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# The traditional uses, secondary metabolites, and pharmacology of *Lycopodium* species

**Bo Wang · Canyuan Guan · Qiang Fu**

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**Abstract** *Lycopodium* is a genus of the family Pteridophytes, which is widely distributed in temperate and tropical climates and tropical mountains. Plants of genus *Lycopodium* are ancient medicinal plants which have been used in different traditional medicinal system to treat many diseases, mainly focus on central nervous system and inflammation-related diseases. Rigorous pharmacological and clinical studies conducted in recent decades have demonstrated their special efficacy in the treatment of Alzheimer's disease (AD). Furthermore, secondary metabolites and extracts from these plants have been proven to possess neuroprotective, anti-tumor, anti-inflammatory, anti-microbial, and antiviral effects, which supports most of traditional medicinal uses of *Lycopodium* plants. To date, a total of 508 secondary metabolites have been reported from the 46 species belonging to genus *Lycopodium*. Among those metabolites, *Lycopodium* alkaloids and serratene triterpenoids represent two major classes of bioactive ingredients. Notably, huperzine A, a *Lycopodium* alkaloid originally isolated from *L. serratum*, was licensed in China as a drug for the treatment of AD and in the United States as a dietary supplement. Besides, serratane-type triterpenoids may be potential candidates for the development of anticancer drugs. This review covers the literatures available from 1947 to 2020 and mainly discusses knowledge on ethnopharmacology, secondary metabolites, pharmacological activities, clinical trials, toxicology, and quality control of *Lycopodium* species. In addition, the present review also draws attention to the gaps that still exist in the scientific studies on *Lycopodium* plants, which would accelerate the contemporary development of this traditional medicinal plant.

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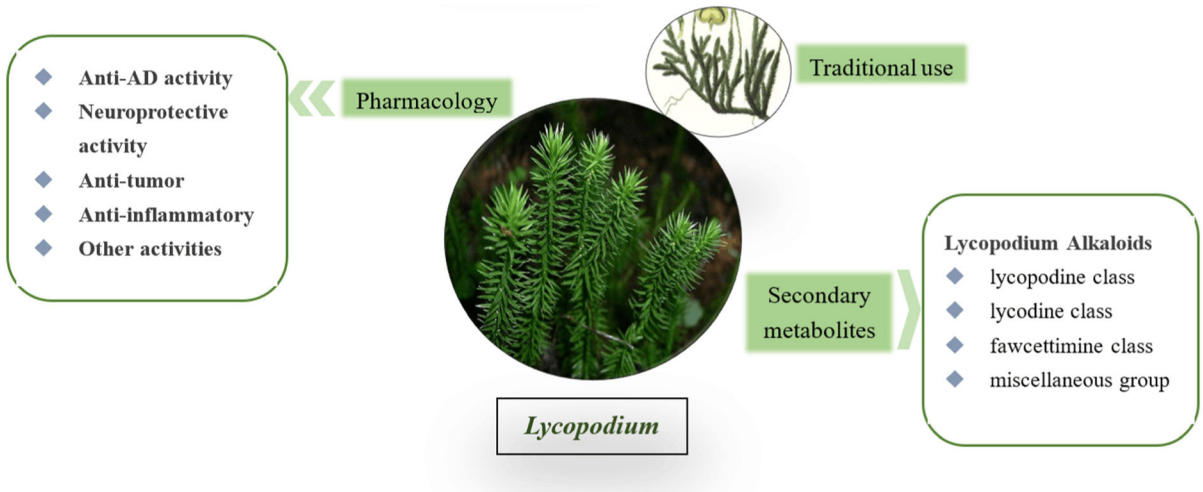
## Graphic abstract




