported. Unfortunately, the cytotoxic activities of positive agents were not investigated in this reference[136]. The alkaloids caused cells to accumulate preferentially at G1 and G2 stages of the cell cycle with increased p16 expression and Chk1 Ser345 phosphorylation. Concerning a pro-apoptotic effect in the Jurkat leukemia cell line, compound **327** was more active than **326**[130]. These results also provided a new clue for developing these alkaloids as potential antitumor agents.

8-Hydroxytubulosine (**351**) from *Alangium longiflorum* also exhibited remarkable antiproliferative activity. It presented better activities against A549, MDA-MB-231, MCF-7 and KB cell lines than the positive drug doxorubicin and the known alkaloid 9-

demethyltubulosine (**352**). The IC_{50} values of **351** were 0.21, 0.06, 0.12 and 0.09 μM, respectively[97].

The aporphine alkaloid (−)-norboldine (**86**) exhibited potent cytotoxicity towards pancreatic cancer cell line BxPC-3 with an IC_{50} value of 27.06 μM, but no toxicity towards the normal pancreatic cell line[60]. Two oxoaporphines, **145** and **146**, showed cytotoxicity against glioma stem cells (GSC-3$^{\#}$) with IC_{50} values of 32.52 and 32.81 μM, respectively, while the IC_{50} of the antitumor drug taxol was 15.92 μM[46]. However, the antitumor activity *in vivo* and the mechanism underlying the cytotoxicity of the compounds are still unclear and should be studied further.

3.1.2. Mechanism of action—During the past five years, numerous studies have investigated and reported antitumor mechanism of known and new isolated isoquinoline alkaloids. In this section, we will briefly introduce the antitumor mechanisms of some prominent molecules.

Berberine (**161**) shows antitumor effects against various tumor cells. Noteworthy, it presents the strongest cytotoxicity against AZ521 cell with the IC_{50} value of 2.60 μM, while the IC_{50} of the antitumor drug cisplatin was 9.50 μM. Berberine inhibited cancer cell proliferation via several mechanisms of action, such as the positive regulation of reactive oxygen species and the apoptotic pathway as well as suppressed cancer metastasis by stopping transferase activity[160-163]. The potential targets also include mitochondrial function, DNA topoisomerase and arylamin *N*-acetyltransferase activity, NF-κB signal pathway, the EGF and the VEGF receptors, etc. In human hepatoma cells, the alkaloid's antiproliferative effect on might be mediated via the CAR metabolic and the arachidonic acid pathways, $cPLA_2$, COX-2 gene expression and mitochondria-mediated apoptosis also were suppressed *in vitro* and *in vivo*[164-166], and the IC_{50} values against human hepatoma Bel-7404, H22 and HepG2 HCC cells were 9.21, 43.20 and 82.80 μM, respectively. However, the cytotoxicity of berberine against the normal hepatic embryonic cells was weak, the IC_{50} value was 122.4 μM for the HL-7702 at 72 h. The further report showed that it blocked the caspase 3-$iPLA_2$-AA-COX-2-PGE_2 pathway of ovarian cancer cells and reversed the repopulation, which was triggered by the chemotherapy drug VP16[167]. In breast tumors, berberine significantly down-regulated the expression of NF-κB and proliferating cell nuclear antigen (PCNA) *In vivo*[168]. However, the targets of berberine against the different breast cancer are different, it activated caspase-9/cytochrome c-mediated apoptosis to inhibit the growth of two triple negative breast cancer cell (TNBC) lines (IC_{50} 43.28 μM for BT549 and 47.51 μM for MDA-MB-231 cells) *in vitro* [169] and inhibited the proliferation and migration of breast cancer ZR-75-30 cells (IC_{50} 5.30 μM) by targeting Ephrin-B2[170].

Reports indicated that berberine mediates epigenetic reprogramming via HDAC inhibition and regulates Bcl-2/Bax family proteins in the human lung cancer A549 cell line[171]. Furthermore, it inhibited the growth of intestinal polyps in animals and patients with the familial adenomatous polyposis and cell growth in colon cancer by down-regulating β-catenin signaling via binding RXRα[172]. In human glioblastoma cells, berberine induced senescence by down-regulating the EGFR-MEK-ERK signaling pathway[173], and modulated the expression of epigenetic regulators in acute myelocytic leukemia cell lines HL-60/ADR

and KG1-α[174]. The PI3K-Akt and mitogen-activated protein kinase (MAPK) signaling pathways in the treatment of thyroid carcinoma also were affected[175,176]. As an berberine isoquinoline alkaloid, coptisine (**165**) also affected PI3K/Akt and mitochondrial-associated apoptotic pathways[177], it exhibited remarkably cytotoxic activities against HCT-116 cells by activating the caspase protease family, inducing G1-phase cell cycle arrest and increasing apoptosis[178].

The protoberberine alkaloid palmatine (**166**) induced cell apoptosis in MCF-7 breast cancer cells, after the treatment (1 μM, 10.8 J/cm^2) the early apoptotic and late apoptotic rates increased significantly up to 21.16% and 9.86% in photodynamic therapy[179]. Meanwhile, protoberberine stylopine (**195**) both functioned as an AKR1C3 inhibitor and significantly inhibited the AKR1C3-mediated reduction of the anthracycline drug daunorubicin within cells, the IC_{50} was 0.9 μM in DHO assay[180]. Liensinine (**62**) induced apoptosis and mitochondrial dysfunction, and significantly inhibited the proliferation and colony-forming ability of colorectal cancer cells accompanied by activation of the JNK signaling pathway in a dose-dependent manner[181]. However, the structurally related neferine (**61**) sensitized A549 cells to low doses of doxorubicin and inhibited human lung cancer cell growth through MAPK activation and cell cycle arrest[182,183].

Through the mitochondria apoptosis pathway, 3,8-diolisoquinoline (**1**) and 1-methoxy-4,5-diolisoquinoline (**2**) induced apoptosis in U87 cells with the IC_{50} values of 3.46 and 2.14 μM, the Bcl-2/Bax protein ratio also was down-regulated[22]. 6,7-Dimethoxy-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid (**7**) had a significant anti-proliferative effect on human hepatoma (Huh-7) cells *in vitro* (EC_{50} 13.97 μM) by inhibiting the action of caspase-8[184], and blocked IL-6/JAK2/STAT3 oncogenic signaling in dimethylhydrazine-induced colorectal carcinoma[185]. Good *in vivo* anti-neoplastic properties were also found[184].

Certain naphthylisoquinoline alkaloids are noteworthy due to their anti-pancreatic cancer activity. In one study[109], ancistroyafungines A–D (**259–262**), 6-*O*-methylhamatine (**235**), 4′-*O*-demethylancistrocladine (**236**), ancistroguineine A (**263**), ancistrobertsonine A (**264**), ancistrobrevine B (**265**), ancistrotectoriline A (**214**), 6,5′-*O,O*-didemethylancistroealaine A (**266**), 6-*O*-demethylancistroealaine A (**267**), 7-*epi*-ancistrobrevine D (**268**), and ancistrocladiniums A (**243**) and B (**269**) showed moderate to strong anti-austerity activities against PANC-1 pancreatic cancer cells in a concentration-dependent manner. Their preferential cytotoxicity $(PC)_{50}$ values ranged from 7.60 to 67.80 μM. Among of these compounds, compound **259** (PC_{50}, 22.7 μM) was found to be almost three times less active than its 5′-*O*-demethyl analog compounds **260** and **262** (PC_{50}, 7.60 μM and 9.70 μM, respectively), which has two methoxy functions at C-5′ and C-4′. Structure-activity relationship (SAR) analysis indicated that *O*-methylation in the naphthalene portion and the substitution pattern of the isoquinoline portion play a crucial role for the cytotoxic activities of the alkaloids, especially an OMe/OH pattern seems favorable for the activity. In a second study,[111] ancistrobonsolines A_1 (**281**) and A_2 (**282**) also displayed significant PC against PANC-1 cells under nutrient-deprived conditions. Above reports suggest that the naphthylisoquinoline alkaloids are promising lead structures for the advancement of antitumor agents.

The benzophenanthridine alkaloids chelidonine (**300**) and homochelidonine (**301**) potently induced cell death in several blood cancer cell lines, such as MOLT-4, Jurkat, HL-60, Raji, PBMCs, MRC-5 and WI-38, their IC_{50} values ranged from 1.80 to >10 μM. For MOLT-4 and Jurkat cells, treatment with chelidonine induced cell cycle arrest at the G2/M cell cycle (IC_{50} 4.60 and 2.20 μM, respectively); treated with homochelidonine underwent biphasic dose-dependent G1 and G2/M cell cycle arrest in MOLT-4 cells (IC_{50} 4.80 μM), and an increase in G2/M cell population in Jurkat cells (IC_{50} 5.60 μM). Both alkaloids inhibited tubulin polymerization in A549 cells[125].

In addition, lycorine (**321**) presented the good therapeutic effect in a patient-derived glioblastoma xenograft by directly interacting with and inhibiting the activation of EGFR cancer cells[186]. The potent cytotoxicity against other various cancer cells, including HL-60, Jurkat, MOLT-4, A549, also were found with IC_{50} values from 0.80 to 1.40 μM. Noroxyhydrastinine (**22**) exhibited potent melanogenesis-inhibitory activities by inhibiting the expression of protein levels of tyrosinase, TRP-1, and TRP-2 partly in a-MSH-stimulated B16 melanoma cells, the melanin content was 76.10% at 10.00 μM[33,159].

Multidrug-resistant (MDR) cancers present a critical clinical problem. Bringmann *et al.* have investigated the effects of naphthylisoquinolines. Mbandakamines C, D and F (**291, 2923, 297**) showed strong cytotoxic effects against human leukemia (CCRF-CEM) and MDR tumor cells (CEM/ADR5000) with IC_{50} values from 1.50 to 19.94 μM[113]. This result indicated that the axial chirality is necessary to the bioactivity. Ancistectorine D (**212**) and ancistrobenomine B (**220**) also demonstrated comparable cytotoxic effects against both cell lines (IC_{50} 4.5 and 3.5 μM for **212**; 25.83 and 21.38 μM for **220**; 0.017 and 30.07 μM for positive control doxorubicin)[105,106]. The overexpression of ATP-binding cassette (ABC) transporters is a common mechanism leading to MDR cancer cells. Tetrandrine (**57**) and tangchinoline (**58**) from *Stephania tetrandra* reversed multidrug resistance by increasing the intracellular concentration of anticancer drugs and inhibiting P-glycoprotein activity in the MDR human cancer cells Caco-2 and CEM/ADR5000, the IC_{50} values were 19.38 and 24.98 μM respectively for compound **57**[49]. Hernandezine (**51**) selectively inhibited the transport function of the ABC drug transporter ABCB1 and enhanced drug-induced apoptosis in cancer cells at nanomolar concentrations (IC_{50} 3.85-27.25 nM). It could be further developed as a novel reversal agent for combination therapy in patients with MDR cancer due to its nontoxicity[45].

Scoulerine (**204**) exhibited promising suppression of cancer cell growth and reduced the mitochondrial dehydrogenases activity of the evaluated leukemic cells with IC_{50} values ranging from 2.70 to 6.50 μM. Further study showed that it also interfered with microtubule elements of the cytoskeleton, checkpoint kinase signaling and p53 proteins[96].

3.2. Effect on diabetes and its complications

Diabetes mellitus (DM) is mainly characterized by abnormal hyperglycemia, polydipsia, polyuria, polyphagia, and emaciation[187,188], and persistent hyperglycemia can lead to several chronic diabetic complications, including neuropathy, nephropathy, cardiopathy, and retinopathy[189]. Currently, the global prevalence of DM is 8.5% among adults and is rising

most rapidly in middle- and low-income countries[190]. Natural products have been increasingly applied to treat DM[191,192]. Over the past five years, the beneficial effects of berberines and protoberberine alkaloids on DM, atherosclerosis and hyperlipidemia have been proved in different animal models[193,194].

Berberine (**161**) affects multiple pathways, including p38 MAPK-GLUT4, JNK, and PI3K-Akt, related to the metabolism of glucose and lipids[89,195]. For anti-diabetic activity, berberine regulated the glyco- and lipo-metabolism and stimulated of adenosine 5′-monophosphate-activated protein kinase (AMPK)[196] in Zucker diabetic fatty (ZDF) rats, and also inhibited miR-106b/SIRT1 pathway by reversing miR-106b over-expression and up-regulating sirtuin 1 (SIRT1) both in islets of diabetic mice and pancreatic NIT-1 cells induced by high glucose[88,197]. By activating the AMPK pathway, the pioglitazone-induced bone loss in diabetic rats also were protected[198]. The toxic towards to mice or rats *in vivo* test is weak. Meanwhile, it may improve insulin resistance by increasing the expression of adiponectin receptors and the ratio of high-molecular weight to total adiponectin in rats fed a high fat diet (HFD)[199], and improved glucose uptake and insulin-stimulated glucose consumption in palmitate-induced insulin-resistant H9c2 cardiomyocytes[200-202].

DM is closely related to the development of cardiovascular diseases[203]. Vascular dysfunction is a distinctive phenotype in DM, and diabetic vascular complication is associated with impaired endothelial function, augmented vasoconstriction, and increased oxidative stress[204]. Berberine can exert a cardio-protective effect by attenuating myocardial apoptosis via Notch1/Hes1-PTEN/Akt signaling as well as inhibiting excessive autophagy in cardiomyocytes through the regulation of AMPK and mTOR signaling[205,206]. In addition, berberine relieved cerebral arterial contractility in a STZ-induced diabetic rat model by regulating intracellular Ca^{2+} management in smooth muscle cells and, thus, has an extra-protective effect on diabetic vascular dysfunction[207].

Diabetic nephropathy (DN) is a major cause of morbidity and mortality in patients with diabetes and is highly prevalent in end-stage renal disease[208]. Many studies have reported that berberine exhibits renoprotective effects in DN rats via regulating the various pathways, such as the PGE_2-EP1-Gαq-Ca^{2+} signaling pathway[209], TLR4/NF-κB[210] and S1P2/MAPK signaling pathway[211]. Tang *et al.*[212] suggested that berberine (50-100 mg/kg) improved histopathological changes in the diabetic kidney, while it significantly reversed the diabetic-induced increases in the levels of intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) as well as the decreases in the levels of β-arrestins 1 and 2. In NIT-1 pancreatic β cells, it inhibited PA-induced lipid accumulation by decreasing lipogenesis and increasing lipid oxidation[213]. In an experimental diabetic kidney model and high glucose-cultured glomerular mesangial cells (GMCs), berberine suppressed the expression of FN, ICAM-1, and TGF-β1 possibly by negatively regulating NF-κB and RhoA/ROCK[214,215]. Furthermore, it inhibited the Sphk1/S1P signaling pathway and MAPK activation, lowered AP-1 activity, and ultimately deceased fibronectin overproduction[216-218]. In 2016, Zhou *et al.*[219] reported that berberine can positively affect DN by improving micro pathology and increasing neuritin expression via the MAPK pathway. In diabetic rats, the alkaloid exhibited renoprotective effects by changing the levels and regulation of the AGEs-RAGE-PKC-b-TGF-b1 signaling pathway[220].

Obesity has become a worldwide public health problem. It is an established risk factor for metabolic diseases including type 2 diabetes[221,222] and closely related to the metabolism of triacylglycerol (TG) in adipocytes. Adipose triglyceride lipase (ATGL) and hormone-sensitive lipase are rate-limiting enzymes that control the hydrolysis of TG. Berberine affects the metabolism of TG[223] by increasing the expression of ATGL and therefore stimulating basal lipolysis in mature adipocytes through the coupled mechanisms linked to the AMPK pathway[224]. In addition, coptisine (**165**), a related alkaloid, inhibited obesity-related inflammation in Syrian golden hamsters through the LPS/TLR4-mediated signaling pathway[225]. The aporphine isoquinoline alkaloid stephalagine (**94**) could be used as a potential anti-obesity agent due to its significant pancreatic lipase inhibitory activity (IC_{50} 8.35 μg/ml).[70]

In 2016, berberine (**161**), coptisine (**165**), palmatine (**166**), epiberberine (**163**), and jatrorrhizine (**162**) were evaluated for antihyperglycemic, antidyslipidemic and antidiabetic hyperlipidemic effects in HepG2 cells and diabetic KK-Ay mice[226]. All five alkaloids effectively modulated hyperglycemia and hyperlipidemia. Berberine and coptisine promoted glucose consumption *in vitro* as well as suppressed fasting blood glucose level and improved glucose tolerance *in vivo*. In the mice, the levels of serum total cholesterol and triglycerides were decreased by palmatine and jatrorrhizine. Moreover, diminished hepatomegaly was found in jatrorrhizine-treated mice[226]. SAR analysis showed that the methylene-dioxy groups at C2, C3, C9, and C10 positions are the key functional groups for the antihyperglycemic and antihyperlipidemic effects. Briefly, the oxidized form of methylene-dioxy group at the C-2 and C-3 positions and/or at C-9 and C-10 positions of compound **163** would inhibit the activities of rat lens aldose reductase and human recombinant aldose reductase activities, and the methylene-dioxy group is very important to the binding activity of coptisine to β-cell membranes. Berberine and coptisine had better antihyperglycemic effects than compounds **162, 163, 166** that may be associated with the methylene-dioxy group at the C-2 and C-3 positions, because the C-2 and C-3 positions of the latter three compounds were substituted by methoxy group or phenolic hydroxyl group.

In a subsequent study, a combination of the five alkaloids showed synergistic cholesterol-lowering in HepG2 cells and hypercholesterolemic hamsters, which was greater than that of the single alkaloids[227]. Activation of AMPK activation and alteration of neutral lipid metabolism may explain the hypoglycemic effect of berberine in differentiated cardiomyocytes[228]. Berberine and its metabolites exert lipid-lowering effects in human hepatoma cells metabolites likely by low density lipoprotein receptor up-regulation[229]. A meta-analysis of randomized clinical trials indicated that berberine can improve lipid profiles in dyslipidemia with acceptable safety[230].

He *et al.*[231] suggested that the related alkaloid coptisine might be used as an anti-hypercholesterolemia agent as it inhibited cholesterol synthesis by suppressing 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) expression and increasing the use and excretion of cholesterol through up-regulation of low-density lipoprotein receptor (LDLR) and CYP7A1 expression.

Atherosclerotic coronary artery disease is a leading cause of death and disability in diabetic patients, and diabetic patients with atherosclerosis usually show moderate hyperhomocysteinemia (HHCY). Berberine increased atherosclerotic plaque stability in Apoe$^{-/-}$ mice with HHCY by activating the peroxisome proliferator-activated receptor-γ (PPARG) and suppressing oxidative stress in endothelial cells[232]. It also protected rat retinal Müller cells from high-glucose-induced apoptosis by enhancing autophagy and activating the AMPK/mTOR signaling pathway[233]. Acting on the TGFβ1-PI3K/Akt pathway, berberine reduced injury to podocytes caused by exosomes derived from high glucose-induced mesangial cells[234]. Berberine showed good effects on bone parameters in the treatment of HFD-fed/streptozocin-induced diabetic rats and, thus, could have therapeutic potential in diabetic osteoporosis[235].

3.3. Antibacterial and antifungal activities

Isoquinoline alkaloids exhibit good antibacterial and antifungal activities. A high content of berberine (**161**) is found in the well-known Chinese drug (*Huangliansu*) taken to treat intestinal infections caused by *Escherichia coli*, *Bacillus dysteriae*, and other microorganisms. The authors have recently described the significant antifungal activity of sanguinarine (**299**) and its possible use as a bio-fungicide for crop protection[236]. From 2014 to 2018, many publications have reported the antibacterial and antifungal activities of isoquinoline alkaloids; findings are briefly discussed below or listed in Table 3.[23,71,77,237,94,146].

Berberine (**161**) exhibited antibacterial activity against *Candida albicans* with an MIC value of 75.53 μM. It affected the synthesis of membrane ergosterol and induced increased membrane permeability causing loss of intracellular material to the outer space (DNA/protein leakage) as well as membrane depolarization and lipid peroxidation of membrane constituents[238]. Berberine also effectively protected mice infected with *Salmonella typhimurium*[239]. Further studies reported that this alkaloid could treat *H. pylori*-induced chronic gastritis by attenuating the BAFF-triggered Th17 response[87]. Berberine as well as palmatine (**166**), coptisine (**165**), epiberberine (**163**), and jatrorrhizine (**162**) acted as concentration-dependent inactivators of urease with IC_{50} values from 3.0 to 5087 μM for HPU (*Helicobacter pylori* urease) and 2.3 to >10,000 μM for JBU (jack bean urease). Epiberberine was the most potent inhibitor against both ureases with IC_{50} values of 3.0 μM for HPU and 2.3 μM for JBU and was more effective than the standard urease inhibitor acetohydroxamic acid (83 μM for HPU and 22 μM for JBU). The further studies showed that two methoxyl groups in the A ring as the polar systems and the dimethylene group in the D ring as the hydrophobic ring system of epiberberine are the functional structural groups for the potent urease inhibition. This alkaloid could be used in the treatment of diseases associated with ureolytic bacteria and could be further developed into a promising therapeutic approach for the treatment of urease-related diseases[240]. Meanwhile, berberine (**161**) and palmatine (**166**) suppressed *Clostridium perfringens* growth with MIC values of 44.7 and 52.2 μM, respectively[77].

In 2017, some manzamine alkaloids from *Acanthostrongylophora sp.* sponge were found to show antibacterial activity[146]. *neo*-Kauluamine (**347**) showed the best activity (MIC ~0.001

μM) against *Bacillus subtilis*, *Kocuria rhizophila* and *Salmonella enterica*, and 11-hydroxymanzamine J (**342**) had the best activity (MIC 0.053 μM) of all isolated compounds against *Staphylococcus aureus* and *Proteus hauseri*. MIC values of the positive drug ampicillin were around 0.001 μM. 3,4-Dihydromanzamine B *N*-oxide (**341**) and 31-hydroxymanzamine A (**343**) demonstrated marked activities against some tested microorganisms. *neo*-Kauluamine and the hydrogen chloride salt of manzamine J *N*-oxide displayed mild inhibition against isocitrate lyase from *Candida albicans*, and the latter manzamine alkaloid was the only compound with activity against bacterial sortase A[146].

The simple isoquinoline alkaloid carnegine (**3**) showed antibacterial activity with MIC ranging from 564-2259 μM against various strains. The time-kill curves indicated potent and rapid bactericidal activity[23]. Michellamine B (**276**), a dimeric naphthylisoquinoline alkaloid, inhibited *E. coli* MraY (IC_{50} 456 μM) and *B. subtilis* MraY (IC_{50} 386 μM) and showed antimicrobial activity against *B. subtilis*[241].