**Keywords** *Lycopodium* · Medicinal plant · Secondary metabolites · Biological activity

**Abbreviations**

| | |
|---|---|
| Aβ | Amyloid β |
| ACh | Acetylcholine |
| AChE | Acetylcholinesterase |
| AD | Alzheimer's disease |
| ADAS-Cog | Alzheimer's disease assessment scale |
| ADL | Activities of daily living |
| AS | Active site |
| BACE1 | β-Site amyloid precursor protein-cleaving enzyme 1 |
| BChE | Butyrylcholinesterase |
| CAP | Cholinergic anti-inflammatory pathway |
| CDR | Clinical dementia rating |
| CNS | Central nervous system |
| DSM IV-R | Diagnostic and statistical manual of mental disorders—fourth revision |
| DMSO | Dimethylsulfoxide |
| EGF | Epidermal growth factor |
| ELS | Extract of *Lycopodium serratum* Thunb. |
| ERK | Extracellular signal-regulated kinase |
| Gal | Galantamine |
| HIV | Human immunodeficiency virus |
| Hup A | Huperzine A |
| LC | *Lycopodium clavatum* L. |
| LPS | Lipopolysaccharide |
| MAPK | Mitogen-activated protein kinase |
| MIC | Minimum inhibitory concentration |
| MNTC | Maximum nontoxic concentration |
| MMSE | Mini-mental state examination |

| | |
|---|---|
| MMP-9 | Matrix metalloproteinase-9 |
| MS | Murashige and skoog medium |
| NGF | Nerve growth factor |
| NINCDS-ADRDA | National Institute of Neurological and Communicative Disorders and Stroke |
| NMDA | *N*-Methyl-D-aspartate |
| NSC | Neural stem cell |
| OXE receptor1 | 5-Oxo-ETE receptor |
| PAS | Peripheral anionic site |
| PARP | Poly-ADP-ribose polymerase |
| PHA | Phytohemagglutinin |
| Phys | Physostigmine |
| PMA | Phorbol myristate acetate |
| ROS | Reactive oxygen species |
| SAP | Secreted aspartic proteases |
| SGZ | Subgranular zone |
| SOD | Superoxide dismutase |
| TCM | Traditional Chinese medicine |
| TEM | Traditional European medicine |
| VaD | Vascular dementia |

## Introduction

The genus *Lycopodium*, widely distributed in temperate and tropical climates and tropical mountains, contains about 40–50 species characterized by low, evergreen, coarsely moss-like and club-shaped strobili at the tips of mosslike branches. Given the wide distribution of club mosses, it is no wonder that various species of this genus have been used to treat multiple diseases dominated by central nervous system and inflammation-related ailments in traditional medicine around the world. In Europe and America, Hildegard of Bingen recorded different recipes and formulas with *Lycopodium clavatum* L. for the treatment of skin irritations and acne, nosebleed, inflammation of the liver, irritation of the intestinal tract, and kidney disorders (Siengalewicz et al. 2013). In addition, *Lycopodium saururus* Lam. is a specie well known in Argentina for its traditional use as an aphrodisiac and for memory improvement (Ortega et al. 2004a). In traditional Chinese medicine, five *Lycopodium* species all named Shi Song have been used as a traditional herbal medicine for the treatment of arthritic pain, quadriplegia, contusions, dysmenorrhea, and other health problems since Tang dynasty (Zhang et al. 2014). *Lycopodium* plants were also used to treat various mental conditions such as amnesia, anxiety, and fatigue in other Asian countries (Banerjee et al. 2014).

The classification of Lycopodiaceae has always been in a confused situation, because of the uncertain boundaries between the genera, which has caused a long-term discussion and research by botanists. The genus *Lycopodium* was established on the basis of *Lycopodium clavatum* L. by Linnaeus in 1753. During the period since its establishment, all Lycopodiaceae plants have been members of this group except *Phylloglossum*. With the development of techniques and methods, this family is divided into 2 to 16 genera by researchers with different viewpoints (Schuettpelz et al. 2016; Christenhusz et al. 2011; Field and Bostock 2013; Holub 1985, 1991; llgaard 1987). Therefore, the scientific name of the genus *Lycopodium* also produced confusion (for instance, *Lycopodium serratum* Thunb. is a synonym of *Huperzia serrata* (Thunb. ex Murray) Trevis.; *Lycopodium phlegmaria* L. is a synonym of *Phlegmariurus phlegmaria* (L.) Holub).