Photodynamic therapy was discovered at the beginning of the last century and mostly used as a cancer therapy; however, it has emerged as a promising treatment alternative against infectious diseases. The oxoaporphine alkaloid isomoschatoline (**129**) had an absorption profile with bands at 600-700 nm, was positive for singlet oxygen production and exhibited photodynamic antimicrobial activity against both gram-positive and gram-negative bacteria and some *Candida* ssp. yeast strains at sub-inhibitory concentrations[237].

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a bacterium that is resistant to many antibiotics and can cause various problems ranging from skin infections to pneumonia to bloodstream infections[242]. Much effort has been put into the fight against this bacterium. Berberine (**161**) was active *in vitro* against clinical isolates of MRSA and lowered the MICs of ampicillin and oxacillin[243]. It also was synergistic with ceftazidime and cefepime against MRSA[41]. Bacteria do not develop resistance to berberine since its MIC within the same bacterial cultures (*E. coli, S. aureus, B. subtilis, Proteus vulgaris, S. typhimurium* and *Pseudomonas aeruginosa*) did not increase over 200 generations[244].

Dihydrocheleryhtrine (**312**) and *N*-methylcanadine (**200**) from *Zanthoxylum tingoassuiba* presented anti-MRSA activity against the four tested clinical isolates *S. aureus* strains 1-4 (MIC ranging from 76.9 to 307.8 μM) and were more active than chloramphenicol against strain 4 and ATCC25923[94]. *N*-Formyl-asimilobine-2-*O*-β-D-glucoside (**95**) was equipotent against *S. aureus* and MRSA strains; the inhibition zone against both strains was 8.0 mm in diameter. The inhibitory diameters with the positive control kanamycin sulfate were 40 and 34 mm, respectively[71]. Bavarsadi *et al.*[245] reported that the administration of incremental levels of sanguinarine (**299**) decreased microbial counts in the ileum and improved other intestinal health indices in laying hens.

3.4. Antiviral activity

Antiviral activity is one of the important bioactivities for berberine (**161**). *In vitro*, it regulated signaling pathways related to inflammation, such as NF-κB[246] and AMPK/mTOR[247] signaling pathways. In addition, berberine attenuated autophagy in adipocytes by targeting BECN1[248] and inhibited the replication of respiratory syncytial virus (RSV),

herpes simplex virus (HSV), human papillomavirus (HPV), and human cytomegalovirus (HCMV)[249-251]. Berberine suppressed viral infection-induced up-regulation in the TLR7 signaling pathway, such as TLR7, MyD88, and NF-κB (p65), at both the Mrna and protein levels, as well as significantly inhibited the viral-induced increases in Th1/Th2 and Th17/Treg ratios and inflammatory cytokine production[252]. In addition, berberine inhibited EV71 replication by down-regulating autophagy and the MEK/ERK signaling pathway, while the 50% toxicity concentration (TC_{50}) was 73.10 μmol/L in Vero cells and the TC_{50} of the positive agent pirodavir was 27.49 μmol/L[253].

Corydine (**90**) and norisoboldine (**91**), aporphine alkaloids from *Croton echinocarpus* leaves, displayed significant in vitro anti-HIV potential. The latter compound more potently inhibited HIV-1 reverse transcriptase enzyme activity[69]. Several michellamine-type dimeric naphthylisoquinoline alkaloids inhibited replication of HIV reference strain IIIB/LAI in A3.01 T lymphoblast cell cultures: michellamine A_2 (**270**) (IC_{50}, 29.6 μM), A_3 (**271**) (IC_{50}, 15.2 μM), A_4 (**272**) (IC_{50}, 35.9 μM), and B (**276**) (IC_{50}, 20.4 μM). However, michellamines A (**275**) and B_3 (**274**) were not active[110].

Emetine (**348**) inhibits protein synthesis in mammalian, yeast and plant cells by inhibiting the aminoacyl-sRNA transfer reaction at the 40S ribosomal subunit[254-256]. It also inhibits DNA synthesis in mammalian cells[257]. Emetine inhibited replication of DNA viruses [buffalopoxvirus (BPXV) and bovine herpesvirus 1 (BHV-1)] as well as RNA viruses [peste des petits ruminants virus (PPRV) and Newcastle disease virus (NDV)]. After treatment, the syntheses of viral RNA (PPRV and NDV) and DNA (BPXV and BHV-1) as well as viral entry (NDV and BHV-1) were reduced and inhibited. Emetine significantly inhibited replication of NDV. Moreover, this alkaloid significantly inhibited BPXV-induced pock lesions on chorioallantoic membrane (CAM) along with associated mortality of embryonated chicken eggs. It significantly delayed NDV-induced mortality in chicken embryos associated with reduced viral titers. Hence, emetine could have significant therapeutic value against certain viruses by inhibiting viral RNA and DNA replication without producing an antiviral drug-resistant phenotype[148].

Japanese encephalitis virus (JEV) is a major cause of severe encephalopathy. Huang *et al.*[258] suggested that the protoberberine isoquinoline alkaloid (−)-tetrahydropalmatine (**192**) could be a strong drug candidate for the treatment of JEV infection, because it exhibited a neuroprotective effect in a JEV strain GP-78 infected mouse model.

3.5. Anti-inflammatory and immunosuppressive activities

The major isoquinoline alkaloid berberine (**161**) exerts significant anti-inflammatory activity[259,260] and could be used to treat inflammation and other related diseases via different mechanisms of action, for example, ischemic stroke through downregulation of pro-inflammatory cytokines and upregulation of anti-inflammatory cytokines[261] or acute pancreatitis via JNK deactivation[262]. Meanwhile, berberine suppressed Th17 responses and improved chronic relapsing colitis induced with dextran sulfate sodium (DSS) in C57BL/6 mice[263]. The alkaloid also improved the survival of septic and LPS-intoxicated mice and decreased inflammation and tissue injuries in the lung, spleen and gut as well as improved disrupted energy utilization, oxidative status, amino acid metabolism and nucleic acid

metabolism[264,265]. In macrophages, berberine has no cellular toxicity on RAW264.7 cells at the concentration up to 5 μM, however, it inhibited M1 polarization via the AKT1/SOCS1/NF-κB signaling pathway[266] and exerted anti-inflammatory effects by inhibiting NF-κB signaling via Sirt1-dependent mechanisms at the same concentration[267].

Furthermore, by inhibiting TH17 cell response, berberine could exert an anti-arthritic effect and improve various autoimmune diseases, such as rheumatoid arthritis[268]. It suppressed NLRP3 (nucleotide-binding oligomerization domain-like receptor [NLR] pyrin domain-containing-3) inflammasome activation in monosodium urate (MSU) crystal-stimulated RAW 264.7 macrophages and pro-inflammatory cytokines through the upregulation of Nrf2 (nuclear factor erythroid-2-related factor 2) transcription factor and alleviated MSU crystal-induced inflammation in rats[269]. One mechanism of action against rheumatoid arthritis was inhibition of IL-21/IL-21R-mediated inflammatory proliferation via attenuation of the PI3K/Akt signaling pathway and amelioration of IL-21 mediated osteoclastogenesis[270].

Norisoboldine (**91**) exerts anti-arthritic activity via anti-inflammatory and immune-regulatory effects. Mechanism of action studies showed that this alkaloid prevented both the infiltration of inflammatory cells and destruction of bone and cartilage in joints in adjuvant-induced arthritic rats, as a substrate of P-glycoprotein (P-gp)[271-273]. The anti-arthritic mechanism involved inhibition of inflammatory synovial hyperplasia by promoting the release of cytochrome C and regulating the expression of Bax and Bcl-2 proteins via a mitochondrial-dependent pathway[274], as well as prevention of synovial angiogenesis by moderating the Notch1 pathway-related endothelial tip cell phenotype[275,276]. Tong *et al.*[277] suggested that norisoboldine induced the generation of intestinal Treg cells by the activation of AhR (aryl hydrocarbon receptor) as well as promoted Treg differentiation and then reduced the development of colitis by regulating AhR/glycolysis axis and subsequent NAD^+/SIRT1/SUV39H1/H3K9me3 signaling pathway[278]. Furthermore, norisoboldine reduced IL-1β production in LPS-stimulated RAW264.7 cells and decreased the serum level of IL-1β in collagen-induced arthritis[273,279]. Finally, the compound inhibited activation of the NLRP3 inflammasome by regulating the AhR/Nrf2/ROS signaling pathway and thereby improved the TNBS (2,4,6-trinitrobenzene sulfonic acid)-induced colitis in mice[271].

Nuclear transcription factor-κB (NF-κB) plays an important role in inflammation, sepsis and immunity[280]. Hence, great attention has been focused on compounds that produce inhibitory effects on the NF-κB pathway. Demethyleneberberine (**164**) reduced inflammatory responses by inhibiting the NF-κB pathway and regulating the balance of Th cells[281]. Chelidonine (**300**) also significant inhibited NF-κB activity and related pathways at the concentrations of 5-20 μM, such as the TLR4/NF-κB signaling pathway, in HCT116 cells and RAW264.7 macrophages[282], and it did not display cytotoxic effect with concentrations up to 20 μM. These results indicated that NF-κB pathway is very important to the anti-inflammatory activity of isoquinoline alkaloids. In addition, this alkaloid inhibited mitogen-activated protein kinase pathway activation by blocking c-Jun *N*-terminal kinase and p38 phosphorylation[283]. Salutaridine (**366**), dauricumine (**369**), dauriporphine (**128**) and cheilanthifoline (**197**) significantly inhibited receptor activator of NF-κB ligand-induced differentiation of mouse bone marrow-derived macrophages into multinucleated osteoclasts[73]. Zhang *et al.*[156] reported that delavatine A (**406**) significantly decreased LPS-

induced activation of NF-κB by suppressing the p65 subunits and the phosphorylation of IκBα[157]. Palmatine (**166**) promoted the proliferation of goat endometrial epithelial cells at the concentrations of 10–100 μg/mL, and reduced LPS-induced inflammatory responses through inhibition of the TRIF-dependent NF-κB pathway[284].

Boldine (**85**) and reticuline (**23**) from *Litsea cubeba* exerted anti-inflammatory activity and potential synergistic effects *in vivo* partly by inhibiting the expression of pro-inflammatory cytokines, such as TNF-α and IL-6, perhaps resulting from interaction with JAK2/STAT3 and NF-κB pathways[67]. Tetrandrine (**57**) inhibited IκBα and NF-κB p65 phosphorylation in LPS-induced RAW 264.7 and chondrogenic ATDC5 cells[285]. Coptisine (**165**) inhibited IL-1β-induced inflammatory responses by suppressing the NF-κB and MAPK pathways signaling pathway, as well as suppressing the expression of iNOS, COX-2, matrix metalloproteinase-3 (MMP-3) and MMP-13, and NF-κB activation in IL-1β-induced human OA chondrocytes[286,287].

Other anti-inflammatory mechanisms of action of isoquinoline alkaloids were also investigated. Palmatine (**166**), which has been used to treat abdominal pain, enteritis, gastritis, chronic endometritis, and pelvic inflammation, exerted protective effects on acute and chronic inflammation in experimental animal models[288-290]. Zhou *et al.*[291] reported that this compound exerted chondroprotective effects in IL-1β-induced rabbit chondrocytes and an experimental OA model by inhibiting the Wnt/β-catenin and Hedgehog signaling pathways. As a potent IDO-1 inhibitor, palmatine improved dextran sulfate sodium-induced colitis by mitigating colonic injury, preventing gut microbiota dysbiosis, and regulating tryptophan catabolism[292].

Compared with mice administered TNBS, mice treated with capnoidine (**378**) showed significantly improved clinical symptoms as well as reduced colon pathology and histological inflammation in the colon. Moreover, inflammatory cytokines profiles within the colon were altered and levels of p-IκB-α (Ser32) and p-NF-κB p65 (Ser536) were reduced[151].

Alkaloids from *Portulaca oleracea* inhibited NO production in lipopolysaccharide-induced murine macrophage RAW 264.7 cells (EC_{50} 18.0–498 μM). Among them, oleracein E (**403**) and (*S*)-(−)-salsolinol **(15**) were more potent (EC_{50} 35.4 and 58.7 μM, respectively) than the positive control 3,4-dihydroxybenzohydroxamic acid. Additionally, some alkaloids showed β2-adrenergic receptor (β2-AR) agonist activity in the CHO-K1/GA15 cell line, which stably expresses β2-AR as detected by a calcium assay. The EC_{50} value of (*R*)-(+)-1-benzyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline was 87.9 nM[31].

Corynoline (**314**) from *Corydalis bungeana* inhibited inflammatory mediators in LPS-stimulated RAW264.7 cells and attenuated LPS-induced acute lung injury in mice by activating Nrf2[129,293,294]. The unique alkaloid dactyllactone A (**126**) inhibited the expression of IL-1β and PGE2 in a dose-dependent manner in LPS-induced RAW264.7 cells[78]. Decarine (**313**) significantly inhibited IL-6 and IL-8 production in TNF-α + IL-1β-induced Caco-2 cells at a concentration of 20 μM[128].

6a*R*-2′-Carboxylthaliadine (**116**), 3-methoxy-2′-methoxycarbonyl-oxohernandalincin (**141**), predicentrine (**119**), oxopurpureine (**143**) and laudanosine (**43**) from *Thalictrum cirrhosum*. significantly inhibited T lymphocytes with IC_{50} values of 43.90, 40.80, 43.70, 39.70 and 42.30 μM, respectively[43].

3.6. Antioxidant activity

Berberine hydrochloride (**161**) has beneficial effects against cellular oxidative stress[295,296]. It reduced H_2O_2-induced growth inhibition and DNA damage as well as apoptosis in C2C12 cells by suppressing the accumulation of intracellular reactive oxygen species via activation of the Nrf2/HO-1 pathway[297]. Additionally, the alkaloid improved the antioxidant status of intestinal tissue in mice[298]. The related alkaloid coptisine (**165**) exerted an antioxidant activity against AAPH-induced toxicity by activating Akt and JNK/Nrf2/NQO1 pathways[299].

The bisbenzylisoquinoline alkaloid (−)-*O*-*O*-dimethylgrisabine (**36**) exhibited potent antioxidant activity (44.3%) in the reducing power assay and IC_{50} values of 18.38 and 64.30 μg/mL in DPPH and metal chelating assays, respectively. Thus, it is a good reductant with the ability to chelate metals and prevent pro-oxidant activity[38]. By preventing NF-κB translocation, neferine (**61**) from the same compound classification protected muscle cells from oxidative stress. It also prevented apoptosis by decreasing the mitochondrial membrane potential and reactive oxygen species (ROS) production in cells subjected to hypoxia as well as inhibited the expression of the downstream regulator COX-2[59,300].

Two aporphine isoquinoline alkaloids, (−)-boldine (**85**) and (−)-norboldine (**86**), exhibited good to low potency in three antioxidant activity assays, DPPH (IC_{50} 136.96, 255.21 μM), reducing power (34.37, 52.10%), and metal chelating (IC_{50} 785.64, 501.55 μM)[59]. Two other aporphines, isocorydine (**92**) and norisocorydine (**93**), also showed antioxidant effects in these assays[59].

The protoberberine phellodendrine (**198**) showed good antioxidant effects *in vivo*. It improved the decreased survival rate and abnormally elevated heart rate of zebrafish embryos. In vitro, the compound decreased the increased ROS production, lipid-peroxidation and cell death rate caused by AAPH-induced oxidative stress, most likely by down-regulation of AKT phosphorylation and NF-κB3 expression[93].

Oleracein E (**403**) has a rare tetrahydroisoquinoline/pyrrolidone tricyclic skeleton and a catechol moiety[301]. It improved cognitive function, reversed abnormal brain antioxidant biomarkers (GSH, T-AOC, MDA and SOD) to normal levels, and inhibited hippocampal neuronal apoptosis in D-galactose/$NaNO_2$-induced senescent mice and in some apoptotic indices induced by $AlCl_3$[302,303].

3.7. Antiparasitic and insecticidal activities

Parasitic diseases present a threat worldwide, particularly among developing countries, and cause considerable morbidity and mortality globally. Examples include trypanosomiasis, leishmaniasis and schistosomiasis[304-310]. Compared with synthetic molecules, natural

products are believed to have significant advantages as lead compounds against these diseases, and some isoquinoline alkaloids have demonstrated antiparasitic activity.

The naphthylisoquinoline alkaloid ancistectorine D (**212**) showed the highest potency against the protozoan parasites *Trypanosoma cruzi* and *Leishmania donovani* with IC_{50} values of 4.40 μM and 1.20 μM, respectively, while ancistrobonsolines A_1 and A_2 (**281, 282**) showed weak-to-moderate antiprotozoal activities[111]. The bisbenzylisoquinoline 6,5′,6′,7′,12-pentamethoxy-2,2′-dimethyloxyacathan (**50**) effectively killed both wild type *L. donovani* (EC_{50} 6.8 μM) and sodium antimony gluconate (SAG)-resistant promastigotes (EC_{50} 8.2 μM). Also, at a concentration of 50 μM, it almost completely inhibited the protozoan DNA topoisomerase IB activity[44]. Alternamine A (**397**) showed moderate antiprotozoal effects against *T. cruzi* trypomastigotes and *L. amazonensis* amastigotes with IC_{50} values of 0.23 and 0.16 μM, respectively. The IC_{50} values of the positive drugs (crystal violet against *T. cruzi* and amphotericin B against *L. amazonensis*) were 0.18 and <0.01 μM[153].

Ealapasamines A–C (**287–289**) exhibited excellent *in vitro* antimalarial activity against chloroquine-sensitive (NF54) and chloroquine-resistant (K1) strains of the malaria parasite *P. falciparum*; the IC_{50} values were 418, 210 and 34 nM (NF54) and 452, 138 and 6.3 nM (K1). Thus, ealapasamine C was the most active naphthylisoquinoline against the resistant strain K1. Its cytotoxicity was comparatively low (6.0 μM), giving a high selectivity index of nearly 1000[106]. Dioncophyllines F, C_2 and D_2 (**249–251**) showed high and specific activity against *P. falciparum*[108], while mbandakamines C (**291**) and D (**292**) exhibited promising activity against the same parasite[32].

Two morphinandienones, (+)-sebiferine (**353**) and (−)-milonine (**354**), from *Dehaasia longipedicellata* showed potent to moderate activity against a chloroquine-resistant strain of *P. falciparum* K1 with IC_{50} values ranging from 0.03 to 30.40 μM. (−)-Milonine exhibited potent activity with an IC_{50} value of 0.10 μM, comparable to that of the positive standard, chloroquine (0.09 μM). Meanwhile, they showed no toxicity towards the normal pancreatic cell line (hTERT-HPNE)[60].

Bisbenzylisoquinolines also exhibit significant antiparasitic activity. In 2014, Omole *et al.*[48] found that two new bisbenzylisoquinoline (−)-pseudocurine (**55**) and (−)-pseudoisocurine (**56**) exhibited strong to moderate anti-plasmodial activity against both strains of *P. falciparum* D6 (CQ-susceptible) (IC_{50} 0.49 μM, 1.26 μM), and W2 (CQ resistant) (IC_{50} 0.522 μM, 2.798 μM). (−)-*O*-*O*-Dimethylgrisabine (**59**), isolated from *Dehaasia longipedicellata*, exhibited significant activity against a chloroquine-resistant strain of *P. falciparum* K1 with an IC_{50} value of less than 0.031 μM and no toxicity towards the normal pancreatic cell line (hTERT-HPNE)[38]. (+)-Laurotetanine (**87**) and (+)-norstephasubine (**69**) exhibited strong antiplasmodial activity against *P. falciparum* strain K1 with IC_{50} values of 0.19 and 0.12 μM, respectively[68].

Two aporphines, (−)-boldine (**85**) and (−)-norboldine (**86**), showed moderate activity against a chloroquine-resistant strain of *P. falciparum* K1 with IC_{50} values of 2.60 and 9.28 μM, respectively, while that of chloroquine was 0.09 μM. Isocorydine (**92**), norisocorydine (**93**)

and boldine (**85**) bound free heme and neutralized the electrons produced during the *P. falciparum*-mediated hemoglobin destruction and prevented oxidative damage in the host[60]. Stephanine (**149**), a dehydroaporphine, displayed antiplasmodial activity against *P. falciparum* strains 3D7 and W2 with IC_{50} values of 0.69 μM and 1.32 μM, but its cytotoxicity against 184B5 cells led to low selectivity indexes (9.10 and 4.70). The positive drug chloroquine had IC_{50} values of 2628.3 and 134.2 against the two respective parasite strains.

Berberine chloride (**161**), coptisine chloride (**165**), palmatine chloride (**166**) and dehydrocorydaline nitrate showed strong anti-malarial effects (IC_{50} < 50 nM) against the *P. falciparum* 3D7 strain. Their cytotoxicity to host cells was low (cell viability > 90%)[311]. Berberine also displayed *in vivo* anticoccidial activity[312].

Among four isoquinoline alkaloids, sanguinarine (**299**) presented the strongest insecticidal activity against 3rd instar *Lymantria dispar* with a LD_{50} value of 4.96 μg/larva. The rank order of insecticidal capacity was sanguinarine > chelidonine (**300**) > berberine hydrochloride (**161**) > coptisine (**165**), and the methylenedioxyphenyl(l,3-benzodioxole) group might play a key role in the larvicidal activity on *L. dispar*. Except for coptisine, the alkaloids also significantly reduced the food intake of the larvae and suppressed activity of digestive enzymes. Hence, the alkaloids induced antifeeding and larval lethality on *L. dispar* larvae[124]. Heitziquinone (**308**) from *Zanthoxylum heitzii* presented the weak or inactive toxicity against brine shrimp (*Artemia salina*) [127].

Cis- and *trans*-protopinium (**187, 188**) from *Fumaria parviflora* showed nematicidal activity against the southern root-knot nematode *Meloidogyne incognita*. In an *in vitro* study, the application of *cis*- and *trans*-protopinium at a concentration of 561.18 μM to nematode eggs and second stage juveniles for 120 h of incubation led to 100% values for the area under cumulative percent hatch inhibition and mortality. In the greenhouse and field settings during spring and autumn, application of the alkaloids at a concentration of 841.77 μM significantly reduced the nematode galling index, the number of females per gram of root, and the reproduction factor, as well as increased plant height, fresh and dry shoot weights, and root length[91].