The earliest studies of secondary metabolites of genus *Lycopodium* dates back to the 1940s. Canadian scientists have studied structures of *Lycopodium* alkaloids, and W. A. Ayer classified theses alkaloids into four structural classes (Ayer et al. 1994). Until 1980s, some *Lycopodium* alkaloids represented by huperzine A (Hup A) were found to possess potent acetylcholinesterase (AChE) inhibition activity by Chinese scientists. Since then, a new wave of research on *Lycopodium* alkaloid has been rising. To date, researches on plants of genus *Lycopodium*

revealed that it was not only a known source of *Lycopodium* alkaloids, but also as a source of serratene-type triterpenoids. Up to now, a total of 508 secondary metabolites have been isolated and identified from the *Lycopodium* plants. Modern pharmacological studies have revealed that secondary metabolites or extracts from plants of genus *Lycopodium* exhibit an extensive range of biological activities including anti- Alzheimer's disease (AD), neuroprotection, anti-tumor, anti-inflammation. Hup A has been approved by FDA as a dietary supplement in 1997. As a second-generation AChE inhibitor, Hup A has also been used for the treatment of AD in China after numerous clinical studies. Besides, serratane-type triterpenoids may be potential candidates for the development of anticancer drugs for cancer therapy.

Scientists have never stopped the study of *Lycopodium* plants because of the unique and abundant biological activities of *Lycopodium* alkaloids. However, there is hardly any systematic in-depth review of genus *Lycopodium*. In this review, we intend to comprehensively present the advances achieved in the aspects of ethnopharmacology, secondary metabolites, pharmacological and biological activity, toxicology, and quality control of *Lycopodium* species. Plant names were also validated by "The Plant List" (www.theplantlist.org). The relationship between traditional uses and modern pharmacological activities is also discussed, aiming to outline existing research gaps and further research directions.

## Traditional uses

The plants of the genus *Lycopodium* were utilized ethnobotanically in mainly temperate and tropical regions, such as most of European and Asian countries, the United States, Argentina, and Brazil, to treat various diseases including central nervous system disease, inflammation-related ailments including hepatitis, arthritis, rheumatism, muscle swelling, pain, fever and dermatosis (Siengalewicz et al. 2013; Halldorsdottir et al. 2015; Namsa et al. 2009; Zhang et al. 2014).

In traditional European medicine (TEM), herbs from genus *Lycopodium* were generally reputed to be nontoxic and were occasionally used for preparing a salubrious tea which was employed to medicate inflammation of the liver, nosebleed, irritation of the intestinal tract and kidney disorders in different recipes and formulas. For example, skin irritations and acne were treated with a tea brewed from *L. clavatum* and couch grass (*Agropyron repens* L.). In Pliny the Elder's report, the Druids of Gaul have pretended that *L. clavatum* should be carried about the person as a preservative against accidents of all kinds, and that the smoke of it is extremely good for all maladies of the eyes (Siengalewicz et al. 2013). The herbal drug made from *L. clavatum* has been used to cure ailments of the kidney and bladder, while the similar-looking plant *Lycopodium* selago L. was used as a drastic emetic and a cathartic. Moreover, *L. selago* was known to be toxic and has been used for centuries to induce abortion. Reportedly, the high efficacy of this drug was well-known to prostitute when committing infanticide (Felgenhauer et al. 2000).

In native American tribes, the standard treatment for injuries and lesions was the application of spores of *L. clavatum* in the open wound. Members of the Blackfoot tribe used *Lycopodium complanatum* L. to treat pulmonary disease, and Iroquois believed in the ability of the plant to induce pregnancy (Siengalewicz et al. 2013). In addition, Upper Tanana Indians often used the whole plant of *L. selago* in a poultice applied to the head for headaches. In Argentinian traditional medicine, the leaves and stems of *L. clavatum* were used as carminative, expectorant and diuretic (Goleniowski et al. 2006). Further, the use of an infusion of aerial parts of *L. saururus* as an aphrodisiac and for memory improvement was widely known (Ortega et al. 2004a). Equally important, the decoction of the entire *Lycopodium thyoides* Humb. and Bonpl. ex Willd was used by the Quechua ethnic group in Ecuador to treat disorders of childbirth and used in Brazilian traditional medicine as a nerve tonic for central nervous system (CNS)-related conditions (Halldorsdottir et al. 2015; Konrath et al. 2012).

In India, Indian Ocean Islanders used the fresh plant infusion of *Lycopodium cernuum* L. to treat rickets of children and intestinal infection (Jain et al. 2005). Locally, the young shoot powder of *L. clavatum* known as Luanha mixed with seeds powder of *Sesamum indicum* Linn. was used for body massaging to relieve muscle pain and fatigue (Namsa et al. 2009). In Anatolia, Turkey, *L. clavatum*, the

most common specie of *Lycopodium* has been used in form of powder against baby skin irritation caused by nappy, therefore, also called "belly powder". Additionally, the spores of this plant have been stated to be protective for tender skin (Orhan et al. 2013). Moreover, the whole plant powder of *L. clavatum* was also used by Nepalese especially rural people to treat burn and headache (Hasan et al. 2013). In Bangladesh, *L. clavatum* was used for the treatment of kidney stone, urinary tract infection and digestive aliment and imperfect erection in aged person by various tribes (Banerjee et al. 2014).

In traditional Chinese medicine (TCM), a series of *Lycopodium* species named Shi Song including *Lycopodium japonicum* Thunb., *Lycopodium annotinum* L., *Lycopodium obscurum* L., *L. complanatum, and Lycopodium serratum* Thunb. have been used to treat various conditions such as arthritic pain, rheumatic numbness, contusion, blood stasis, muscle pain, dysmenorrheal, digestive problems, recognitive disorder and inflammation states. (Ma et al. 2007). The earliest record of medicinal usage of *Lycopodium* species can be traced back to an ancient Chinese pharmacopeia "Bencao Shiyi" (《本草拾遗》), which was written by Cangqi Chen in A.D. 739 (during the Tang Dynasty). It was recorded that *L. serratum* could be used to relieve rheumatism and cold, relax muscle and tendon, and promote blood circulation. This herb can also be found in "Compendium of Materia Medica" (《本草纲目》) by Shizhen Li in A.D. 1578 (during the Ming Dynasty) and "Chih-wu ming-shih t'u kao" (《植物名实图考》) by Qijun Wu in A.D. 1848 (during the Qing Dynasty) with a different name "Qian Ceng Ta". Besides, According to the Great Dictionary of Chinese Medicine (《中药大辞典》), fresh "Qian Ceng Ta" mixed with distiller's grains and brown sugar are mashed and heated to treat bruise, sprain, swelling and pain by external application. The dried whole plant of *L. japonicum also named* "Lycopodii Herba" was mentioned in "Gleaning Herb" to be able to dispel wind, dehumidify, activate collaterals, and used for the treatment of inconvenient flexing and stretching, wind dampness arthralgia syndrome, bruises, and other diseases (Zhang et al. 2014; Cai et al. 2015). In the coastal areas, Chinese often cure shingles by using the powder of *L. japonicum*, mixing it into paste with the seed oil of *Sapium sebiferum* (L.) Roxb. and smearing the affected area several times a day. In the traditional Yao communities of Yunnan Province, southwest of China, the aerial part of *L. japonicum* and *L. complanatum* were used to treat rheumatalgia, skin diseases and activate the blood circulation with medicinal baths, an important traditional way of adding proper herbal medicines to water, decocting them for a proper time, and then using the decocted liquid to bathe in proper temperature (Li et al. 2006a; Lee et al. 2008).

Overall, *Lycopodium* species were highly valued herbal remedies in several early cultures all over the world. Table 1 includes the detailed uses of different species in the diverse traditional medicines.