3.8. Neuroprotective Effects

Alzheimer's disease (AD), a common neurodegenerative disease, is characterized by low levels of the neurotransmitter acetylcholine in the brain region involved with cognition. Berberine was highly tolerated when taken orally and freely blood-brain-barrier permeable[313]. Hence, it shows significant promise and activity for treating numerous neurodegenerative conditions, including Alzheimer's, Huntington's, and Parkinson's diseases[314,315]. Berberine (**161**) provided neuroprotection via inhibition of the mTOR signaling pathways and activation of cell survival and antioxidative signaling pathways, such as up-regulated PI3K/AKT/Bcl-2 and Nrf2/HO-1 antioxidative signaling pathways[246,316]. Berberine reduced the accumulation of amyloid β (Aβ) and decreased the expression of β-site APP cleaving enzyme-1 by activating AMPK in N2a mouse neuroblastoma cells stably expressing human Swedish mutant APP695 (N2a/APP695sw), N2a cells[316], and also inhibited Aβ-protein-induced apoptosis in primary cultured hippocampal neurons via the

mitochondria-related caspase pathway[317]. Subsequently, Huang *et al.*[318] suggested that berberine improves cognitive impairment by promoting autophagic clearance and inhibits production of Aβ in an APP/tau/PS1 mouse model of Alzheimer's disease. Furthermore, berberine presented a neuroprotective effect against environmental heavy metal-induced neurotoxicity and Alzheimer's-like disease in rats via its anti-inflammatory/antioxidant mechanisms[319].

Postoperative cognitive dysfunction (POCD) is a significant cause of morbidity after surgery, especially in elderly patients. In an *in vivo* study, berberine alleviated POCD by suppressing neuroinflammation in aged mice and, in an *in vitro* study, it suppressed LPS stimulated production of TNF-α and IL-1β in BV2 cells[320]. Meanwhile, the alkaloid markedly improved aging-related reductions in cognitive ability and muscular function and activation of the AMPK/SIRT1/PGC-1α pathway in skeletal muscle[321]. Also, berberine is a potential alternative therapy for TDP-43-related neuropathology in frontotemporal dementia and amyotrophic lateral sclerosis[322].

Depression is the most common mental disorder in humans. Berberine up-regulated BDNF expression in the hippocampus to lessen corticosterone-induced depressive-like behavior in mice [323] and enhanced dopamine expression to alleviate symptoms of anxiety in rats with post-traumatic stress disorder[324]. It also exerted antidepressant-like effects in ovariectomized mice and decreased immobility time in a dose-dependent manner. Berberine's activation of the 5-HT_2 receptor via the BDNF-CREB and eEF_2 pathways activation may be partially related to these antidepressant-like effects. Furthermore, after berberine treatment, greater reduction was seen in c-Fos induced by ovariectomy[325].

Epileptogenesis transforms a normal brain to an epileptic condition, eventually leading to seizures. Status epilepticus is a life-threatening neurologic condition with seizures of longer duration. Studies showed that berberine relieved status epilepticus and spontaneous recurrent seizures in an intrahippocampal kainite model of epilepsy and exerted neuroprotective effect via suppression of oxidative stress, neuroinflammation, and possibly apoptosis. Berberine also reduced cognitive deficits and hyperphosphorylation of tau by inhibiting the activation of the NF-κB signaling pathway[326].

Cholinesterase (acetylcholinesterase, AChE; butyrylcholinesterase, BChE) inhibitors enhance cholinergic function by prolonging the availability of ACh released into the neuronal synaptic cleft. While several isoquinoline alkaloids, (+)-nornantenine (**88**), (+)-laurotetanine (79), (+)-*N*-methyllaurotetanine (**89**), (+)-oridine (**153**), (+)-*N*-methylisococlaurine (**24**) and (+)-reticuline (**23**), were inactive or exhibited poor inhibitory effects against AChE (IC_{50} > 200 μM), they exhibited a wide range of BChE inhibitory activity (IC_{50} 3.95–288.34 μM)[37]. The protoberberine alkaloids (−)-stylopine (**195**) and (−)-sinactine (**196**) displayed weak inhibitory activity against AChE; however, sinactine potently inhibited the activity of prolyl oligopepetidase (POP), a neuronal enzyme involved in cognitive disorders, with IC_{50} of 53 μM[24]. Protopine (**210**) and cryptopine (**211**) showed weak inhibitory activities against AChE (IC_{50} 230 and 209 μM) and BuChE (IC_{50} 477 and 271 μM)[24]. Among phthalideisoquinoline alkaloids, (−)-mucroniferanine D (**382**), mucroniferanine F (**384**) and mucroniferanine G (**385**), exhibited AChE inhibitory activities

with IC_{50} values of 28.3, 12.2 and 11.3 μM, respectively[99], while (+)-bicuculline (**372**) was only weakly active against AChE, BuChE, and POP with higher IC_{50} values of 626 μM, 329 μM and 190 μM, respectively[24,150]. The pyrrolophenanthridine alkaloids seco-isopowellaminone (**336**), haemanthamine (**326**) and incartine (**337**) also exhibited weak anti-human AChE activity[138]. (+)-Parfumidine (**79**), a spirobenzylisoquinoline alkaloid, exhibited POP inhibitory activity with an IC_{50} value of 99 μM, compared with 3.27 μM for the positive drug (Z)-pro-prolinal[24].

The known benzophenanthridine alkaloid chelerythrine potently and selectively inhibited an isoform of recombinant human monoamine oxidase A (MAO-A) with an IC_{50} value of 0.55 μM. It acted as a reversible competitive inhibitor (IC_{50} 0.22 μM) and was more potent than the antidepressant drug toloxatone (IC_{50} 1.10 μM), which also is a selective, reversible MOA inhibitor. Chelerythrine can be deemed a potential lead compound for the design of novel reversible MAO-A inhibitors[327].

3.9. Hepatoprotective

Berberine (**161**) caused signification reduction in hepatic steatosis[328,329]. Although its bioavailability was less than 1% in some studies[330,331], the alkaloid was typically concentrated in the liver after oral administration[332]. Berberine exerts anti-hyperglycemic and anti-dyslipidemic effects and can also ameliorate nonalcoholic fatty liver disease (NAFLD) via regulation of the hepatic SIRT1-UCP2 pathway[332-334]. By regulating cholesterol metabolism and inhibiting COX2-prostaglandin synthesis, the compound improved blockade of autophagic flux in the liver[335]. Moreover, berberine lessened the deposition of triglycerides in the liver following intraperitoneal injection or oral gavage[336]. It also protected against methotrexate-induced liver injury and attenuated oxidative stress and apoptosis, possibly through up-regulating the Nrf2/HO-1 pathway and PPARγ[337]. Moreover, berberine reduced staphylococcal enterotoxin B-mediated acute liver injury via regulation of HDAC expression[338].

Wang *et al.*[339] investigated the effects of tetrahydroberberine (**179**) and tetrahydropalmatine (**192**) on the expression of mouse liver cytochrome P450s and their liver toxicity in mice. Tetrahydroberberine induced mRNA expression of *Cyp1a2*, *Cyp3a,* and *Cyp2e1*, while tetrahydropalmatine inhibited *Cyp1a2*. While oral tetrahydroberberine increased mouse serum aspartate transaminase, total bilirubin, and liver malondialdehyde levels, as well as induced liver edema, tetrahydropalmatine did not cause such effects.

In 2018, study results showed that tiliamosine (**54**) could be used to treat non-alcoholic steatohepatitis[53]. Norsanguinarine (**316**), (−)-6-acetonyldihydrisanguinarine (**317**) and cavidilinine (**318**) from *Corydalis tomentella* exhibited moderate hepatoprotective activities at a concentration of 10 μM[28]. At a concentration of 10 μM, three stereoisomeric isoquinoline alkaloids (9*S*,7′*S*) tomentelline A (**374**), (9*S*,7′*R*) tomentelline A (**375**), (9*R*,7′*S*) tomentelline B (**376**), together with hendersine B methyl ester (**46**), bicucullinine (**47**), hendersine B (**48**), and (+)-capnoidine (**378**) presented moderate hepatoprotective activities with relative survival rates of 33.28–52.57%[28].

3.10. Anti-platelets and myocardial protective effect

The aporphine alkaloid norpurpureine (**101**) exhibited activity (IC_{50} 80 μM) against platelet aggregation stimulated by adenosine 5′-diphosphate (ADP), collagen and thrombin. It gradually inhibited granule secretion and adhesion of activated platelets to immobilized fibrinogen. At the intra-platelet level, norpurpureine prevented agonist-stimulated calcium mobilization and cAMP reduction. Its molecular target could be an effector common effector to Ca^{2+} and cAMP signaling, such as the PLC-PKC-Ca^{2+} pathway and phosphodiesterases[74].

In addition, the isoquinoline alkalkaloid berberine (**161**) has been associated with myocardial protective effects[340-342]. By differentially modulating the activities of p-STAT1, p-STAT3 and p-STAT4 and, thus, suppressing Th17 and Th1 cell differentiation, the compound protected against myosin-induced myocardial injury in rats[340]. Subsequent reports showed that berberine protected the heart from ischemia/reperfusion injury induced by NaH_2PO_4 partly though reducing myocardial autophagy and apoptosis via the AMPK/mTOR and AK2/STAT3 signaling pathways *in vivo* and *in vitro*[343,344] as well as reducing the striatum apoptosis via activation of the BDNF-TrkB-PI3K/Akt signaling pathway in the middle cerebral artery occlusion-induced cerebral ischemia/reperfusion model[345]. The related compound coptisine (**165**) also attenuated pro-inflammatory cytokines, including IL-1β, IL-6, and tumor necrosis factor-α, in heart tissue after myocardial ischemia/reperfusion injury[346].

Neferine (**61**), a bisbenzylisoquinoline-type alkaloid, prevented hyperglycemia-induced endothelial cell apoptosis through suppression of ROS/Akt/NF-κB[347]. Also, it blocked $Na_v1.5$ channels in myocardia under the open and inactivating states and, thus, was an open channel blocker of $Na_v1.5$ channels[348,349]. Finally, ambinine (**315**), a benzophenanthridine alkaloid, had protective effects on H9C2 myocardial cells. It demonstrated anticoagulation and thrombolytic effects *in vitro* by significantly degrading blood clots and delaying plasma recalcification time in a dose-dependent manner (1.21-4.84 mM)[228].

3.11. Anti-ulcer activity

Gastric ulcers are one of the most common gastrointestinal disorders. The anti-ulcer/gastroprotective effect of berberine (**161**) might involve positive regulation of antioxidant and anti-inflammatory status mediated, at least partially, through the Nrf2 signaling pathway and p38 MAPK translocation[350]. Palmatine (**166**) hydrochloride tablets have been used clinically to cure intestinal and gynecological inflammation, bacillary dysentery, respiratory and urinary tract infections, surgical infections and eye conjunctivitis. Wang *et al.*[351] also reported that this alkaloid may protect the gastric mucosa by increasing PGE_2 and decreasing PAF as well as against gastric ulcers, perhaps associated with anti-inflammatory status. After orally administrating palmatine for seven consecutive days, ulcer areas were significantly decreased with inhibitory rates of 51% to 62%.

Cavidine (**194**), a protoberberine isoquinoline alkaloid and potent inhibitor of COX-2, exerted a gastroprotective effect against gastric ulceration, which might be associated with the stimulation of PGE2, reduction of oxidative stress, suppression of NF-κB expression and

subsequently reduced COX-2 and pro-inflammatory cytokines[352,92]. Pretreatment with this compound had a protective effect on acetic acid-induced ulcerative colitis in mice[264].

3.12. Renoprotective effects

Berberine (**161**) is a good candidate to protect against the deleterious effect of chronic lead intoxication on the kidney[353]. Molecular, biochemical, and histopathological analysis indicated that this alkaloid exerted renoprotective effects in an animal model of lead-induced nephrotoxicity by inhibiting lipid peroxidation and enhancing antioxidant defense system mechanisms. Berberine also protected against renal ischemia/reperfusion injury by regulating the Sirt1/p53 pathway[354].

3.13. Anti-muscle atrophy activity

Magnoflorine (**100**), an aporphine isoquinoline alkaloid, efficiently enhanced myoblast differentiation by activating the p38 MAP kinase and Akt pathways and increased the numbers of multinucleated and cylinder-shaped myotubes. It might be a promising lead compound for the development of a drug to combat muscle atrophy[73].

3.14. Retinal effects

Berberine (**161**) exhibited a protective effect against light-induced photoreceptor degeneration associated with diminished oxidative stress in the mouse retina. Thus, it could provide protection against retinal diseases[250].

3.15. Analgesic effects

Neuropathic pain is a major public health problem. Berberine (**161**) administration (i.p.) increased both mechanical and thermal pain thresholds in a dose-dependent manner. Moreover, berberine administration reversed the mRNA and protein expression of TRPV1 in dorsal root ganglion neurons after peripheral nerve injury and significantly inhibited capsaicin-induced pain behaviors. This action on neuropathic pain may be associated with the down-regulation of the heat and capsaicin receptor, TRPV1, in the dorsal root ganglia of rat neurons. Accordingly, berberine could be used to treat neuropathic pain originated in the peripheral nervous system[355].

3.16. Others

Osteoarthritis, a common degenerative joint disease, is a major cause of joint dysfunction in the elderly[356]. Berberine (**161**) prevented articular degeneration cartilage by activating the Akt/p70S6K/S6 signaling pathway in interleukin-1β-induced rat chondrocytes as well as a rat model[357]. It also prevented NO-induced rat chondrocyte apoptosis and cartilage degeneration via AMPK and p38 MAPK signaling[358]. Moreover, the compound promoted sodium nitroprusside-stimulated chondrocyte proliferation by promotion of G1/S phase transition and synthesis of proliferating cell nuclear antigen in cartilage and bone marrow-derived mesenchymal stem cells as well as osteogenic differentiation through activation of the Wnt/β-catenin signaling pathway[359,360].

In addition, berberine may be used to treat adenomyosis by inhibiting growth and inflammatory invasive phenotypes of ectopic stromal cells[361] and acute respiratory distress syndrome (ARDS) by alleviating endothelial glycocalyx degradation and promoting glycocalyx restoration in LPS-induced ARDS[362].

4. CONCLUSION

As an important class of alkaloids, isoquinoline alkaloids have various chemical structures and pharmacological activities. However, the potential of this promising and expanding platform of active natural compounds has only been partially developed by both the academic community and the pharmaceutical industry to date. Over the past century, the discovery of morphine opened a new area for the development of central analgesic agents, and the application of berberine in the clinic has inspired a new wave for the discovery of alternative, green antibacterial drugs. During the past five years, the identification of additional new compounds, significant biological activities or novel mechanism of actions will undoubtedly contribute to the continual development of future new drugs. Continued attention and long-lasting research on the isolation and identification of naturally occurring isoquinoline alkaloids will open the way to targeted pharmacological modelling and synthetic modifications, resulting in new and better drugs based on the original effects of these alkaloids.

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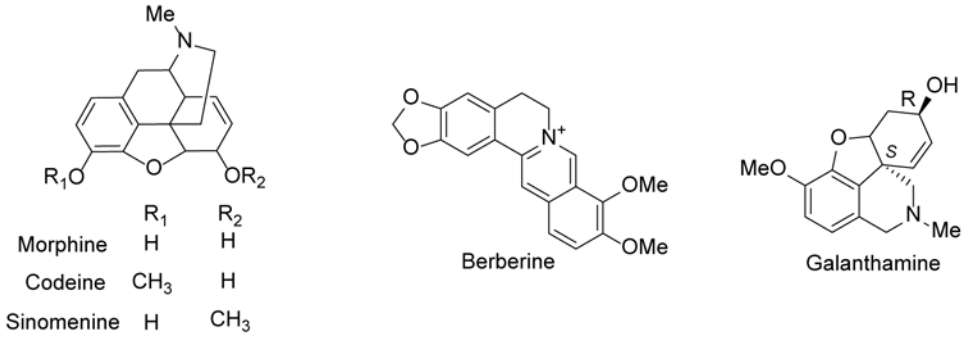