## Secondary metabolites from *Lycopodium* species

*Lycopodium* species have been investigated since 1840s. Review of literature reveals the presence of altogether 508 secondary metabolites from around 46 *Lycopodium* species. we categorize them into alkaloids (**1–443**), triterpenoids (**444–503**), glycosides (**504–508**). Their structures are shown in Fig. 1 and chemical names, chemical class and the corresponding plant sources are summarized in Table 2. Detailed and extensive chemical investigation of quite a few species, exactly used in common traditional medicine, such as *L. serratum*, *L. complanatum* and *L. japonicum*, led to the characterization of a large number of bioactive constituents. Hup A (**172**), originally isolated from *L. serratum*, is the main focus of numerous studies concerning the biological activities represented by anti-AD, of the genus *Lycopodium*.

### Alkaloids

*Lycopodium* alkaloids are a family of structurally diverse natural products with complex polycyclic skeletons. They are a kind of nitrogen heterocyclic compounds with novel skeleton, which is a tricyclic or tetracyclic compound composed of the basic skeleton $C_{16}N$ and $C_{16}N_2$, as well as a small amount of $C_{11}N$, $C_{15}N_2$, $C_{22}N_2$ and $C_{27}N_3$ alkaloids. A common feature in all *Lycopodium* alkaloids is a polycyclic carbon skeleton with varying levels of oxidation (Hirasawa et al. 2004).

W. A. Ayer was an outstanding chemist who spent most of his professional career investigating

**Table 1** Latin names, local name, distributions, and traditional uses of reported *Lycopodium* species

| Latin name | Local name | Distribution | Traditional uses | Plant part | References |
|---|---|---|---|---|---|
| *Lycopodium alpinum* L | Gaoshanbianzhishiso-ng, Alpine clubmoss | China (Heilongjiang, Jilin Province), India, Japan, Korea, Mongolia, Russia (Siberia), Sri Lanka; Europe, North America | Used for the treatment of bruises, joint pain, wounds and rashes | The whole plant | Flora of China; Halldorsdottir et al. (2015) |
| *Lycopodium annotinum* L | Duosuishisong, Interrupted club-moss, Stiff clubmoss | China (Chongqing, Gansu, Heilongjiang, Hubei, Jilin, Liaoning, Shaanxi, Sichuan, Taiwan Province), Bhutan, NE India(Assam), Japan, Korea, Nepal, Russia, most of Europe, North America (Greenland, St. Pierre & Miquelon, all 10 provinces and all 3 territories of Canada, Alaska, and mountains of the contiguous United States) | Used to dispel wind and dehumidify, relax muscles and blood circulation, and used for the treatment of joint pain, bruises, rheumatic numbness, digestive problems and dysentery | The whole plant, spore | Halldorsdottir et al. (2015) |
| *Lycopodium cernuum* L | Chuisuishisong, Staghorn clubmoss, Wāwaeiole, Rat's foot | India and Indian Ocean, China (Chongqing, Fujian, Guangdong, Guangxi, Guizhou, Hainan, Hunan et al. Provinces), Pacific islands (Hawaii), Central and South America | Used to dispel wind and dehumidify, activate channels and collaterals, and used for the treatment of rheumatic numbness, hepatitis, dysentery, rubella, red eye, vomiting blood, epistaxis, hematochezia, bruises, rickets of children, intestinal infect | The whole plant | Jain et al. (2005) |
| *Lycopodium clavatum* L | Dongbeishisong, Belly powder, Nagbeli; Luanha, Selago; Pillijan, Ground pine, Common club moss, Stag's-horn clubmoss, Running clubmoss, Wolf's claw clubmoss, Clubfoot Moss, Foxtail, Sulfer | China (Heilongjiang, Jilin, Liaoning, Nei Mongol Province), Turkey, Nepal, India (the Lohit community of Arunachal Pradesh), North and South America (Argentina, Brazil, Peru, Canada), Jamaica, Papua New Guinea, Japan, Korea, Anatolia | Used for the treatment of rheumatic disease, pulmonary disease, dermatological diseases including rashes, rush in babies and protection of tender skin, muscle pain and fatigue, stomach pain, headache, Burns, wounds,and inducing pregnancy, Alzheimers disease, central nervous system conditions, as nerve tonics and for motor disorders, and used as expectorants, laxatives and diuretics | The whole plant, spore, aerial parts, leaves and stems | Vasudeva et al. (1999), Orhan et al. (2013), Banerjee et al. (2014), Hasan et al. (2013), Konrath et al. (2012), Namsa et al. (2009), Golenioeski et al. (2006), Siengalewicz et al. (2013) |