Figure 1.
The chemical structures of five major isoquinoline molecules

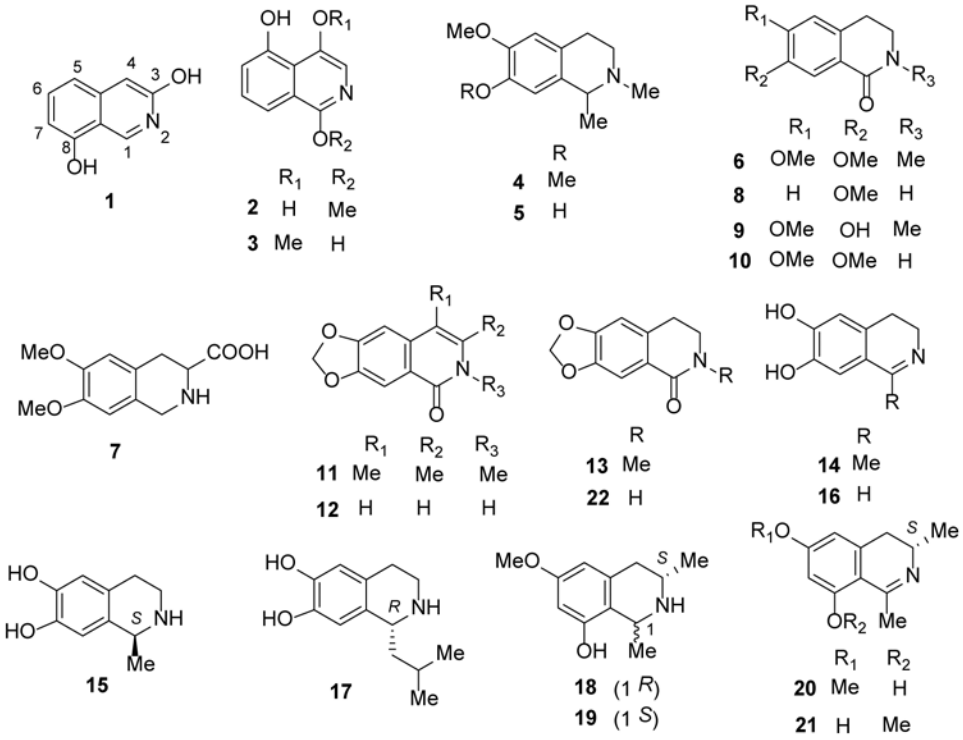


Figure 2.
The Chemical Structures of Compounds **1-22**

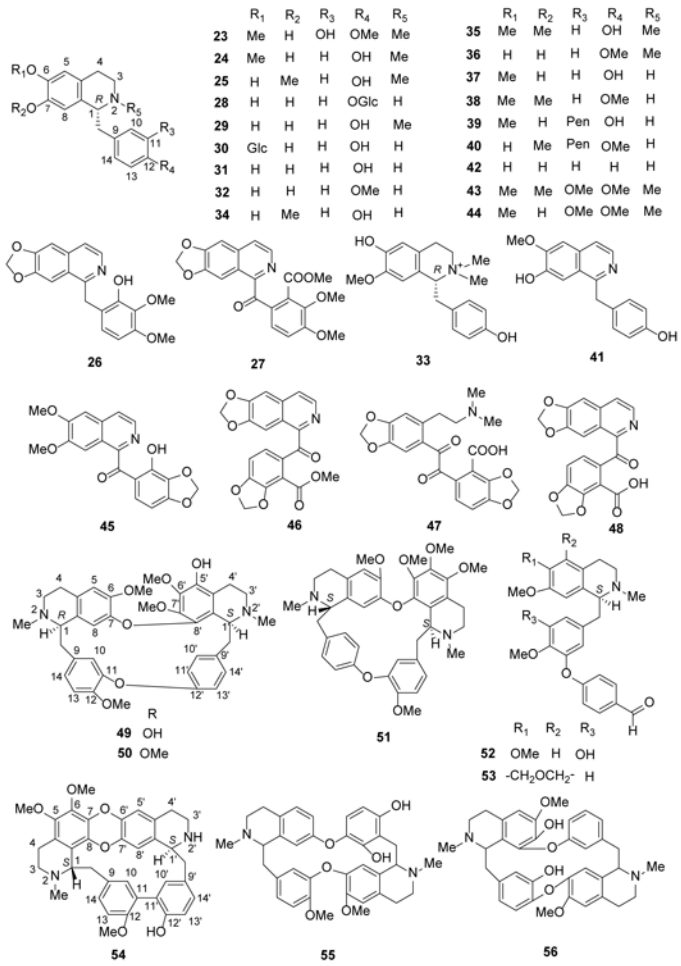


Figure 3.
The Chemical Structures of Compounds **23-56**

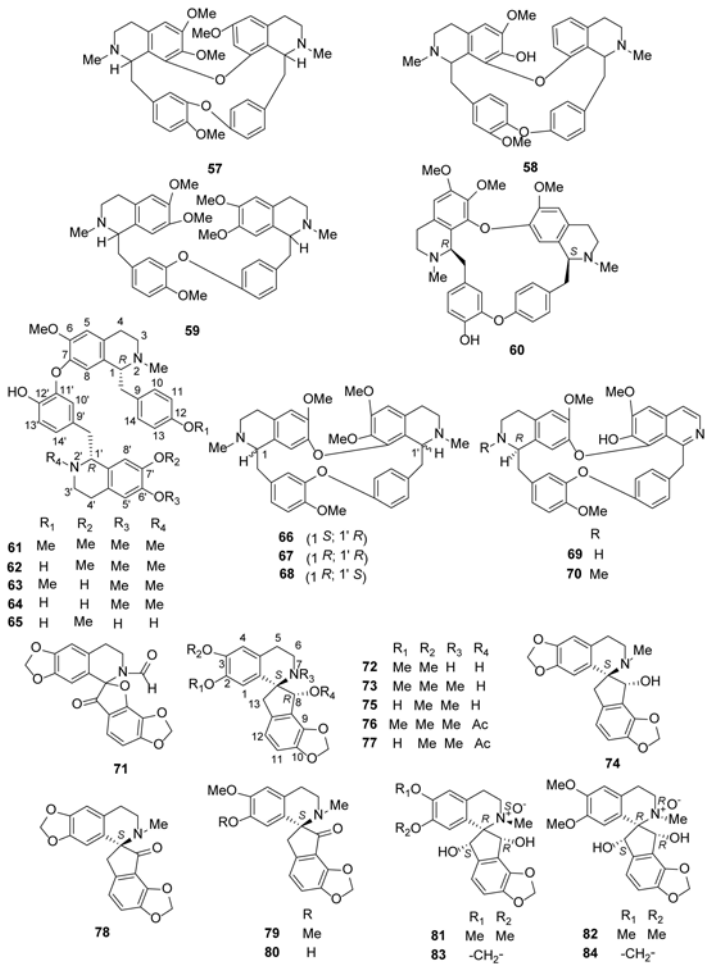


Figure 4.
The Chemical Structures of Compounds **57**-**84**

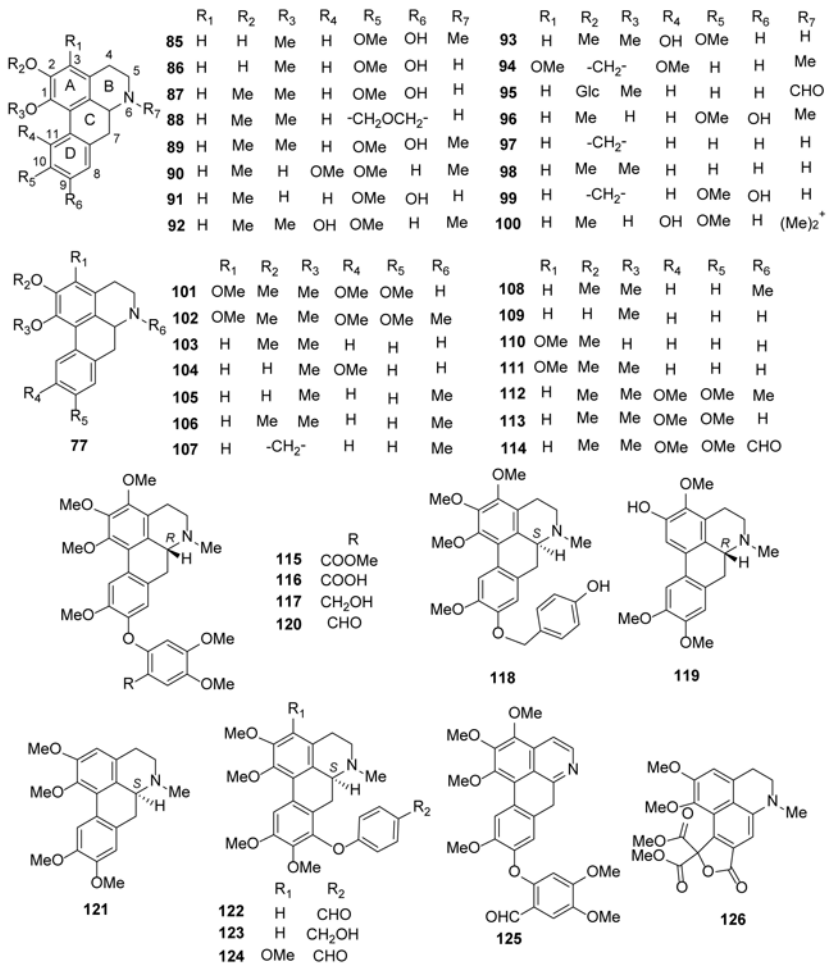


Figure 5.
The Chemical Structures of Compounds **85-126**

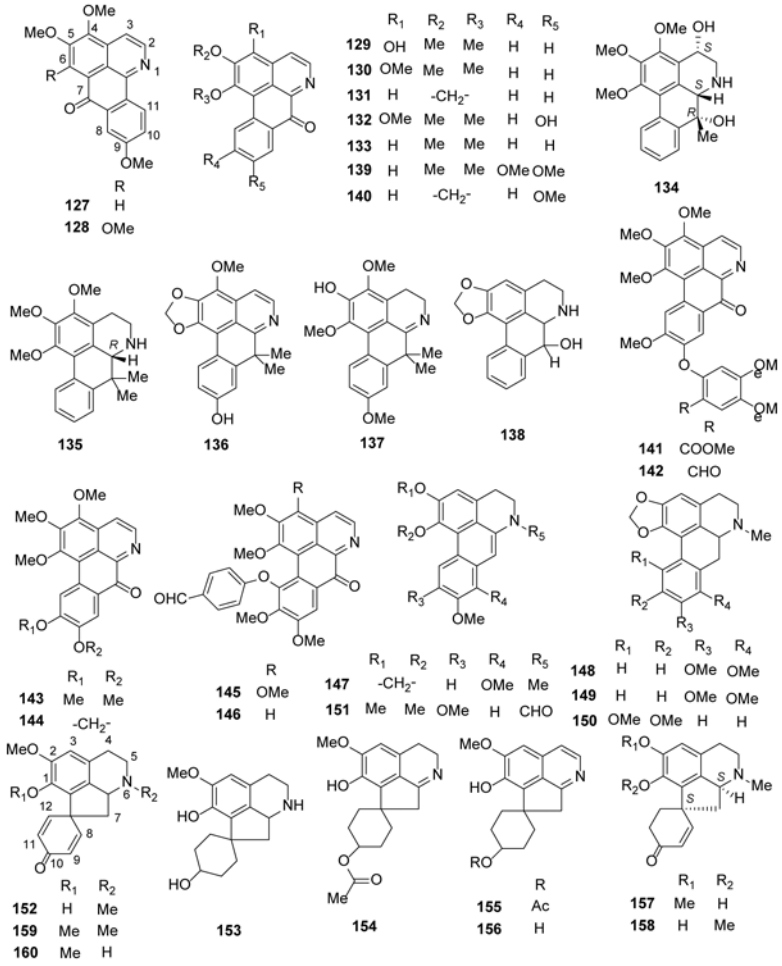


Figure 6.
The Chemical Structures of Compounds **127-160**

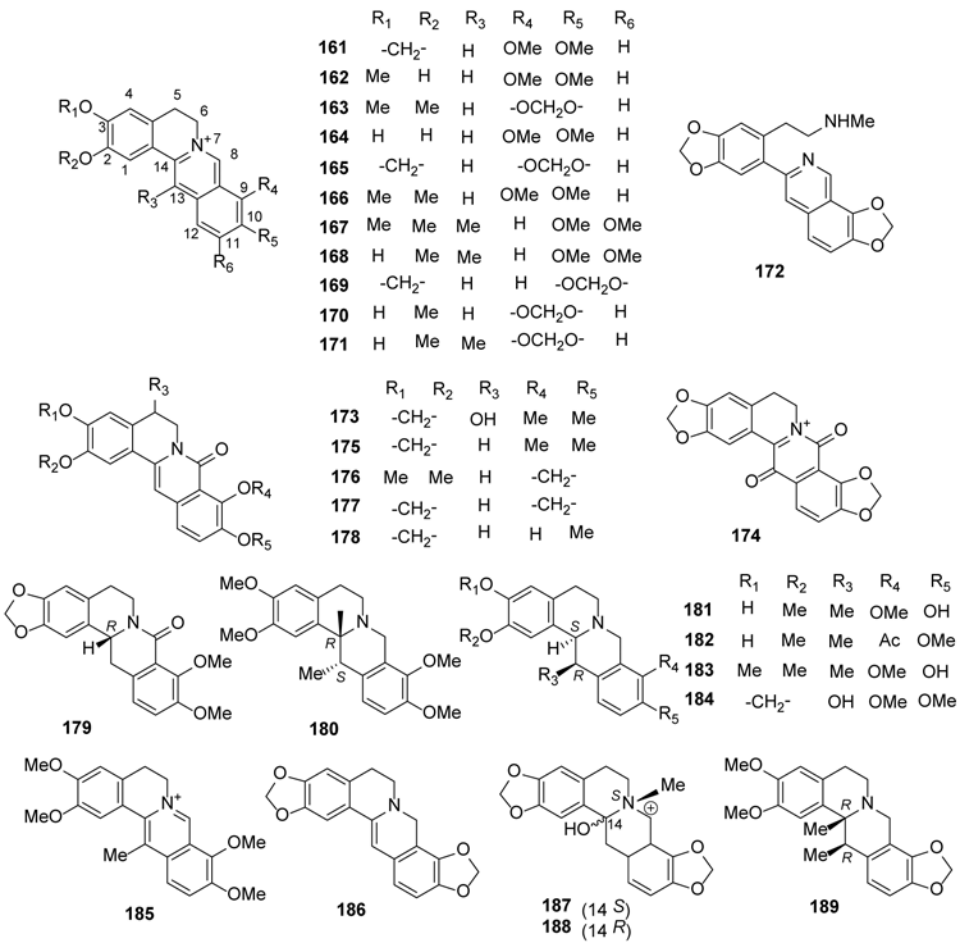


Figure 7.
The Chemical Structures of Compounds **161**-**189**

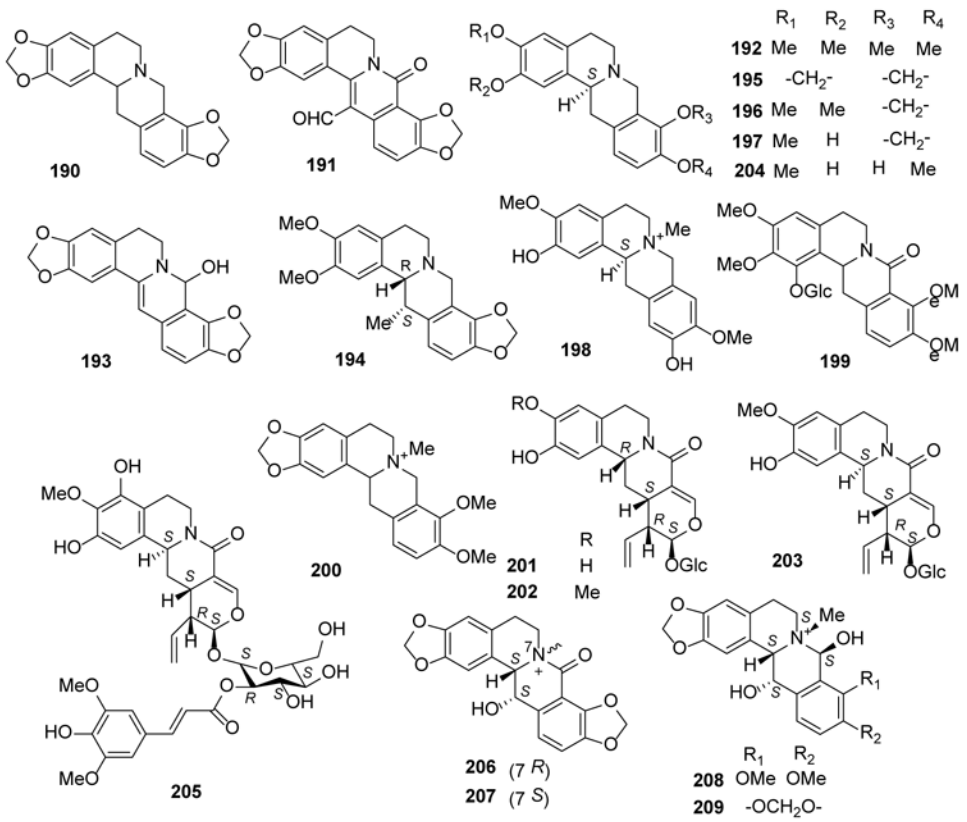
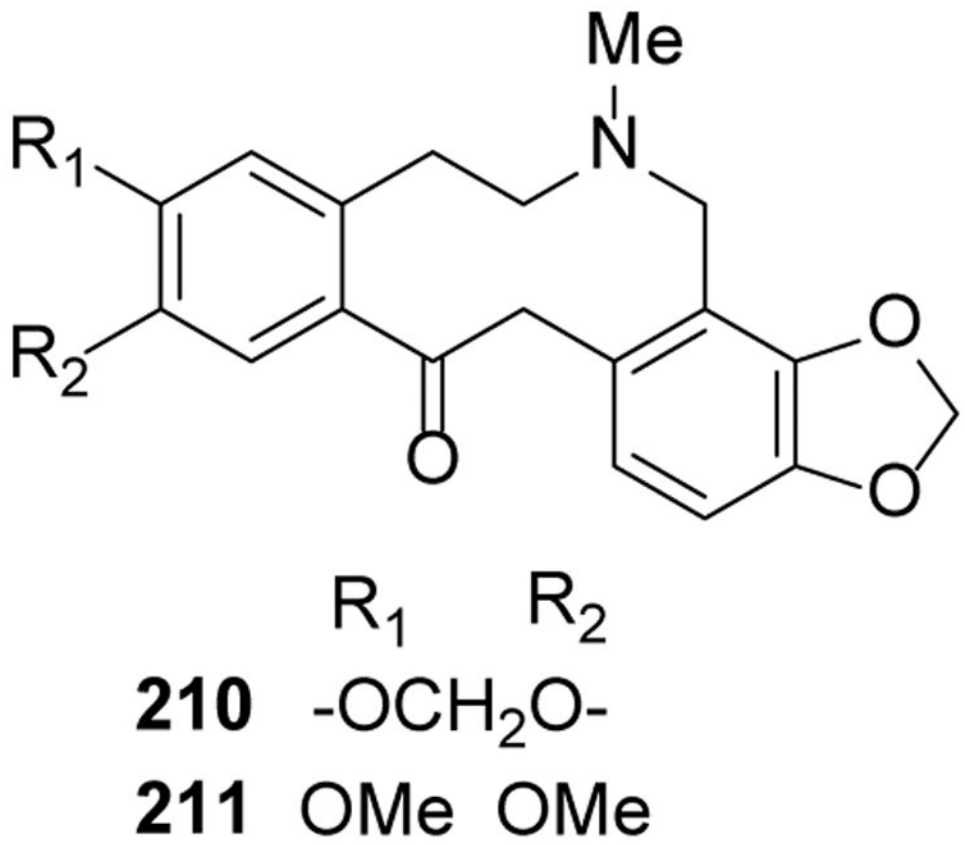


Figure 8.
The Chemical Structures of Compounds **190**-**209**



	R_1	R_2
210	$-OCH_2O-$	
211	OMe	OMe

Figure 9.
The Chemical Structures of Compounds **210-211**

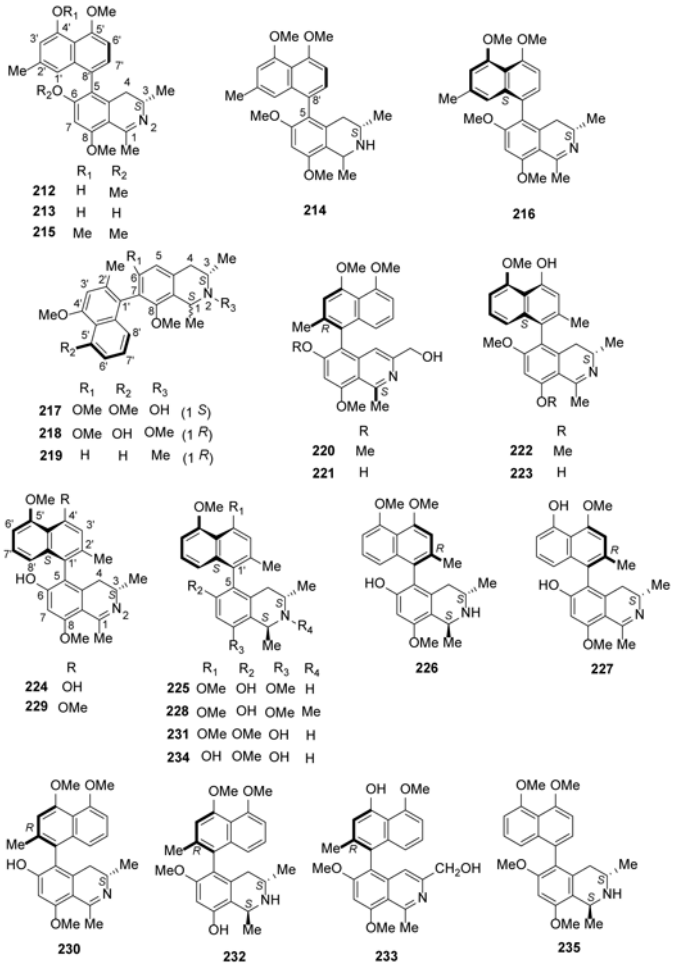


Figure 10.
The Chemical Structures of Compounds **212-235**

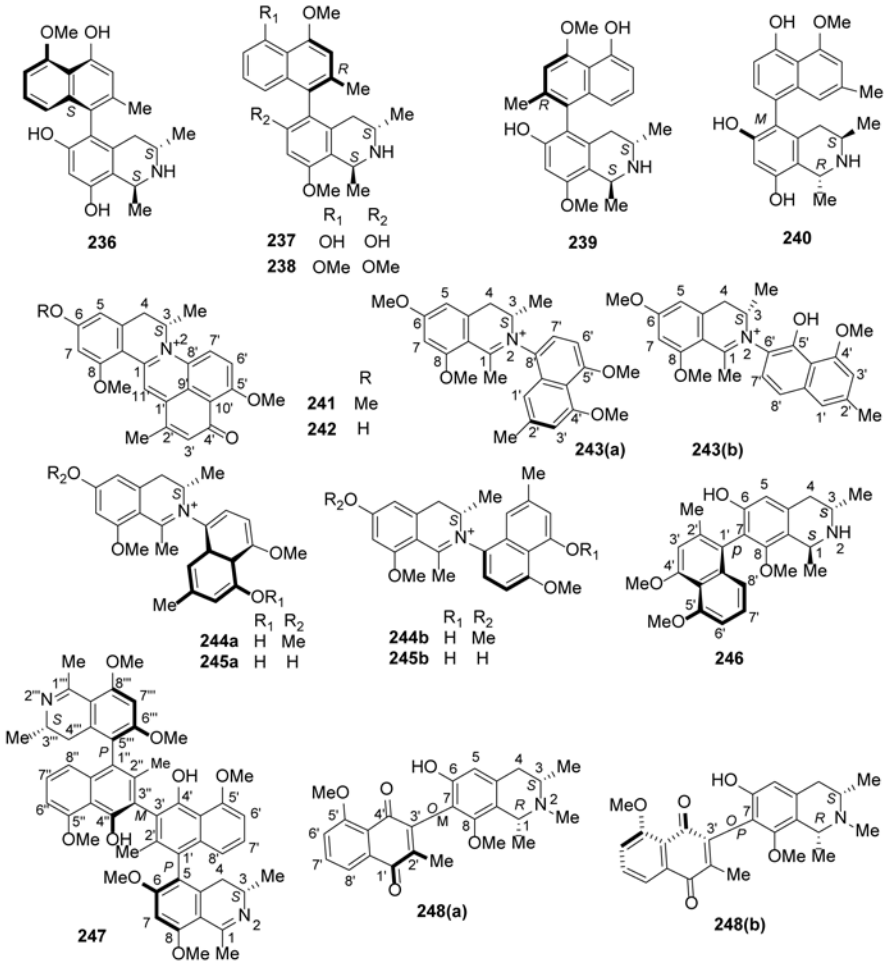


Figure 11.
The Chemical Structures of Compounds **236**-**248**

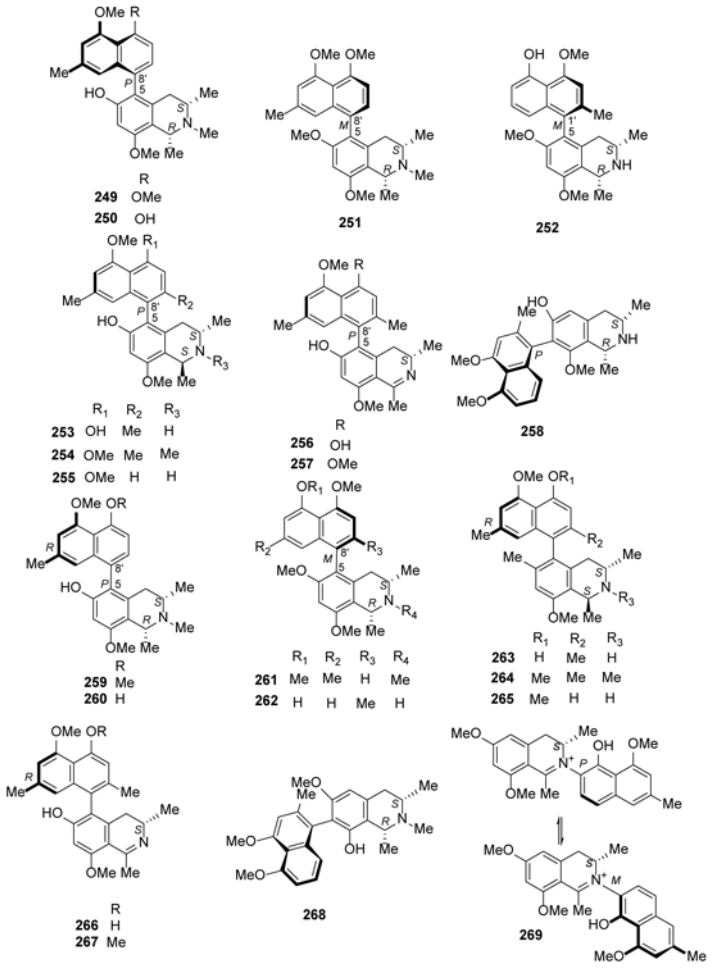


Figure 12.
The Chemical Structures of Compounds **249**-**269**

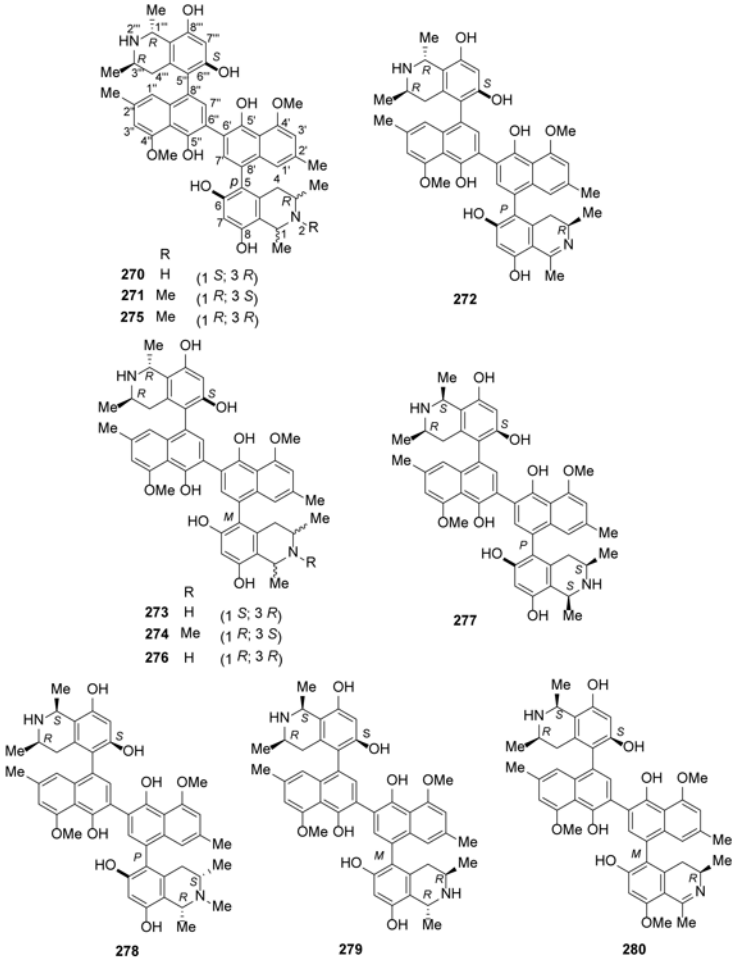


Figure 13.
The Chemical Structures of Compounds **270**-**280**

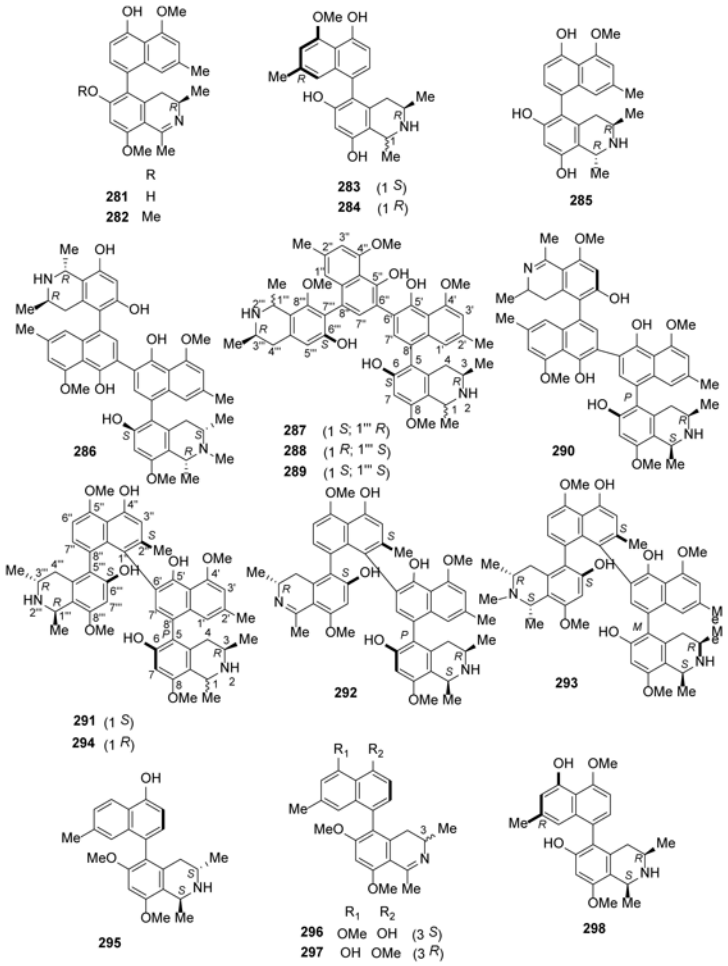


Figure 14.
The Chemical Structures of Compounds **281**-**298**

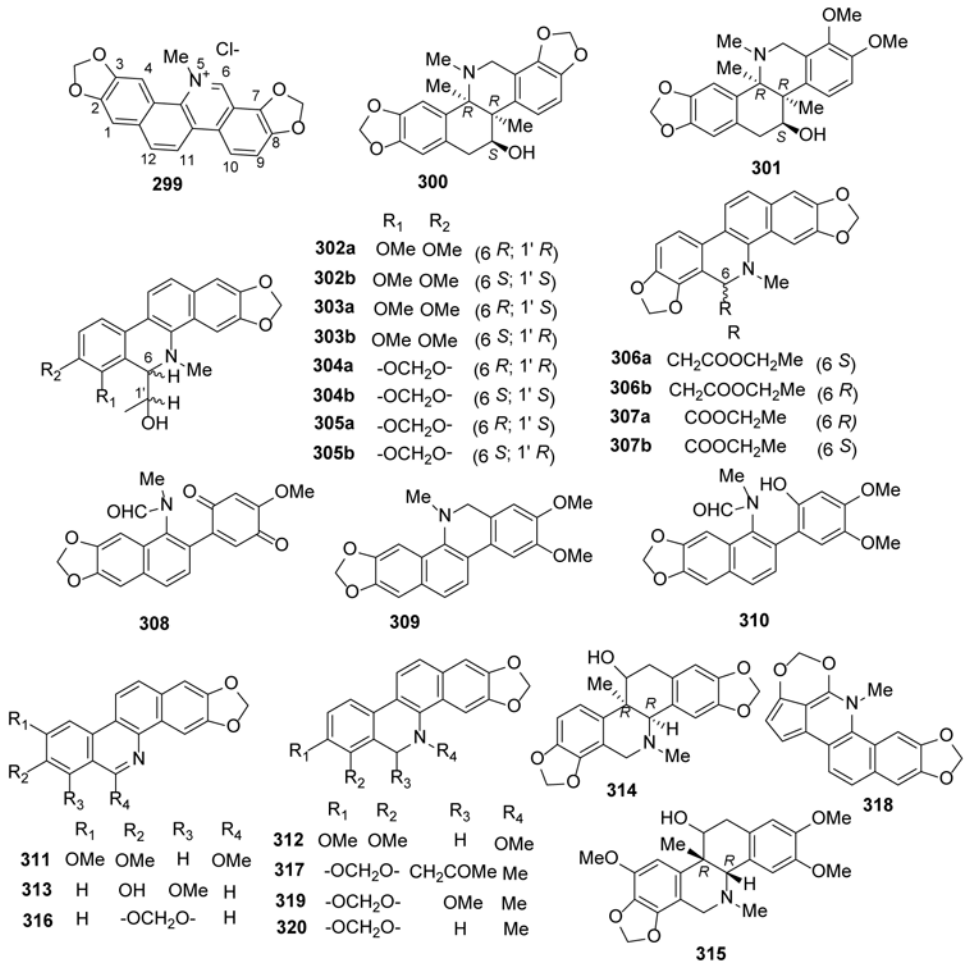


Figure 15.
The Chemical Structures of Compounds **299**-**320**

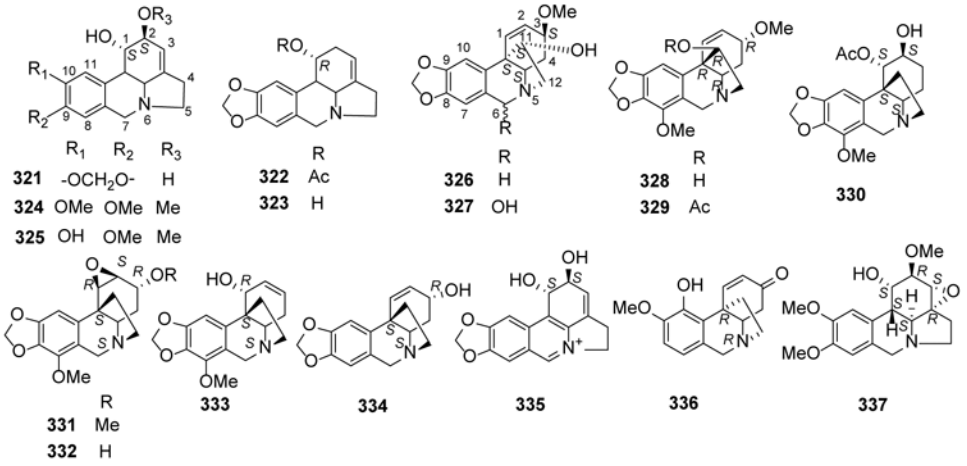


Figure 16.
The Chemical Structures of Compounds **321**-**337**

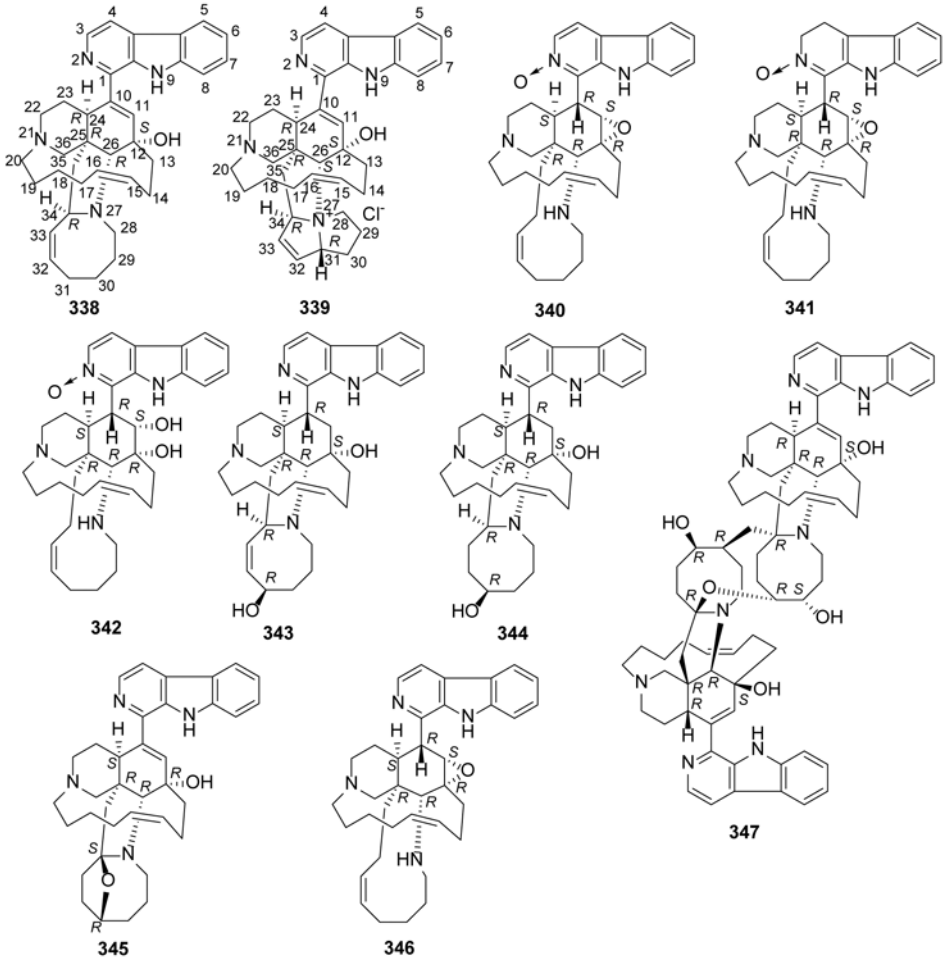


Figure 17.
The Chemical Structures of Compounds **338**-**347**

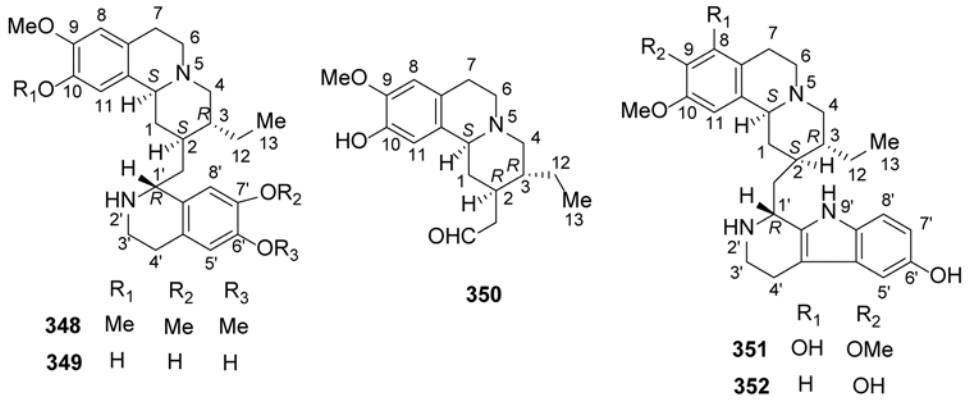


Figure 18.
The Chemical Structures of Compounds **348**-**352**

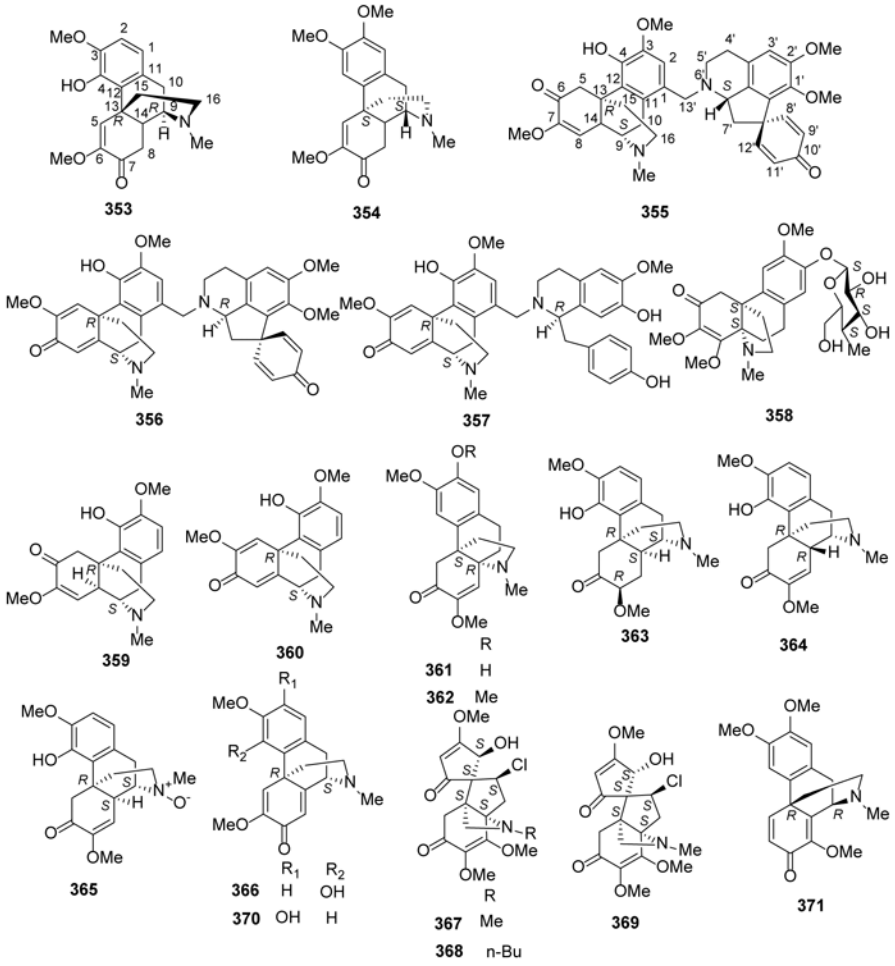


Figure 19.
The Chemical Structures of Compounds **353-371**

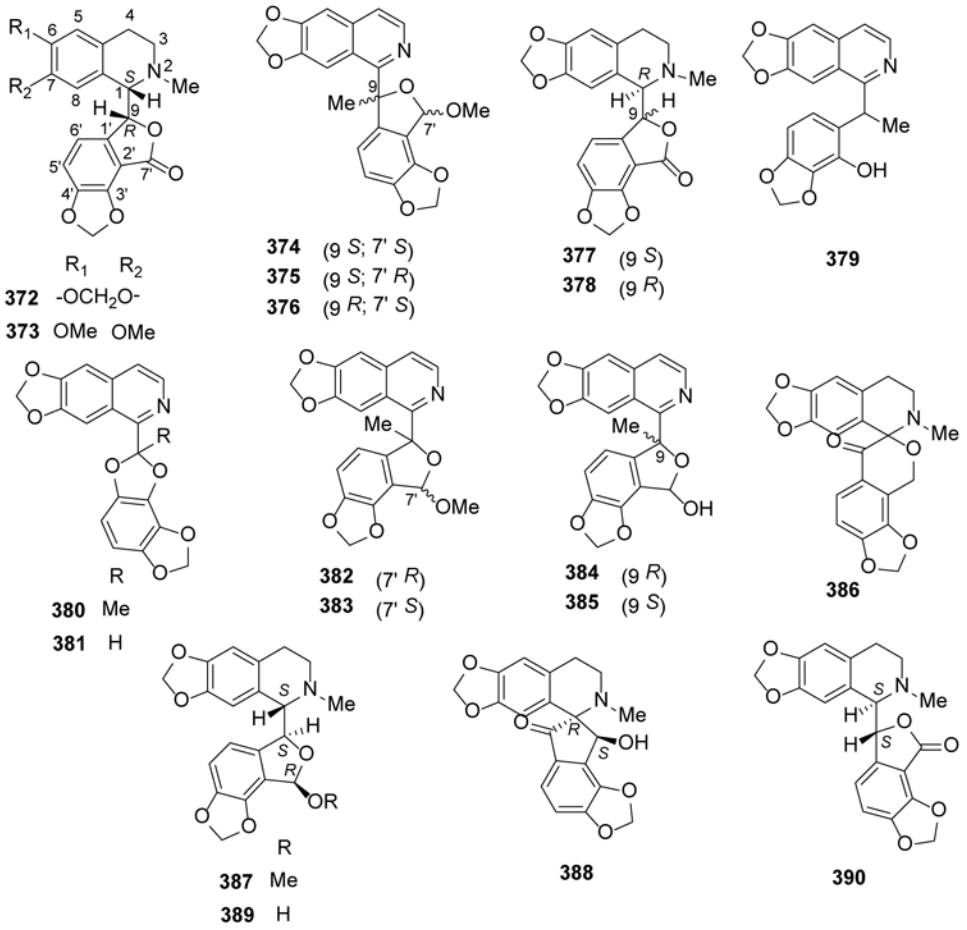
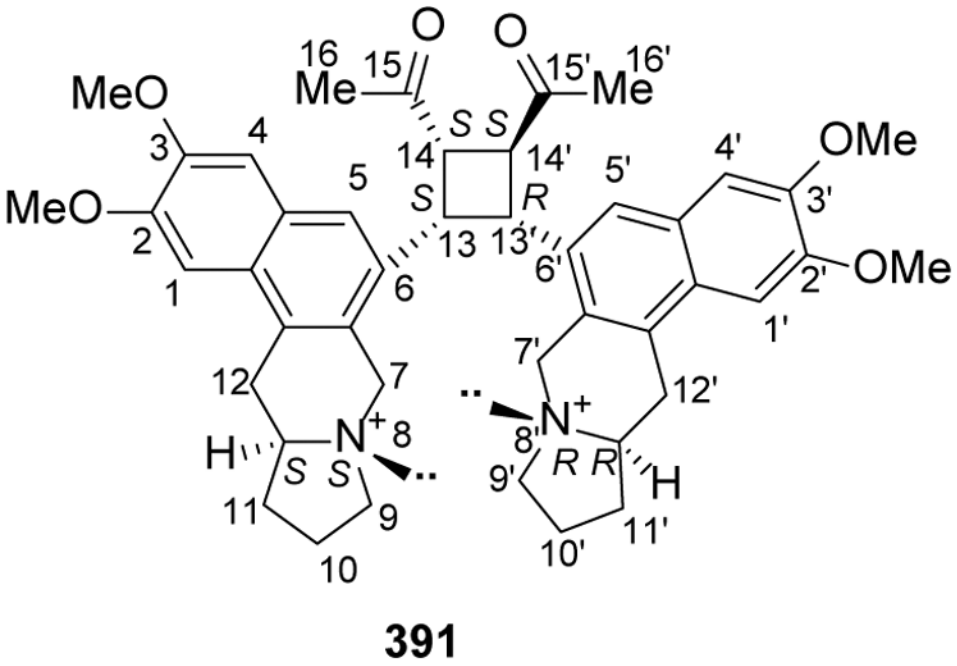


Figure 20.
The Chemical Structures of Compounds **372-390**



391

Figure 21.
The Chemical Structure of Compound **391**

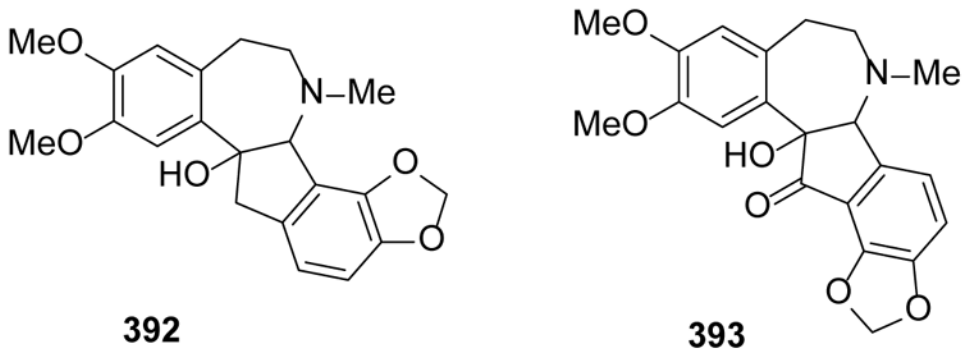


Figure 22.
The Chemical Structures of Compounds **392**-**393**

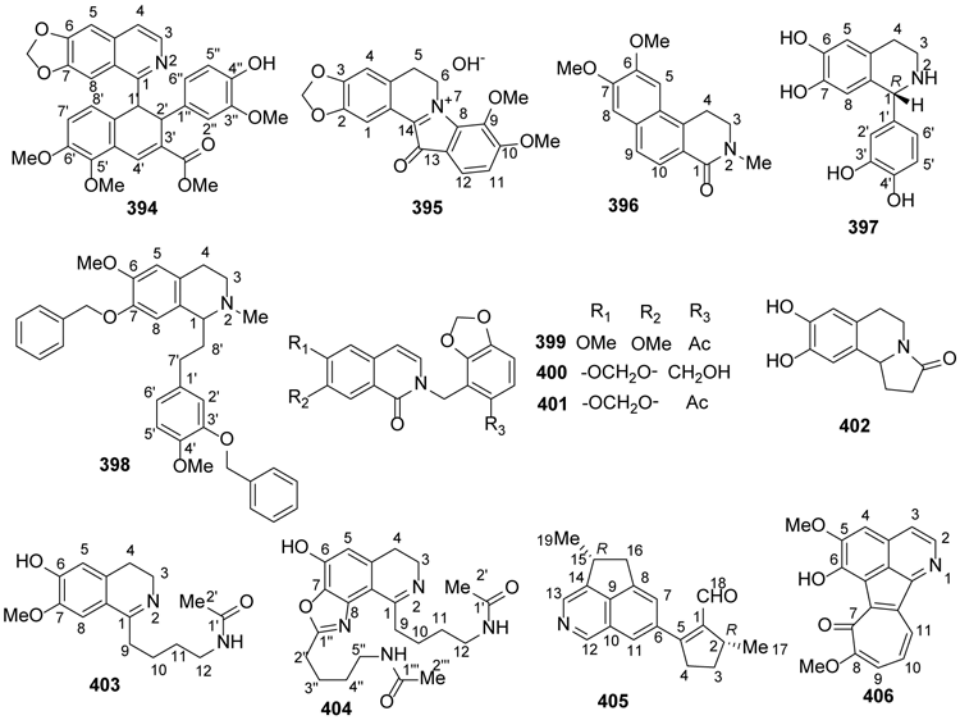


Figure 23.
The Chemical Structures of Compounds **394-406**

Table 1.