**Table 1** continued

| Latin name | Local name | Distribution | Traditional uses | Plant part | References |
|---|---|---|---|---|---|
| *Lycopodium* | *complanatum* L | Bianzhizhizong, "Guo-Jiang-Long", Feng you, Christmas-green, Ground-cedar, Running-evergreen, Trailing-evergreen | China (Anhui, Guangdong, Guangxi, Guizhou, Hainan, Hubei, Hunan, Jiangxi, Sichuan, Xinjiang, Xizang, Zhejiang, Yunnan Province), North America (Alaska) | Used for the | treatment of Rheumatalgia, arthritic pain, quadriplegia, contusion, and blood stasis |
| The whole plant | Nguyen et al. (2017), Tang et al. (2015), Li et al. (2006a, b) | | | | |
| *Lycopodium japonicum* Thunb | Shenjincao, Naagabelee | China (except north and northeast China), Nepal, Bhutan, Cambodia, India, Japan, Laos, Myanmar, Vietnam | Used for the treatment of arthritic pain, quadriplegia, dysmenorrhea, and contusion | The whole plant | Yan et al. (2005a, b) |
| *Lycopodium* | *multispicatum* J.H. Wilce | Aixiaobianzhishisong, Dishuazi | China (Guangdong, Guangxi, Taiwan, Tibet Provinces, south Yunnan), Assam, east Himalaya, Philippines, Thailand, Vietnam, Benguet, Northern Luzon, Mount Santo Tomas | Used to dispel wind and | dehumidify, activate channels and collaterals, and used for the treatment of rheumatic joint pain |
| | Bennert et al. (2007) | | | | |
| *Lycopodium obscurum* L | Yubaishisong, Rare clubmoss, Ground pine, Prince's pine, Princess pine | China (the mountain areas of the north-east and the Middle and upper reaches of the Yangtze River), Japan, Korea, Russia, North America (Wisconsin) | Used for the treatment of contusions, dysmenorrheal, quadriplegia, and arthritic pain, muscle pain and rheumatism | The whole plant | Jiang et al. (2016), Wang et al. (2016) |
| *Lycopodium phlegmaria* L | Chuizhishisong | China (Taiwan, Guangdong, Guangxi, Hainan, and Yunnan Provinces) | Used for the treatment of angina, dropsy, rheumatoid arthritis, rheumatic pain, arthritis, traumatic injury, sore throat, and urticaria | The whole plant | Shi et al. (2005), Yang et al. (2016a, b) |
| *Lycopodium saururus* Lam | Cola de quirquincho | Argentine (from the northwest region to the sierras of the center and south of Buenos Aires) | Used as aphrodisiac and memory improver | Aerial parts | Vallejo et al. (2013), Ortega et al. (2004a) |
| *Lycopodium selago* L | Northern firmoss, Fir clubmoss, Virgin Mary's Furze | Europe(Western and northern Europe), Northern Russia, North America, Japan, the Aleutian Islands, Greenland, Iceland | Used for the treatment of headaches and inducing abortion, and used as a drastic emetic and cathartic | The whole plant | Felgenhauer et al. (2000) |
| *Lycopodium squarrosum* G. Forst | Shanyeshisong | China (Yunnan, Taiwan and southern Tibet), North East India (the state Manipur) | Used for the treatment of pyrexia, detumescence, limb numbness, joint pains, and injuries from falls | The whole plant | Nilsu et al. (2016) |