Isolated isoquinoline alkaloids between 2014 to 2018

No.	Names	Species	Year	Ref.
Simple isoquinoline alkaloids				
1	3,8-Diolisoquinoline	*Scolopendra subspinipes mutilans*		22
2	1-Methoxy-4,5-diolisoquinoline	*Scolopendra subspinipes mutilans*		22
3	1,5-Dihydroxy-4-methoxyisoquinoline	Centipede species		23
4	Carnegine	*Hammada scoparia*		24
5	*N*-Methylisosalsoline	*Hammada scoparia*		24
6	*N*-Methylcorydaldine	*Fumaria officinalis* *Michelia champaca*		25 27
7	6,7-Dimethoxy-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid	*Mucuna pruriens*		26
8	7-Methoxy-1,2,3,4-tetrahydroisoquinolin-1-one, thalifoline	*Michelia champaca*		27
9	Thalifoline	*Corydalis tomentella* *Plumula nelumbinis*		27-30
10	Corydaldine	*Corydalis tomentella* *Corydalis hendersonii*		27-30
11	Oxohydrastinine	*Corydalis tomentella*		28
12	6,7-Methylenedioxy-1(2*H*)-isoquinolinone	*Corydalis tomentella*		28
		Corydalis hendersonii		29
13	Oxyhydrastinine	*Corydalis hendersonii*		29
14	6,7-Dihydroxy-1-methyl-3,4-dihydroisoquinolone,	*Portulaca oleracea*		31
15	(*S*)-(−)-Salsolinol	*Portulaca oleracea*		31
16	6,7-Dihydroxy-3,4-dihydroisoquinolone	*Portulaca oleracea*		31
17	(*R*)-(+)-1-Isobutyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline	*Portulaca oleracea*		31
18	Ealaine A	*Ancistrocladus ealaensis*		32
19	Ealaine B	*Ancistrocladus ealaensis*		32
20	Ealaine C	*Ancistrocladus ealaensis*		32
21	Ealaine D	*Ancistrocladus ealaensis*		32
22	Noroxyhydrastinine	*Phellodendron amurense*		33
Benzylisoquinoline alkaloids				
23	Reticuline	*Litsea cubeba* *Cryptocarya densiflora,* *Cryptocarya infectoria,* *Cryptocarya griffithiana* *Unonopsis floribunda* *Dehaasia longipedicellata* *Bocageopsis pleiosperma*		34 35 36 37 38 39
24	(+)-*N*-Methylisococlaurine	*Cryptocarya species* *Plumula nelumbinis*		37 30
25	(−)-*N*-Methylcoclaurine	*Sinomenium acutum* *Plumula nelumbinis*		40 30
26	Berbithine	*Coptis chinensis*		41
27	6-([1,3]Dioxolo[4,5-*g*]isoquinoline-5-carbonyl)-2,3-dimethoxybenzoic acid methyl ester	*Coptis chinensis*		41
28	Norcolaurine-4′-*O*-glucoside	*Plumula nelumbinis*		30
29	*N*-Methylhigenamine	*Plumula nelumbinis*		30

No.	Names	Species	Year	Ref.
30	Norcoclaurine-6-*O*-glucoside	*Plumula nelumbinis*		30
31	Norcoclaurine	*Plumula nelumbinis*		30
32	Argemexirine	*Plumula nelumbinis*		30
33	Lotusine	*Plumula nelumbinis*		30
34	Isococlaurine	*Plumula nelumbinis*		30
35	Armepavine	*Plumula nelumbinis*		30
36	6-Demethy-4′-methyl-N-methylcoclaurine	*Plumula nelumbinis*		30
37	Coclaurine	*Plumula nelumbinis*		30
38	*N*-Nor-*O*-methylarmepavine	*Plumula nelumbinis*		30
39	Isococlaurine-5′-*O*-pentoside	*Plumula nelumbinis*		30
40	Coclaurine-5′-*O*-pentoside	*Plumula nelumbinis*		30
41	Juzirine	*Leonurus japonicus*		42
42	(*R*)-(+)-1-Benzyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline	*Portulaca oleracea*		31
43	Laudanosine	*Thalictrum cirrhosum*		31
44	Pseudolaudanine	*Thalictrum cirrhosum*		43
45	Rugosinone	*Thalictrum cirrhosum*		43
46	Hendersine B methyl ester	*Corydalis tomentella*		28
47	Bicucullinine	*Corydalis tomentella*		28
48	Hendersine B	*Corydalis tomentella*		28
49	6,6′,7′,12-Tetramethoxy-5′-hydroxy-2,2′-dimethyloxycanthan	*Thalictrum foliolosum*		44
50	6,5′,6′,7′,12-Pentamethoxy-2,2′-dimethoxyethane	*Thalictrum foliolosum*		44
51	Hernandezine	*Thalictrum flavum*		45
52	6,7,12-Trimethoxy-2-methyl-13-hydroxy-11-(4′-formylphenoxy) benzylisoquinoline	*Thalictrum wangii*		46
53	5,6-(Methylenedioxy)-7,12-dimethoxy-2-methyl-10-(4′-formylphenoxy) benzylisoquinoline	*Thalictrum wangii*		46
54	Tiliamosine	*Thalictrum racemosa*		47
55	(−)-Pseudocurine	*Stephania abyssinica*		48
56	(−)-Pseudoisocurine	*Stephania abyssinica*		48
57	Tetrandrine	*Stephania tetrandra*		49
58	Tangchinoline	*Stephania tetrandra*		49
59	(−)-*O*-*O*-Dimethylgrisabine	*Dehaasia longipedicellata*		38
60	Berbamine	*Mahonia aquifolium*		50
61	Neferine	*Nelumbo nucifera* *Plumula nelumbinis*		59 30
62	Liensinine	*Plumula nelumbinis*		30
63	Isoliensinine	*Plumula nelumbinis*		30
64	Norisoliensinine	*Plumula nelumbinis*		30
65	6-Hydroxynorisoliensinine	*Plumula nelumbinis*		30
66	(−)-Gyrolidine	*Alseodaphne corneri*		60
67	(+)-*O*-Methyllimacusine	*Alseodaphne corneri*		60
68	(+)-2-Norobaberine	*Alseodaphne corneri*		60
69	Norstephasubine	*Alseodaphne corneri*		60

No.	Names	Species	Year	Ref.
70	(+)-Stephasubine	*Alseodaphne corneri*		60
71	Coptichic aldehyde	*Coptidis Rhizoma-Euodiae Fructus couple*		61
72	Fumaranine	*Fumaria officinalis*		24
73	(−)-Fumaricine	*Fumaria officinalis*		24
74	(+)-Dihydrofumariline	*Fumaria officinalis*		24
75	(−)-Fumaritine	*Fumaria officinalis*		24
76	(−)-*O*-Methylfumarophycine	*Fumaria officinalis*		24
77	(−)-Fumarophycine	*Fumaria officinalis*		24
78	(+)-Fumariline	*Fumaria officinalis*		24
79	(+)-Parfumidine	*Fumaria officinalis*		24
80	(+)-Parfumine	*Fumaria officinalis*		24
81	Hendersine C	*Corydalis hendersonii*		29
82	Hendersine D	*Corydalis hendersonii*		29
83	Hendersine E	*Corydalis hendersonii*		29
84	Hendersine F	*Corydalis hendersonii*		29
Aporphine alkaloids				
85	Boldine	*Litsea cubeba* *Dehaasia longipedicellata*		67 60, 38
86	(−)-Norboldine	*Dehaasia longipedicellata*		38
87	(+)-Laurotetanine	*Alseodaphne corneri*		68
		Cryptocarya densiflora, *Cryptocarya infectoria* *Cryptocarya griffithiana* *Bocageopsis pleiosperma*		37 39
88	(+)-Nornantenine	*Cryptocarya densiflora,* *Cryptocarya infectoria* *Cryptocarya griffithiana*		37
89	(+)-*N*-Methyllaurotetanine	*Cryptocarya densiflora,* *Cryptocarya infectoria* *Cryptocarya griffithiana* *Thalictrum cirrhosum* *Bocageopsis pleiosperma*		37 43 39
90	Corydine	*Croton echinocarpus*		69
91	Norisoboldine	*Croton echinocarpus*		69
92	Isocorydine	*Alseodaphne corneri*		60
93	Norisocorydine	*Alseodaphne corneri*		60
		Unonopsis floribunda		35, 36
94	1,2-Methylenedioxy-3-methoxyaporphine	*Aconitum carmichaelii*		70
95	*N*-Formyl-asimilobine-2-*O*-β-D-glucoside	*Stephania succifera*		71
96	Isoboldine	*Annona hypoglauca*		72
		Bocageopsis pleiosperma		39
97	Anonaine	*Annona hypoglauca*		72
		Plumula nelumbinis		30
		Unonopsis floribunda		35, 36
		Unonopsis duckei		75
		Bocageopsis pleiosperma		39

No.	Names	Species	Year	Ref.
98	Nornuciferine	*Annona hypoglauca*		72
		Plumula nelumbinis		30
		Unonopsis floribunda		35, 36
		Unonopsis duckei		75
99	Actinodaphnine	*Annona hypoglauca*		72
100	Magnoflorine	*Mahonia aquifolium* *Coptis japonica* *Sinomenium acutum*		50 73 40
101	Norpurpureine	*Annona purpurea*		74
102	Purpureine	*Annona purpurea*		74
103	Nornuciferidine	*Plumula nelumbinis*		30
104	*N*-Nornuciferine	*Plumula nelumbinis*		30
105	*O*-Nornuciferine	*Plumula nelumbinis*		30
106	Nuciferine	*Plumula nelumbinis*		30
107	Roemerine	*Plumula nelumbinis*		30
108	Oxidation-nuciferine	*Plumula nelumbinis*		30
109	Asimilobine	*Unonopsis floribunda*		35, 36
		Unonopsis duckei		75
		Bocageopsis pleiosperma		39
110	Isopiline	*Unonopsis floribunda*		35, 36
111	*O*-Methylisopiline	*Unonopsis floribunda*		35, 36
112	Glaucine	*Unonopsis floribunda*		35, 36
		Unonopsis duckei		75
113	Norglaucine	*Unonopsis floribunda*		35, 36
114	(+)-*N*-Formylnorglaucine	*Unonopsis stipitata*		76
115	6a*R*-2′-Methoxycarbonyl-thaliadin	*Thalictrum cirrhosum*		43
116	6a*R*-2′-Carboxylthaliadin	*Thalictrum cirrhosum*		43
117	6a*R*-3-Methoxy-hernandalinol	*Thalictrum cirrhosum*		43
118	6a*S*-1,3,10-Trimethoxy-natalamine	*Thalictrum cirrhosum*		43
119	Predicentrine	*Thalictrum cirrhosum*		43
120	Thaliadine	*Thalictrum cirrhosum* *Thalictrum wangii*		43

No.	Names	Species	Year	Ref.
121	Glaucine	*Corydalis turtschaninovii*		77
122	(+)-8-(4′-Formylphenoxy)glaucine	*Thalictrum wangii*		46
123	(+)-8-(4′-Hydroxymethylphenoxy) glaucine	*Thalictrum wangii*		46
124	(+)-3-Methoxy-8-(4′-formylphenoxy) glaucine	*Thalictrum wangii*		46
125	4-Methoxyoxohernandaline	*Thalictrum wangii*		46
126	Dactyllactone A	*Dactylicapnos scandens*		78
127	Sallisonine E	*Sinomenium acutum*		39
128	Dauriporphine	*Sinomenium acutum*		81
129	Isomoschaltoline	*Guatteria blepharophylla*		237
130	*O*-Methylmoschatoline	*Guatteria blepharophylla*		237
131	Liriodenine	*Guatteria blepharophylla* *Unonopsis floribunda* *Unonopsis duckei*		237 35 75
132	Subsessiline	*Guatteria blepharophylla*		237
133	Lysicamine	*Guatteria blepharophylla* *Unonopsis floribunda* *Unonopsis duckei*		237 35 75
134	7-Hydroxyguatteriopsiscine	*Guatteria friesiana*		82
135	(*R*)-Dihydroguatteriscine	*Guatteria friesiana*		82
136	Guatterfriesidine	*Guatteria friesiana*		82
137	Iso-9-methoxyguatterfriesine	*Guatteria friesiana*		82
138	Norushinsunine	*Unonopsis floribunda*		35
139	Oxoglaucine	*Unonopsis floribunda*		35
140	Lanuginosine	*Unonopsis floribunda*		35
141	3-Methoxy-2′-methoxycarbonyl-oxohernandalincin	*Thalictrum cirrhosum*		43
142	3-Methoxy-oxohernandaline	*Thalictrum cirrhosum*		43
143	Oxopurpureine	*Thalictrum cirrhosum*		43
144	Oxophoebine	*Thalictrum cirrhosum*		43
145	1,2,3,9,10-Pentamethoxy-11-(4′-formylphenoxy)-7-oxoaporphine	*Thalictrum wangii*		46
146	1,2,9,10-Tetramethoxy-11-(4′-formylphenoxy)-7-oxoaporphine	*Thalictrum wangii*		46

No.	Names	Species	Year	Ref.
147	Dehydrocrebanine	*Stephania venosa*		85
148	Crebanine	*Stephania venosa*		85
149	Stephanine	*Stephania venosa*		85
150	*O*-Methylbulbocapnine	*Stephania venosa*		85
151	6-Formyl-1,2,9,10-tetramethoxy-6α,7-dehydroaporphine	*Annona crassiflora*		70
152	Glaziovine	*Unonopsis duckei*		75
153	(+)-Oridine	*Cryptocarya densiflora,* *Cryptocarya infectoria* *Cryptocarya griffithiana*		37
154	(−)-10-*O*-Acetyl prodensiflorin A	*Thalictrum wangii*		46
155	(−)-10-*O*-Acetyl prodensiflorin B	*Thalictrum wangii*		46
156	Prodensiflorin B	*Thalictrum wangii*		46
157	Dihydroglaziovine	*Thalictrum cirrhosum*		43
158	Linearisine	*Thalictrum cirrhosum*		43
159	Pronuciferine	*Plumula nelumbinis*		30
160	Stepharine	*Unonopsis* genus *Bocageopsis pleiosperma*		35, 36 39
Berberines and tetrahydroberberines isoquinoline alkaloids				
161	Berberine	*Berberis sp.* *Thalictrum foliolosum* *Chelidonium majus* *Mahonia aquifolium* *Mahonia bealei* *Coptis chinensis* *Corydalis turtschaninovii* *Ancistrocladus tectorius*		33 44 123 50 87 41 89 77 127
162	Jatrorrhizine	*Corydalis turtschaninovii*		77
163	Epiberberine	*Chelidonium majus* *Mahonia aquifolium* *Mahonia bealei*		50 87
164	Demethyleneberberine	*Chelidonium majus* *Mahonia aquifolium* *Mahonia bealei*		50 87
165	Coptisine	*Corydalis turtschaninovii*		77
166	Palmatine	*Corydalis turtschaninovii*		77
167	Pseudodehydrocorydaline	*Corydalis turtschaninovii*		77
168	Dehydrocorybulbine	*Corydalis turtschaninovii*		77

No.	Names	Species	Year	Ref.
169	Pseudocoptisine	*Corydalis turtschaninovii*		77
170	Dehydroisoapocavidine	*Corydalis tomentella*		28
171	Dehydrocheilanthifoline	*Corydalis tomentella*		28
172	Corydamine	*Fumaria officinalis*		24
173	5-Hydroxyl-8-oxyberberine	*Coptis chinensis*		41, 89
174	8,13-Dioxocoptisine hydroxide	*Coptis chinensis*		41, 89
175	8-Oxyberberine	*Coptis chinensis*		41, 89
176	8-Oxo-epiberberine	*Coptis chinensis*		41, 89
177	8-Oxocoptisine	*Coptis chinensis* *Coptis pallida* *Coptidis Rhizoma-Euodiae Fructus* couple		41, 89 90 61
178	8-Oxyberberrubine	*Coptis chinensis*		41, 89
179	Tetrahydroberberine	*Coptis chinensis*		41, 89
180	Corydaline	*Coptis chinensis* *Corydalis turtschaninovii*		41, 89 77
181	Orydalidzine	*Coptis pallida*		90
182	(−)-Corybulbine	*Coptis pallida*		90
183	(−)-Yuanhunine	*Coptis pallida*		90
184	(−)-Ophiocarpine	*Coptis pallida*		90
185	Dehydrocorydaline	*Coptis pallida*		90
186	Dihydrocoptisine	*Corydalis tomentella*		28
187	*Trans*-Protopinium	*Corydalis tomentella* *Fumaria parviflora*		28 91
188	*Cis*-Protopinium	*Corydalis tomentella* *Fumaria parviflora*		28 91
189	Thalictrifoline	*Corydalis tomentella*		28
190	Tetrahydrocoptisine	*Corydalis turtschaninovii*		77
191	13-Carboxaldehyde-8-oxocoptisine	*Coptidis Rhizoma-Euodiae Fructus* couple		61
192	Tetrahydropalmatine	*Corydalis hendersonii*		29
193	8-Hydroxy-7, 8-dihydrocoptisine	*Coptis japonica*		73
194	Cavidine	*Corydalis impatiens*		92

No.	Names	Species	Year	Ref.
195	(−)-Stylopine	*Fumaria officinalis* *Corydalis rupestris*		24 98
196	(−)-Sinactine	*Fumaria officinalis*		24
197	Cheilanthifoline	*Fumaria officinalis* *Sinomenium acutum*		24 81
198	Phellodendrine	*Phellodendri chinensis*		93
199	(−)-1-*O*-β-D-Glucoside-8-oxotetrahydropalmatine	*Stephania succifera*		71
200	*N*-Methylcanadine	*Zanthoxylum tingoassuiba*		94
201	Demethylalangiside	*Ophiorrhiza nutans*		95
202	Alangiside	*Ophiorrhiza nutans*		95
203	Isoalangiside	*Ophiorrhiza nutans* *Alangium longiflorum*		95 97
204	Scoulerine	*Corydalis dubia*		96
205	2′-*O*-*Trans*-Sinapoylisoalangiside	*Alangium longiflorum*		97
206	Rupestrine A	*Corydalis rupestris*		98
207	Rupestrine B	*Corydalis rupestris*		98
208	Rupestrine C	*Corydalis rupestris*		98
209	Rupestrine D	*Corydalis rupestris*		98
Protopine isoquinoline alkaloids				
210	Protopine	*Fumaria officinalis* *Corydalis mucronifera*		24 99
211	Cryptopine	*Fumaria officinalis*		24
Naphthylisoquinoline alkaloids				
212	Ancistectorine D	*Ancistrocladus tectorius*		105, 107
213	6-*O*-Demethyl ancistectorine D	*Ancistrocladus tectorius*		105
214	Ancistrotectoriline A	*Ancistrocladus tectorius* Unidentified *Ancistrocladus* plant *Ancistrocladus ealaensis*		105 109 113
215	Ancistrotanzanine B	*Ancistrocladus tectorius*		105
216	Ancistroealaine A	*Ancistrocladus tectorius*		105
217	6-*O*-Methylancistectorine B_1	*Ancistrocladus tectorius*		105
218	Ancistectorine B_2	*Ancistrocladus tectorius*		105
219	6-*O*-Demethyl-8-*O*-methyl-7-epi-ancistrobrevine D	*Ancistrocladus tectorius*		105

No.	Names	Species	Year	Ref.
220	Ancistrobenomine B	*Ancistrocladus tectorius*		106
221	Ancistrobenomine C	*Ancistrocladus tectorius*		106
222	6-*O*-Methylancistectorine A_3	*Ancistrocladus tectorius*		106
223	4′-*O*-Demethylancistectorine A_2	*Ancistrocladus tectorius*		106
224	Ancistectorine A_3	*Ancistrocladus tectorius*		106
225	Ancistrocladine	*Ancistrocladus tectorius* *Ancistrocladus ileboensis*		106 108
226	Hamatine	*Ancistrocladus tectorius*		106
		Ancistrocladus congolensis		110
227	5′-*O*-Demethylhamatine	*Ancistrocladus tectorius*		106
228	Ancistrocline	*Ancistrocladus tectorius*		106
229	Ancistrocladinine	*Ancistrocladus tectorius*		106
230	Hamatinine	*Ancistrocladus tectorius*		106
231	Ancistectorine A_2	*Ancistrocladus tectorius*		106
232	5-*Epi*-ancistectorine A_2	*Ancistrocladus tectorius*		106
233	Ancistrobenomine A	*Ancistrocladus tectorius*		106
234	6-*O*-Methylancistrocladine	*Ancistrocladus tectorius*		106
235	6-*O*-Methylhamatine	*Ancistrocladus tectorius* Unidentified *Ancistrocladus* plant		106 109
		Ancistrocladus congolensis		110
236	4′-*O*-Demethylancistrocladine	*Ancistrocladus tectorius* Unidentified *Ancistrocladus* plant		106 109
237	5′-*O*-Demethylhamatine	*Ancistrocladus tectorius* *Ancistrocladus congolensis*		106 110
238	6-*O*-Methylhamatinine	*Ancistrocladus tectorius* *Ancistrocladus congolensis*		106 110
239	5′-*O*-Demethylhamatinine	*Ancistrocladus tectorius*		106
240	Korupensamine D	*Ancistrocladus congolensis*		110
241	Ancistrocyclinone A	*Ancistrocladus tectorius*		107
242	Ancistrocyclinone B	*Ancistrocladus tectorius*		107
243	Ancistrocladinium A (a/b)	*Ancistrocladus tectorius* Unidentified *Ancistrocladus* plant *Ancistrocladus ealaensis*		107 109 113
244	4′-*O*-Demethylancistrocladinium A (a/b)	*Ancistrocladus tectorius*		107

No.	Names	Species	Year	Ref.
245	6,4′-*O*,*O*-Didemethylancistrocladinium A (a/b)	*Ancistrocladus tectorius* *Ancistrocladus ealaensis*		107 113
246	Ancistrotectorine B_1	*Ancistrocladus tectorius*		107
247	Shuangancistrotectorine C	*Ancistrocladus tectorius*		107
248	Ancistrotectoquinone B (a/b)	*Ancistrocladus tectorius*		107
249	Dioncophylline F	*Ancistrocladus ileboensis*		108
250	Dioncophylline C_2	*Ancistrocladus ileboensis*		108
251	Dioncophylline D_2	*Ancistrocladus ileboensis*		108
252	5′-*O*-Methyldioncophylline D	*Ancistrocladus ileboensis*		108
253	Dioncophylline A	*Ancistrocladus ileboensis*		108
254	4′-*O*-Demethyldioncophylline A	*Ancistrocladus ileboensis*		108
255	Ancistrocladisine B	*Ancistrocladus ileboensis*		108
256	Ancistrobrevine C	*Ancistrocladus ileboensis*		108
257	Ancistrocladisine A	*Ancistrocladus ileboensis*		108
258	Ancistrobertsonine D	*Ancistrocladus ileboensis*		108
259	Ancistroyafungine A	Unidentified *Ancistrocladus* plant		109
260	Ancistroyafungine B	Unidentified *Ancistrocladus* plant		109
261	Ancistroyafungine C	Unidentified *Ancistrocladus* plant		109
262	Ancistroyafungine D	Unidentified *Ancistrocladus* plant		109
263	Ancistroguineine A	Unidentified *Ancistrocladus* plant		109
264	Ancistrobertsonine A	Unidentified *Ancistrocladus* plant		109
265	Ancistrobrevine B	Unidentified *Ancistrocladus* plant *Ancistrocladus congolensis*		109 110
266	6,5′-*O*,*O*-Didemethylancistroealaine A	Unidentified *Ancistrocladus* plant		109
267	6-*O*-Demethylancistroealaine A	Unidentified *Ancistrocladus* plant		109
268	7-*Epi*-ancistrobrevine D	Unidentified *Ancistrocladus* plant		109
269	Ancistrocladinium B	Unidentified *Ancistrocladus* plant		109
270	Michellamine A_2	*Ancistrocladus congolensis* Unidentified *Ancistrocladus* plant		110 111
271	Michellamine A_3	*Ancistrocladus congolensis*		110