**Table 1** continued

| Latin name | Local name | Distribution | Traditional uses | Plant part | References |
|---|---|---|---|---|---|
| *Lycopodium* | *veitchii* Christ | Yushangshisong | China (west Hubei, west Sichuan, Taiwan, Tibet, northwest Yunnan), Bhutan, India, Myanmar, Nepal | Used to dispel wind and | dehumidify, activate channels and collaterals, and the treatment of swelling, rheumatism pain of waist and leg, joint pain, bruises, knife wounds, burns |
| | Flora of China | | | | |
| *Lycopodium serratum* Thumb | Shezushisong, Qiancengta | China (southwest, central south, east and north China) | Used for the treatment of Alzheimer's disease, amnesia, contusion, strain, swelling, myasthenia gravis, haematuria, organophosphate poisoning, schizophrenia, fever, and inflammation states, and as a therapeutic agent to human cancer | The whole plant | Xiao et al. (2002), Ham et al. (2012), Tao et al. (2013), Bai et al. (1993), Ma et al. (2006), Zhang et al. (2008), Ma et al. (2007), Borloz et al. (2006) |
| *Lycopodium thyoides* Humb. &Bonpl. ex Willd | | South America (Brazil, Venezuela, Ecuador) | Used for the treatment of central nervous system conditions, as nerve tonics and for motor disorders, and treating parturition disorders | The whole plant | Konrath et al. (2012) |

*Lycopodium* alkaloids and published many important articles and reviews on them. According to the structure characteristics of *Lycopodium* alkaloids, Ayer divided them into four structural classes: the lycopodine class, the lycodine class, the fawcettimine class and the miscellaneous group, with lycopodine, lycodine, fawcettimine and phlegmarine as representative compounds, respectively (Ayer et al. 1994).

*Lycopodine class*

A total of 157 *Lycopodium* alkaloids (**1–157**) have been isolated from the whole plant of *Lycopodium* species that belong to this class. This is the largest group of known *Lycopodium* alkaloids, and appears to be the most widely distributed.

This class is characterized by four connected six-membered rings, with rings A and C being a *cis* quinolizidine ring system (C-4 and C-13 are connected). Most of the ring B have carbonyl groups at C-5 and a few at C-6. Examples are huperzines E (**26**), F (**91**) and O (**107**) which were isolated from *L. serratum* (Ma et al. 2004). Lycopodine (**1**) is a representative compound of this class, which was also the first identified and belongs to this class (Ma et al. 2004). And its C-4, C-6 of the carbonyl alpha position and H atoms at tertiary C-7 are easily oxidized to hydroxyl groups, such as 4α,8β-dihydroxylycopodine (**10**), 8β-hydroxylycoposerramine K (**21**), 11β-hydroxy-12-epilycodoline (**14**) (Cai et al. 2015). Besides, its N atom also can be oxidized, as miyoshianine C (**23**). Lannotinidine H (**113**) is the first *Lycopodium* alkaloid possessing a lycopodine skeleton with an additional $C_3$ unit (Ishiuchi et al. 2009a, b). The rings A, B and C of these compounds are relatively stable, and the changes of the skeleton are mainly concentrated in the D ring. For example, C-15 of the D ring related to C-12 in lannotinidine E (**43**) after breaking with C-8. At the same time, C-8 formed an epoxide ring with C-5. It is worth mentioning that it can enhance the mRNA expressions for nerve growth factor (NGF) (Koyama et al. 2005).

*Lycodine class*

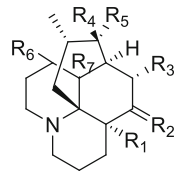
A total of 67 *Lycopodium* alkaloids (**158–224**) have been identified from the whole plant of *Lycopodium* species that belong to this class. So far, it is found that most of the *Lycopodium* alkaloids with AChE inhibition activity comes from this class, most notably: Hup A (**172**), huperzine B (**173**), *N*-methyl-huperzine B (**191**) and huperzinine (**176**). Generally, the character of structure is also four-ring. The difference with lycopodine class is that the A ring is opened and rearranged to form a pyridine or pyridone A ring, and the C ring is converted into separate hexahydropyridine C ring. Its representative compound is lycodine (**179**). Intriguingly, complanadine E (**165**) was a new unsymmetrical dimeric alkaloid, which was the first example forming a piperidine ring at C-1–C-5 and N-1 of lycodine-type alkaloids (Ishiuchi et al. 2011).