No.	Names	Species	Year	Ref.
272	Michellamine A_4	*Ancistrocladus congolensis*		110
273	Michellamine B_2	*Ancistrocladus congolensis*		110
274	Michellamine B_3	*Ancistrocladus congolensis*		110
275	Michellamine A	*Ancistrocladus congolensis*		110
276	Michellamine B	*Ancistrocladus congolensis*		110
277	Michellamine A_6	Unidentified *Ancistrocladus* plant		111
278	Michellamine A_7	Unidentified *Ancistrocladus* plant		111
279	Michellamine B_4	Unidentified *Ancistrocladus* plant		111
280	Michellamine B_5	Unidentified *Ancistrocladus* plant		111
281	Ancistrobonsoline A_1	Unidentified *Ancistrocladus* plant		111
282	Ancistrobonsoline A_2	Unidentified *Ancistrocladus* plant		111
283	Ancistroealaine C	Unidentified *Ancistrocladus* plant *Ancistrocladus ealaensis*		111 113
284	Korupensamine A	Unidentified *Ancistrocladus* plant		111
		Ancistrocladus ealaensis		113
285	Korupensamine B	Unidentified *Ancistrocladus* plant		111
286	Michellamine E	Unidentified *Ancistrocladus* plant		111
287	Ealapasamine A	*Ancistrocladus ealaensis*		112
288	Ealapasamine B	*Ancistrocladus ealaensis*		112
289	Ealapasamine C	*Ancistrocladus ealaensis*		112
290	Mbandakamine A	*Ancistrocladus ealaensis*		107
291	Mbandakamine C	*Ancistrocladus ealaensis*		113
292	Mbandakamine D	*Ancistrocladus ealaensis*		113
293	Mbandakamine E	*Ancistrocladus ealaensis*		113
294	Mbandakamine A	*Ancistrocladus ealaensis*		113
295	Ancistroealaine D	*Ancistrocladus ealaensis*		113
296	Ancistroealaine E	*Ancistrocladus ealaensis*		113
297	Ancistroealaine F	*Ancistrocladus ealaensis*		113

No.	Names	Species	Year	Ref.
298	Ancistrolikokine B	*Ancistrocladus ealaensis*		113
Phenanthridine alkaloids				
299	Sanguinarine	*Chelidonium majus*		124
300	Chelidonine	*Chelidonium majus*		125
301	Homochelidonine	*Chelidonium majus*		125
302	(1′*R*,6*R*/1′*S*,6*S*)-1-(Dihydrochelerythrine-6-yl) ethanol	*Chelidonium majus*		126
303	(1′*S*,6*R*/1′*R*,6*S*)-1-(Dihydrochelerythrine-6-yl) ethanol	*Chelidonium majus*		126
304	(1′*R*,6*R*)/(1′*S*,6*S*)-1-(Dihydrosanguinarine-6-yl)ethanol	*Chelidonium majus*		126
305	(1′*S*,6*R*)/(1′*R*,6*S*)-1-(Dihydrosanguinarine-6-yl)ethanol	*Chelidonium majus*		126
306	(±)-Ethyl 2-(dihydrosanguinarine-6-yl) acetate	*Chelidonium majus*		126
307	(±)-Ethyl dihydrosanguinarine-6- carboxylate	*Chelidonium majus*		126
308	Heitziquinone	*Zanthoxylum heitzii*		127
309	Dihydronitidine	*Zanthoxylum heitzii*		127
310	Isoarnottianamide	*Zanthoxylum heitzii*		127
311	Rhoifoline B	*Zanthoxylum heitzii*		127
312	Dihydrocheleryhtrine	*Zanthoxylum tingoassuiba*		94
313	Decarine	*Zanthoxylum myriacanthum var. pubescens*		128
314	Corynoline	*Corydalis bungeana*		129
315	Ambinine	*Corydalis ambigua var. amurensis*		130
316	Norsanguinarine	*Corydalis tomentella*		28
317	(−)-6-Acetonyldihydrisanguinarine	*Corydalis tomentella* *Corydali pallida*		28 90
318	Cavidilinine	*Corydalis tomentella*		28
319	8-Methoxydihydrosanguinarine	*Corydalis mucronifera*		99
320	Dihydrosanguinarine	*Corydalis mucronifera*		99
321	Lycorine	Amaryllidaceae family		136
322	Acetycaranine	Amaryllidaceae family		136
323	Caranine	Amaryllidaceae family		136

No.	Names	Species	Year	Ref.
324	Galanthine	Amaryllidaceae family		136
325	9-*O*-Demthylgalanthine	Amaryllidaceae family		136
326	Haemanthamine	Amaryllidaceae family		136
		Narcissus poeticus cv. Pink Parasol		138
327	Haemanthidine	Amaryllidaceae family		136
328	Ambelline	Amaryllidaceae family		136
329	11-*O*-Acetylambelline	Amaryllidaceae family		136
330	1-*O*-Acetylbulbisine	Amaryllidaceae family		136
331	Undulatine	Amaryllidaceae family		136
332	Crinamidine	Amaryllidaceae family		136
333	Buphanamine	Amaryllidaceae family		136
334	Crinine	Amaryllidaceae family		136
335	6,7,11b,11c-Didehydrolycorinium salt	*Crinum firmifolium* *Crinum hardyi*		137
336	*Seco*-isopowellaminone	*Narcissus poeticus* cv. Pink Parasol		138
337	Incartine	*Narcissus poeticus* cv. Pink Parasol		138
Manzamine alkaloids				
338	Manzamine A	*Acanthostrongylophora sp.* sponge		146
339	Kepulauamine A	*Acanthostrongylophora sp.* sponge		146
340	Manzamine B *N*-oxide	*Acanthostrongylophora sp.* sponge		146
341	3,4-Dihydromanzamine B *N*-oxide	*Acanthostrongylophora sp.* sponge		146
342	11-Hydroxymanzamine J	*Acanthostrongylophora sp.* sponge		146
343	31-Hydroxymanzamine A	*Acanthostrongylophora sp.* sponge		146
344	32,33-Dihydro-31-hydroxymanzamine A	*Acanthostrongylophora sp.* sponge		146
345	6-Deoxymanzamine X	*Acanthostrongylophora sp.* sponge		146
346	Manzamine B	*Acanthostrongylophora sp.* sponge		146
347	*neo*-Kauluamine	*Acanthostrongylophora sp.* sponge		146
Emetine isoquinoline alkaloids				
348	Emetine	*Alangiaceae, Icacinaceae*, and *Rubiaceae*		149

No.	Names	Species	Year	Ref.
349	7′,10-Dide-*O*-methylcephaeline	*Ophiorrhiza nutans*		95
350	10-*O*-Demethylprotoemetine	*Ophiorrhiza nutans*		95
351	8-Hydroxytubulosine	*Alangium longiflorum*		97
352	9-Demethyltubulosine	*Alangium longiflorum*		97
353	(+)-Sebiferine	*Dehaasia longipedicellata*		38
354	(−)-Milonine	*Dehaasia longipedicellata*		38
355	Sinomacutine A	*Sinomenium acutum*		40
356	Sinomacutine B	*Sinomenium acutum*		40
357	Sinomacutine C	*Sinomenium acutum*		40
358	Cephalonine-2-*O*-β-D-glucopyranoside	*Sinomenium acutum*		40
359	Sinomenine	*Sinomenium acutum*		40
		Sinomenium acutum		81
360	Sinoacutine	*Sinomenium acutum*		40
361	8-Demethoxycephatonine	*Sinomenium acutum*		81
362	7(*R*)-7,8-dihydrosinomenine	*Sinomenium acutum*		81
363	8-Demethoxyrunanine	*Sinomenium acutum*		81
364	14-Episinomenine	*Sinomenium acutum*		81
365	Sinomenine *N*-oxide	*Sinomenium acutum*		81
366	Salutaridine	*Sinomenium acutum*		81
367	Acutumine	*Sinomenium acutum*		81
368	Acutumidine	*Sinomenium acutum*		81
369	Dauricumine	*Sinomenium acutum*		81
370	Pallidine	*Unonopsis floribunda*		36
371	*O*-Methylflavinantine	*Thalictrum cirrhosum*		43
Phthalideisoquinoline alkaloids				
372	(+)-Bicuculline	*Fumaria officinalis*		24
373	(+)-Corlumine	*Viola tianschanica*		150
374	(9*S*, 7′*S*) Tomentelline A	*Corydalis tomentella*		28

No.	Names	Species	Year	Ref.
375	(9*S*, 7′*R*) Tomentelline A	*Corydalis tomentella*		28
376	(9*R*, 7′*S*) Tomentelline B	*Corydalis tomentella*		28
377	Adlumidine	*Corydalis tomentella* *Corydalis mucronifera*		28 99
378	(+)-Capnoidine	*Corydalis tomentella*		28
379	Mucroniferanine A	*Corydalis mucronifera*		99
380	Mucroniferanine B	*Corydalis mucronifera*		99
381	Mucroniferanine C	*Corydalis mucronifera*		99
382	Mucroniferanine D	*Corydalis mucronifera*		99
383	Mucroniferanine E	*Corydalis mucronifera*		99
384	Mucroniferanine F	*Corydalis mucronifera*		99
385	Mucroniferanine G	*Corydalis mucronifera*		99
386	(±)-Hypecorinine	*Corydalis mucronifera*		99
387	(−)-7′-*O*-Methylegenine	*Corydalis mucronifera*		99
388	Sibiricine	*Corydalis mucronifera*		99
389	(+)-Humosine A	*Corydalis mucronifera*		99
390	Capnoidine	*Corydalis dubia*		151
Benzopyrroloisoquinoline Alkaloids				
391	Tengerensine	*Ficus fistulosa* var. *tengerensis*		152
Phenylethyl tetrahydroisoquinoline alkaloids				
392	Fumarostrejdine	*Fumaria officinalis*		24
393	(±)-*O*-Methylfumarofine	*Fumaria officinalis*		24
Others				
394	Coptichine	*Coptidis Rhizoma–Euodiae Fructus* couple		61
395	Coptisonine	*Coptis chinensis*		89
396	Sallisonine D	*Sinomenium acutum*		40
397	Alternamine A	*Alternanthera littoralis*		153
398	(±)-7-Benzyloxy-1-(3-benzyloxy-4-methoxyphenethyl)-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline oxalate	Chemical library		154
399	Tomentelline C	*Corydalis tomentella*		28

No.	Names	Species	Year	Ref.
400	Tomentelline D	*Corydalis tomentella*		28
401	6,7-Methylenedioxy-2-(6-acetyl-2,3-methylenedioxybenzyl)-1(2*H*)-isoquinolinone	*Corydalis tomentella*		28
402	Oleracein E	*Portulaca oleracea*		31
403	Pipermullesine B	*Piper mullesua*		155
404	Pipermullesine C	*Piper mullesua*		155
405	Delavatine A	*Incarvillea delavayi*		156
406	Neotatarine	*Acorus calamus*		158

Table 2

The cytotoxic activity of isoquinoline alkaloids

Compound	Cell lines or organism	Biological results	Positive drug	Ref.
3,8-Diolisoquinoline (**1**)	HT-29 U87 A549 Bel-7402 MGC-803 Hela cells	4.40 μM (IC_{50}) 3.46 μM (IC_{50}) 6.20 μM (IC_{50}) 8.05 μM (IC_{50}) 25.75 μM (IC_{50}) >30.00μM (IC_{50})	Paclitaxel 0.77 μM (IC_{50}), 2.74 μM (IC_{50}), 2.67 μM (IC_{50}), 1.98 μM (IC_{50}), 3.87 μM (IC_{50}), 0.90 μM (IC_{50})	22
1-Methoxy-4,5-diolisoquinoline (**2**)	HT-29 U87 A549 Bel-7402 MGC-803 Hela cells	1.19 μM (IC_{50}) 2.14 μM (IC_{50}) 2.46 μM (IC_{50}) 4.10 μM (IC_{50}) 9.73 μM (IC_{50}) 16.15 μM (IC_{50})	Paclitaxel 0.77 μM (IC_{50}), 2.74 μM (IC_{50}), 2.67 μM (IC_{50}), 1.98 μM (IC_{50}), 3.87 μM (IC_{50}), 0.90 μM (IC_{50})	22
4-Methoxy-1,5-dihydroisoquinoline (**3**)	HT29 A549 Bel7402 MGC803 U87	18.63 μM (IC_{50}) 29.25 μM (IC_{50}) 29.92 μM (IC_{50}) 35.26 μM (IC_{50}) 41.20 μM (IC_{50})	--	23
6,7-Dimethoxy-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid (**7**)	Huh-7	13.97 μM (EC_{50})		26
(−)-Reticuline (**19**)	A549 A375 BxPC-3	>200.00 μM (IC_{50}) 97.60 μM (IC_{50}) 82.57 μM (IC_{50})	Cisplatin 17.52 μM, 35.9 μM, 26.86 μM (IC_{50})	38
Hernandezine (**43**)	pcDNA-HEK 293 (parental) MDR19-HEK293 (resistant) KB-3-1(parental) KB-V-1 (resistant)	3.85, 27.25 nM (IC_{50}, 500 nm + Doxorubicine); 0.11 and 0.10 μM (IC_{50}, 500 nM + Doxorubicine)	5.28 and 504.65 nM (IC_{50}, Doxorubicine only) 0.15 and 5.07 μM (IC_{50}, doxorubicine only)	45
6,7,12-Trimethoxy-2-methyl-13-hydroxy-11-(4′-formylphenoxy) benzylisoquin oline (**44**)	GSC-3#	43.15 μM (IC_{50})	Taxol IC_{50} 15.92 μM; Temozolomide IC_{50} > 257.53 μM.	46
(−)-*O*-*O*-Dimethylgrisabine (**51**)	A549 A375 BxPC-3	>200.00 μM (IC_{50}) 82.85 μM (IC_{50}) >200.00 μM (IC_{50})	Cisplatin 17.52 μM, 35.90 μM, 26.86 μM (IC_{50})	38
Coptichic aldehyde (**63**)	NCI-N87 Caco-2	30.14 μM (IC_{50}) >100.00 μM (IC_{50})	Vinorelbine 12.19 μM (IC_{50}), 21.64 μM (IC_{50})	61
(−)-Boldine (**77**)	A549 A375 BxPC-3	117.57 μM (IC_{50}) 112.53 μM (IC_{50}) 45.50 μM (IC_{50})	Cisplatin 17.52 μM, 35.90 μM, 26.86 μM (IC_{50})	38

Compound	Cell lines or organism	Biological results	Positive drug	Ref.
(−)-Norboldine (**78**)	A549 A375 BxPC-3	>200.00 μM (IC_{50}) 82.89 μM (IC_{50}) 27.06 μM (IC_{50})	Cisplatin 17.52 μM, 35.90 μM, 26.86 μM (IC_{50})	38
(+)-8-(4′-Formylphenoxy) glaucine (**113**)	GSC-3#	40.48 μM (IC_{50})	Taxol IC_{50} 15.92 μM; Temozolomide IC_{50} > 257.53 μM.	46
(+)-3-Methoxy-8-(4′-formylphenoxy) glaucine (**115**)	GSC-3#	30.12 μM (IC_{50})	Taxol IC_{50} 15.92 μM; Temozolomide IC_{50} > 257.53 μM.	46
1,2,3,9,10-Pentamethoxy-11-(4′-formylphenoxy)-7-oxoaporphine (**136**)	GSC-3#	32.52 μM (IC_{50})	Taxol IC_{50} 15.92 μM; Temozolomide IC_{50} > 257.53 μM.	46
1,2,9,10-Tetramethoxy-11-(4′-formylphenoxy)-7-oxoaporphine (**137**)	GSC-3#	32.81 μM (IC_{50})	Taxol IC_{50} 15.92 μM; Temozolomide IC_{50} > 257.53 μM.	46
Dehydrocrebanine (**138**)	HeLa MDA-MB231 MCF-7	18.73 μM (IC_{50}) 14.52 μM (IC_{50}) 10.64 μM (IC_{50})	Paclitaxel 2.29 μM (IC_{50}), 2.56 μM (IC_{50}), 3.99 μM (IC_{50})	85
Crebanine (**139**)	HeLa MDA-MB231 MCF-7	48.13 μM (IC_{50}) 38.94 μM (IC_{50}) 30.50 μM (IC_{50})	Paclitaxel 2.29 μM (IC_{50}), 2.56 μM (IC_{50}), 3.99 μM (IC_{50})	85
Stephanine (**140**)	HeLa MDA-MB231 MCF-7	3.33 μM (IC_{50}) 5.66 μM (IC_{50}) 6.49 μM (IC_{50})	Paclitaxel 2.29 μM (IC_{50}), 2.56 μM (IC_{50}), 3.99 μM (IC_{50})	85
O-Methylbulbocapnine (**141**)	HeLa MDA-MB231 MCF-7	70.37 μM (IC_{50}) 56.59 μM (IC_{50}) 39.36 μM (IC_{50})	Paclitaxel 2.29 μM (IC_{50}), 2.56 μM (IC_{50}), 3.99 μM (IC_{50})	85
Berberine (**151**)	HL60 AZ521 SK-BR-3 B16 melanoma	29.40 μM (IC_{50}) 2.60 μM (IC_{50}) 21.00 μM (IC_{50}) Melanin content 8.9% at 10 μM	Cisplatin 4.20 μM (IC_{50}), 9.50 μM (IC_{50}), 18.80 μM (IC_{50}) Melanin content 92.7% for arbutin at 10 μM	33
8-Oxocoptisine (**168**)	NCI-N87 Caco-2	20.31 μM (IC_{50}) >100.00 μM (IC_{50})	Vinorelbine 12.19 μM (IC_{50}), 21.64 μM (IC_{50})	61
13-Carboxaldehyde-8-oxocoptisine (**182**)	NCI-N87 Caco-2	35.98 μM (IC_{50}) >100.00 μM (IC_{50})	Vinorelbine 12.19 μM (IC_{50}), 21.64 μM (IC_{50})	61
Ancistectorine D (**203**)	CCRF-CEM CEM/ADR5000	4.50 μM (IC_{50}) 25.83 μM (IC_{50})	Doxorubicin 0.02 μM (IC_{50}), 30.07 μM (IC_{50})	105
Ancistrotectoriline A (**205**)	PANC-1	67.80 μM (PC_{50})	Arctigenin 0.80 μM (PC_{50})	109
Ancistrobenomine B (**211**)	CCRF-CEM CEM/ADR5000	3.50 μM (IC_{50}) 21.38 μM (IC_{50})	Doxorubicin 0.02 μM (IC_{50}), 30.07 μM (IC_{50})	106
6-*O*-Methylhamatine (**226**)	PANC-1	31.90 μM (PC_{50})	Arctigenin 0.80 μM (PC_{50})	109
4′-*O*-Demethylancistrocladine (**227**)	PANC-1	11.20 μM (PC_{50})	Arctigenin 0.80 μM (PC_{50})	109

Compound	Cell lines or organism	Biological results	Positive drug	Ref.
Ancistrocyclinone A (**231**)	CCRF-CEM CEM/ADR5000	16.21 μM (IC_{50}) 25.32 μM (IC_{50})	Doxorubicin 0.02 μM, 30.07 (IC_{50})	107
Ancistrocladinium A (**233**)	CCRF-CEM CEM/ADR5000	1.40 μM (IC_{50}) >100.00 μM (IC_{50})	Doxorubicin 0.02 μM, 30.07 (IC_{50})	107
4′-*O*-Demethylancistrocladinium A (**234**)	CCRF-CEM CEM/ADR5000	1.50 μM (IC_{50}) >100.00 μM (IC_{50})	Doxorubicin 0.02 μM, 30.07 μM (IC_{50})	107
6,4′-*O,O*-Didemethylancistrocladinium A (**235**)	CCRF-CEM CEM/ADR5000	>100.00 μM (IC_{50}) >100.00 μM (IC_{50})	Doxorubicin 0.02 μM, 30.07 μM (IC_{50})	107
Dioncophylline F (**239**)	L6 cells INA-6 PMBCs	14.52 μM (IC_{50}) 21.00 μM (EC_{50}) 16.00 μM (EC_{50})	Podophyllotoxin 0.02 μM (IC_{50}) Melphalan 2.00 μM (EC_{50}); 3.00 μM (EC_{50})	108
Dioncophylline C_2 (**240**)	L6 cells	43.31 μM (IC_{50})	Podophyllotoxin 0.02 μM (IC_{50})	108
Dioncophylline D_2 (**241**)	L6 cells INA-6	62.84 μM (IC_{50}) 32.00 μM (EC_{50})	Podophyllotoxin 0.02 μM (IC_{50}) Melphalan 2.00 μM (EC_{50})	108
5′-*O*-Methyldioncophylline D (**242**)	L6 cells INA-6 PMBCs	4.02 μM (IC_{50}) 2.60 μM (EC_{50}) 19.00 μM (EC_{50})	Podophyllotoxin 0.02 μM (IC_{50}) Melphalan 2.00 μM (EC_{50}); 3.00 μM (EC_{50})	108
Dioncophylline A (**243**)	INA-6	0.22 μM (EC_{50})	Melphalan 2.00 μM (EC_{50})	108
4′-*O*-Demethyldioncophylline A (**244**)	INA-6 INA-6 PMBCs	2.70 μM (EC_{50}) *P* 16.00 μM (EC_{50}) *M* 50.00 μM (EC_{50})*M*	Melphalan 2.00 μM (EC_{50}) 3.00 μM (EC_{50})	108
Ancistrobrevine C (**246**)	L6 cells	34.85 μM (IC_{50})	Podophyllotoxin 0.02 μM (IC_{50})	108
Ancistrocladisine A (**247**)	L6 cells INA-6	30.01 μM (IC_{50}) 4.80 μM (EC_{50})	Podophyllotoxin 0.02 μM (IC_{50}) Melphalan 2.00 μM (EC_{50})	108
Ancistroyafungine A (**249**)	PANC-1	22.70 μM (PC_{50})	Arctigenin 0.80 μM (PC_{50})	109
Ancistroyafungine B (**250**)	PANC-1	7.60 μM (PC_{50})	Arctigenin 0.80 μM (PC_{50})	109
Ancistroyafungine C (**251**)	PANC-1	15.00 μM (PC_{50})	Arctigenin 0.80 μM (PC_{50})	109
Ancistroyafungine D (**252**)	PANC-1	9.70 μM (PC_{50})	Arctigenin 0.80 μM (PC_{50})	109
Ancistroguineine A (**253**)	PANC-1	15.80 μM (PC_{50})	Arctigenin 0.80 μM (PC_{50})	109
Ancistrobertsonine A (**254**)	PANC-1	11.80 μM (PC_{50})	Arctigenin 0.80 μM (PC_{50})	109
Ancistrobrevine B (**255**)	PANC-1	20.20 μM (PC_{50})	Arctigenin 0.80 μM (PC_{50})	109
6,5′-*O,O*-Didemethylancistroealaine A (**256**)	PANC-1	9.80 μM (PC_{50})	Arctigenin 0.80 μM (PC_{50})	109
6-*O*-Demethylancistroealaine A (**257**)	PANC-1	14.00 μM (PC_{50})	Arctigenin 0.80 μM (PC_{50})	109

Compound	Cell lines or organism	Biological results	Positive drug	Ref.
7-Epi-ancistrobrevine D (**258**)	PANC-1	29.90 μM (PC_{50})	Arctigenin 0.80 μM (PC_{50})	109
Michellamine A_2 (**260**)	Hela PANC-1	32.10 μM (IC_{50}) 19.30 μM (IC_{50})	5-Fluorouracil 13.90 μM; Arctigenin 0.80 μM (IC_{50})	111
Michellamine A_6 (**268**)	Hela PANC-1	14.80 μM (IC_{50}) 54.20 μM (IC_{50})	5-Fluorouracil 13.90 μM; Arctigenin 0.80 μM (IC_{50})	111
Michellamine A_7 (**269**)	Hela PANC-1	20.60 μM (IC_{50}) 24.30 μM (IC_{50})	5-Fluorouracil 13.90 μM; Arctigenin 0.80 μM (IC_{50})	111
Michellamine B_4 (**270**)	Hela PANC-1	46.30 μM (IC_{50}) 50.30 μM (IC_{50})	5-Fluorouracil 13.90 μM; Arctigenin 0.80 μM (IC_{50})	111
Michellamine B_5 (**271**)	Hela PANC-1	29.80 μM (IC_{50}) 60.20 μM (IC_{50})	5-Fluorouracil 13.90 μM; Arctigenin 0.80 μM (IC_{50})	111
Ancistrobonsoline A_1 (**272**)	Hela PANC-1	14.30 μM (IC_{50}) 7.50 μM (IC_{50})	5-Fluorouracil 13.90 μM; Arctigenin 0.80 μM (IC_{50})	111
Ancistrobonsoline A_2 (**273**)	Hela PANC-1	21.50 μM (IC_{50}) 12.10 μM (IC_{50})	5-Fluorouracil 13.90 μM; Arctigenin 0.80 μM (IC_{50})	111
Ancistroealaine C (**274**)	Hela PANC-1	30.50 μM (IC_{50}) >100.00 μM (IC_{50})	5-Fluorouracil 13.90 μM; Arctigenin 0.80 μM (IC_{50})	111
Korupensamine A (**275**)	Hela PANC-1	48.30 μM (IC_{50}) >100.00 μM (IC_{50})	5-Fluorouracil 13.90 μM; Arctigenin 0.80 μM (IC_{50})	111
Korupensamine B (**276**)	Hela PANC-1	37.80 μM (IC_{50}) 94.90 μM (IC_{50})	5-Fluorouracil 13.90 μM; Arctigenin 0.80 μM (IC_{50})	111
Michellamine E (**277**)	Hela PANC-1	8.80 μM (IC_{50}) 18.90 μM (IC_{50})	5-Fluorouracil 13.90 μM; Arctigenin 0.80 μM (IC_{50})	111
Mbandakamine A (**281**)	CCRF-CEM CEM/ADR5000	7.40 μM (IC_{50}) 23.88 μM (IC_{50})	Doxorubicin 0.02 μM, 30.07 μM (IC_{50})	113
Mbandakamine C (**282**)	CCRF-CEM CEM/ADR5000	1.50 μM (IC_{50}) 27.71 μM (IC_{50})	Doxorubicin 0.02 μM, 30.07 μM (IC_{50})	113
Mbandakamine D (**283**)	CCRF-CEM, CEM/ADR5000	2.96 μM (IC_{50}) 19.03 μM (IC_{50})	Doxorubicin 0.02 μM, 30.07 μM (IC_{50})	113
Ancistroealaine F (**288**)	CCRF-CEM CEM/ADR5000	11.69 μM (IC_{50}) 19.94 μM (IC_{50})	Doxorubicin 0.02 μM, 30.07 μM (IC_{50})	113
Chelidonine (**291**)	MOLT-4, Jurkat, HL-60, Raji, U-937, HEL 92.1.7., PBMCs, MRC-5, WI-38	4.60, 2.20, 4.40, 3.20, 5.00, 3.40, >10.00, 1.8., >10.00 μM (IC_{50})	--	125
Homochelidonine (**292**)	MOLT-4, Jurkat, HL-60, Raji, U-937, HEL 92.1.7., PBMCs, MRC-5, WI-38	4.80, 5.60, 8.30, 6.80, >10.00, >10.00, >10.00, >10.00, >10.00 μM (IC_{50})		125

Compound	Cell lines or organism	Biological results	Positive drug	Ref.
Lycorine (**312**)	HL-60, Jurkat, MOLT-4, A549, H1299, COLO- 201, HT-29, SW-480, AGS, PANC-1, A2780, HeLa, BT-549, MCF-7, MDA-MD-231, SAOS-2, SK-BR-3	0.80-1.40 μM (IC_{50})	--	136
Haemanthamine (**317**)	HL-60, Jurkat, MOLT-4, A549, H1299, COLO-201, HT-29, SW-480, AGS, PANC-1, A2780, HeLa, BT-549, MCF-7, MDA-MD-231, SAOS-2, SK-BR-3	0.30-9.80 μM (IC_{50})	--	136
Haemanthidine (**318**)	HL-60, Jurkat, MOLT-4, A549, H1299, COLO- 201, HT-29, SW-480, AGS, PANC-1, A2780, HeLa, BT-549, MCF-7, MDA-MD-231, SAOS-2, SK-BR-3	1.60-9.70 μM (IC_{50})	--	136
Manzamine A (**329**)	A549 K562	8.30 μM (IC_{50}) 11.00 μM (IC_{50})	Doxorubicin 0.92 μM (IC_{50}) and 1.10 μM (IC_{50})	146
Kepulauamine A (**330**)	A549 K562	4.60 μM (IC_{50}) 7.20 μM (IC_{50})	Doxorubicin 0.92 μM (IC_{50}) and 1.10 μM (IC_{50})	146
Manzamine B *N*-oxide (**331**)	A549 K562	12.00 μM (IC_{50}) 9.80 μM (IC_{50})	Doxorubicin 0.92 μM (IC_{50}) and 1.10 μM (IC_{50})	146
3,4-Dihydromanzamine B *N*-oxide (**332**)	A549 K562	5.80 μM (IC_{50}) 5.20 μM (IC_{50})	Doxorubicin 0.92μM (IC_{50}) and 1.1μM (IC_{50})	146
11-Hydroxymanzamine J (**333**)	A549 K562	6.20 μM (IC_{50}) 8.20 μM (IC_{50})	Doxorubicin 0.92 μM (IC_{50}) and 1.10 μM (IC_{50})	146
31-Hydroxymanzamine A (**334**)	A549 K562	5.80 μM (IC_{50}) 7.20 μM (IC_{50})	Doxorubicin 0.92 μM (IC_{50}) and 1.10 μM (IC_{50})	146
32,33-Dihydro-31-hydroxymanzamine A (**335**)	A549 K562	8.20 μM (IC_{50}) 8.40 μM (IC_{50})	Doxorubicin 0.92 μM (IC_{50}) and 1.10 μM (IC_{50})	146
6-Deoxymanzamine X (**336**)	A549 K562	6.70 μM (IC_{50}) 9.10 μM (IC_{50})	Doxorubicin 0.92 μM (IC_{50}) and 1.10 μM (IC_{50})	146
Manzamine B (**337**)	A549 K562	6.50 μM (IC_{50}) 9.60 μM (IC_{50})	Doxorubicin 0.92 μM (IC_{50}) and 1.10 μM (IC_{50})	146
neo-Kauluamine (**338**)	A549 K562	13.00 μM (IC_{50}) 12.00 μM (IC_{50})	Doxorubicin 0.92 μM (IC_{50}) and 1.10 μM (IC_{50})	146
8-Hydroxytubulosine (**342**)	A549 MDA-MB-231 MCF-7 KB KB-VIN	0.21 μM (IC_{50}) 0.06 μM (IC_{50}) 0.12 μM (IC_{50}) 0.09 μM (IC_{50}) 8.90 μM (IC_{50})	Doxorubicin 0.48 μM, 0.78 μM (IC_{50}), 0.72 μM (IC_{50}), 0.82 μM (IC_{50}), >1.00 μM (IC_{50})	97

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Compound	Cell lines or organism	Biological results	Positive drug	Ref.
9-Demethyltubulosine (**343**)	A549 MDA-MB-231 MCF-7 KB KB-VIN	0.36 μM (IC_{50}) 0.19 μM (IC_{50}) 0.25 μM (IC_{50}) 0.29 μM (IC_{50}) >10.00 μM (IC_{50})	Doxorubicin 0.48 μM, 0.78 μM (IC_{50}), 0.72 μM (IC_{50}), 0.82 μM (IC_{50}), >1.00 μM (IC_{50})	97
(+)-Sebiferine (**344**)	A549 A375 BxPC-3	>200.00 μM (IC_{50}) >200.00 μM (IC_{50}) 93.39 μM (IC_{50})	Cisplatin 17.52 μM, 35.90 μM, 26.86 μM (IC_{50})	38
(−)-Milonine (**345**)	A549 A375 BxPC-3	>200.00 μM (IC_{50}) >200.00 μM (IC_{50}) >200.00 μM (IC_{50})	Cisplatin 17.52 μM, 35.90 μM, 26.86 μM (IC_{50})	38
(+)-Tengerensine (**382**)	MDA-MB-468	7.40 μM (IC_{50})	Paclitaxel 0.01 μM (IC_{50})	152
Coptichine (**385**)	NCI-N87 Caco-2	8.92 μM (IC_{50}) >100.00 μM (IC_{50})	Vinorelbine 12.19 μM (IC_{50}), 21.64 μM (IC_{50})	61
Noroxyhydrastinine (**389**)	B16 melanoma cells	Melanin content 76.1% at 10.00 μM	Melanin content 92.7% for arbutin at 10.00 μM	33
Delavatine A (**401**)	MCF7 HCT116 SKOV3 SMMC-7721 HeLa	22.32 μM (IC_{50}) 19.90 μM (IC_{50}) 15.43 μM (IC_{50}) 17.27 μM (IC_{50}) 23.83 μM (IC_{50})	Celastrol 2.04 μM (IC_{50}), 3.20 μM (IC_{50}), 3.93 μM (IC_{50}), 1.31μM (IC_{50}), 1.73 μM (IC_{50})	156
Neotatarine (**402**)	PC12	At 2.00, 4.00, 8.00 μM inhibit $A_{\beta 25-35}$ induced cell death	--	158

INA-6 Multiple Myeloma Cells and Peripheral Mononuclear Blood Cells (PMBCs); Human breast cancer cell lines: MDA-MB-468, HL-60 (acute promyelocytic leukemia), Jurkat (acute T cell leukemia), MOLT-4 (acute lymphoblastic leukemia), A549 (lung carcinoma), H1299 (non-small cell lung cancer), COLO-201 (colorectal adenocarcinoma), HT-29 (colorectal adenocarcinoma, p53 mutant), SW-480 (colorectal adenocarcinoma), AGS (gastric adenocarcinoma), PANC-1 (pancreas epithelioid carcinoma), A2780 (ovarian carcinoma), HeLa (cervix adenocarcinoma), BT-549 (breast ductal carcinoma, triple negative), MCF-7 (breast adenocarcinoma), MDA-MD-231 (breast adenocarcinoma, triple negative), SAOS-2 (osteosarcoma) and SK-BR-3 (breast adenocarcinoma, p53-deficient), Huh-7 cells (human hepatic carcinoma cell line), Parental pcDNA3.1-HEK293, MDR19-HEK293 (HEK293 cells transfected with human ABCB1), GSC-3$^{\#}$ (glioma stem cells); CCRF-CEM (human leukemia cells), CEM/ADR5000 (human multi-drug-resistant tumor cells).

NR: not reached.

--: No determination

Table 3

The antibacterial and antifungal activities of isoquinoline alkaloids

Compound	Bacteria	Biological results	Positive drug	Ref.
Carnegine (**4**)			Gentamicine	24
	Staphylococcus aureus	1129.69 μM (MIC)	1438.11 μM (MIC)	
	Bacillus cereus	2259.38 μM (MIC)	719.06 μM (MIC)	
	Enterococcus faecalis	1129.69 μM (MIC)	11504.91 μM (MIC)	
	Escherichia coli	564.84 μM (MIC)	1438.11 μM (MIC)	
	Pseudomonas aeruginosa	2259.38 μM (MIC)	1438.11 μM (MIC)	
	Klebsiella pneumoniae	1129.69 μM (MIC)	1438.11 μM (MIC)	
	Proteus vulgaris	1129.69 μM (MIC)	1438.11 μM (MIC)	
N-Methylisosalsoline (**5**)			Gentamicine	24
	Staphylococcus aureus	19298.50 μM (MIC)	1438.11 μM (MIC)	
	Bacillus cereus	9649.24 μM (MIC)	719.06 μM (MIC)	
	Enterococcus faecalis	9649.24 μM (MIC)	11504.91 μM (MIC)	
	Escherichia coli	19298.50 μM (MIC)	1438.11 μM (MIC)	
	Pseudomonas aeruginosa	2412.31 μM (MIC)	1438.11 μM (MIC)	
	Klebsiella pneumoniae	19298.50 μM (MIC)	1438.11 μM (MIC)	
	Proteus vulgaris	19298.50 μM (MIC)	1438.11 μM (MIC)	
N-Formyl-asimilobine-2-*O*-*β*-D-glucoside (**87**)	*Staphylococcus aureus MRSA strains*	Diameters of inhibition zones 8.0 and 8.0 mm	Kanamycin sulfate was 40 and 34 mm	71
Isomoschatoline (**120**)	*Staphylococcus aureus* *Staphylococcus epidermidis* *Escherichia coli* *Candida albicans* *Candida dubliniensis*	Non-irradiated (CFU/mL) 1.55×10^7; 9.10×10^7; 1.10×10^7; 1.03×10^7; 9.10×10^7 Irradiated (CFU/mL) 1.38×10^4; 4.05×10^4; 1.12×10^5; 8.53×10^3; 6.68×10^3	Methylene blue (0.01 mg/mL) Non-irradiated 2.61×10^5; 6.53×10^4; 0; 4.78×10^7; $>1\times10^8$ Irradiated (CFU/mL) 0; 0; 0; 0; 0	237
Berberine (**151**)	*Clostridium perfringens* *Candida albicans*	52.20 μM (MIC) 75.53 μM (MIC)	Ampicillin 300 nM (MIC)	77 238
Palmatine (**156**)	*Clostridium perfringens*	44.70 μM (MIC)	Ampicillin 300 nM (MIC)	77
(−)-1-*O*-*β*-D-Glucoside-8-oxotetrahydropalmatine (**190**)	*Staphylococcus aureus*	Diameters of inhibition zones 15 mm	Kanamycin sulfate was 34 mm	71
N-Methylcanadine (**191**)	ATCC 25923, Clinical isolates *Staphylococcus aureus strains 1-4*	307.80 μM (MIC) 76.90 μM (MIC) 153.90 μM (MIC) 153.90 μM (MIC) 307.80 μM (MIC)	Chloramphenicol >49.51 μM (MIC); >198.10 μM (MIC); >24.76 μM (MIC); >24.76 μM (MIC); 198.1μM (MIC)	94
Michellamine B (**263**)	*Bacillus subtilis*	21.14 μM (MIC)	--	110
Dihydrocheleryhtrine (**303**)	Clinical isolates *Staphylococcus aureus strains 1-4*	76.9 - 307.8 μM (MIC)	--	94
Manzamine A (**329**)			Ampicillin	146

Compound	Bacteria	Biological results	Positive drug	Ref.
	Staphylococcus aureus	>0.18 μM (MIC)	0.001 μM (MIC),	
	Bacillus subtilis	0.09 μM (MIC)	0.002 μM (MIC)	
	Kocuria rhizophila	0.09 μM (MIC)	0.001 μM (MIC)	
	Salmonella enterica	0.01 μM (MIC)	0.001 μM (MIC)	
	Proteus hauseri	>0.18 μM (MIC)	0.005 μM (MIC)	
	Escherichia coli	>0.18 μM (MIC)	0.018 μM (MIC)	
Kepulauamine A (**330**)			Ampicillin	146
	Staphylococcus aureus	0.014 μM (MIC)	0.001 μM (MIC),	
	Bacillus subtilis	0.055 μM (MIC)	0.002 μM (MIC)	
	Kocuria rhizophila	0.028 μM (MIC)	0.001 μM (MIC)	
	Salmonella enterica	0.028 μM (MIC)	0.001 μM (MIC)	
	Proteus hauseri	0.014 μM (MIC)	0.005 μM (MIC)	
	Escherichia coli	0.110 μM (MIC)	0.018 μM (MIC)	
Manzamine B N-oxide (**331**)			Ampicillin	146
	Staphylococcus aureus	>0.176 μM (MIC)	0.001 μM (MIC),	
	Bacillus subtilis	0.176 μM (MIC)	0.002 μM (MIC)	
	Kocuria rhizophila	0.176 μM (MIC)	0.001 μM (MIC)	
	Salmonella enterica	0.088 μM (MIC)	0.001 μM (MIC)	
	Proteus hauseri	>0.176 μM (MIC)	0.005 μM (MIC)	
	Escherichia coli	>0.176 μM (MIC)	0.018 μM (MIC)	
3,4-Dihydromanzamine B *N*-oxide (**332**)			Ampicillin	146
	Staphylococcus aureus	0.023 μM (MIC)	0.001 μM (MIC),	
	Bacillus subtilis	0.011 μM (MIC)	0.002 μM (MIC)	
	Kocuria rhizophila	0.005 μM (MIC)	0.001 μM(MIC)	
	Salmonella enterica	0.005 μM (MIC)	0.001 μM (MIC)	
	Proteus hauseri	0.044 μM (MIC)	0.005 μM (MIC)	
	Escherichia coli	>0.176 μM (MIC)	0.018 μM (MIC)	
11-Hydroxymanzamine J (**333**)			Ampicillin	146
	Staphylococcus aureus	0.003 μM (MIC)	0.001 μM (MIC),	
	Bacillus subtilis	0.007 μM (MIC)	0.002 μM (MIC)	
	Kocuria rhizophila	0.007 μM (MIC)	0.001 μM (MIC)	
	Salmonella enterica	0.014 μM (MIC)	0.001 μM (MIC)	
	Proteus hauseri	0.003 μM (MIC)	0.005 μM (MIC)	
	Escherichia coli	0.027 μM (MIC)	0.018 μM (MIC)	
31-Hydroxymanzamine A (**334**)			Ampicillin	146
	Staphylococcus aureus	0.044 μM (MIC)	0.001 μM (MIC),	
	Bacillus subtilis	0.011 μM (MIC)	0.002 μM (MIC)	
	Kocuria rhizophila	0.011 μM (MIC)	0.001 μM (MIC)	
	Salmonella enterica	0.003 μM (MIC)	0.001 μM (MIC)	
	Proteus hauseri	0.023 μM (MIC)	0.005 μM (MIC)	
	Escherichia coli	>0.176 μM (MIC)	0.018 μM (MIC)	
32,33-Dihydro-31-hydroxymanzamine A (**335**)			Ampicillin	146
	Staphylococcus aureus	0.088 μM (MIC)	0.001 μM (MIC),	
	Bacillus subtilis	0.044 μM (MIC)	0.002 μM (MIC)	

Compound	Bacteria	Biological results	Positive drug	Ref.
	Kocuria rhizophila	0.023 μM (MIC)	0.001 μM (MIC)	
	Salmonella enterica	0.003 μM (MIC)	0.001 μM (MIC)	
	Proteus hauseri	0.176 μM (MIC)	0.005 μM (MIC)	
	Escherichia coli	>0.176 μM (MIC)	0.018 μM (MIC)	
6-Deoxymanzamine X (**336**)			Ampicillin	146
	Staphylococcus aureus	0.177 μM (MIC)	0.001 μM (MIC),	
	Bacillus subtilis	0.177 μM (MIC)	0.002 μM (MIC)	
	Kocuria rhizophila	0.089 μM (MIC)	0.001 μM (MIC)	
	Salmonella enterica	0.005 μM (MIC)	0.001 μM (MIC)	
	Proteus hauseri	>0.177 μM (MIC)	0.005 μM (MIC)	
	Escherichia coli	>0.177 μM (MIC)	0.018 μM (MIC)	
Manzamine B (**337**)			Ampicillin	146
	Staphylococcus aureus	>0.182 μM (MIC)	0.001 μM (MIC),	
	Bacillus subtilis	0.182 μM (MIC)	0.002 μM (MIC)	
	Kocuria rhizophila	0.182 μM (MIC)	0.001 μM (MIC)	
	Salmonella enterica	0.091 μM (MIC)	0.001 μM (MIC)	
	Proteus hauseri	>0.182 μM (MIC)	0.005 μM (MIC)	
	Escherichia coli	>0.182 μM (MIC)	0.018 μM (MIC)	
neo-Kauluamine (**338**)			Ampicillin	146
	Staphylococcus aureus	>0.086 μM (MIC)	0.001 μM (MIC),	
	Bacillus subtilis	0.001 μM (MIC)	0.002 μM (MIC)	
	Kocuria rhizophila	0.001 μM (MIC)	0.001 μM (MIC)	
	Salmonella enterica	0.001 μM (MIC)	0.001 μM (MIC)	
	Proteus hauseri	>0.086 μM (MIC)	0.005 μM (MIC)	
	Escherichia coli	>0.086 μM (MIC)	0.018 μM (MIC)	