Among the *Lycopodium* alkaloids, Hup A (**172**) isolated from *L. serratum* in 1986 has been shown to have highly specific and potent inhibitory activity against AChE and to improve memory disorders in AD patients (Liu et al. 1986). It has greatly stimulated interest in this group of alkaloids. Relevant investigation has been conducted to study their pharmacology in depth.

*Fawcettimine class*

144 of the *Lycopodium* alkaloids belong to the fawcettimine class (**225–368**). This class of compound can be regarded as the result of $C_4$-$C_{13}$ bond breaking and forming $C_4$-$C_{12}$ bond in lycopodine class. The C-13 connected with N atom is unstable and easy to be oxidized to hydroxyl group or break the $C_{13}$-N bond to form $C_{13}$-carbonyl group. Therefore, a characteristic of this class not shared with the other classes is the presence of a five-membered ring B. Its representative compound, fawcettimine (**251**), has been proved to be an equilibrium mixture between the alcohol-amine type and keto-amine type, and thus evolved into two major groups of the carbinolamine form and the keto-amine form. In the carbinolamine form, N atom is linked to C-13, such as lycopoclavamine A (245); the keto-amine form does not have N-$C_{13}$ bond, such as palhinine A (**272**).

Obscurumines H (**306**) and I (**307**) represent rare naturally occurring structures based on the fawcettimine-type skeleton, including a new $C_{17}N_2$ skeleton that is formed a ring via the linkage of C-9–N-2′, which is rarely present in *Lycopodium* alkaloids (Jiang et al. 2015). Moreover, it was found that three




| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 1 | $R_1$=H | $R_2$=O | $R_3$=H | $R_4$=H | $R_5$=H | $R_6$=H | $R_7$=H | |
| 2 | $R_1$=H | $R_{2\beta}$=OAc | $R_{2\alpha}$=H | $R_3$=H | $R_4$=OAc | $R_5$=H | $R_6$=H | $R_7$=OH |
| 3 | $R_1$=H | $R_2$=O | $R_3$=H | $R_4$=OAc | $R_5$=H | $R_6$=H | $R_7$=OH | |
| 4 | $R_1$=H | $R_2$=O | $R_3$=H | $R_4$=OAc | $R_5$=H | $R_6$=OH | $R_7$=H | |
| 5 | $R_1$=H | $R_2$=O | $R_3$=H | $R_4$=H | $R_5$=H | $R_6$=OH | $R_7$=H | |
| 6 | $R_1$=H | $R_{2\beta}$=OAc | $R_{2\alpha}$=H | $R_3$=H | $R_4$=OAc | $R_5$=H | $R_6$=H | $R_7$=H |
| 7 | $R_1$=H | $R_2$=O | $R_3$=H | $R_4$=OH | $R_5$=H | $R_6$=H | $R_7$=H | |
| 8 | $R_1$=H | $R_{2\beta}$=OAc | $R_{2\alpha}$=H | $R_3$=H | $R_4$=OH | $R_5$=H | $R_6$=H | $R_7$=H |
| 9 | $R_1$=H | $R_2$=O | $R_3$=OH | $R_4$=OH | $R_5$=H | $R_6$=H | $R_7$=H | |
| 10 | $R_1$=OH | $R_2$=O | $R_3$=H | $R_4$=OH | $R_5$=H | $R_6$=H | $R_7$=H | |
| 11 | $R_1$=H | $R_2$=O | $R_3$=H | $R_4$=OH | $R_5$=H | $R_6$=H | $R_7$=OH | |
| 12 | $R_1$=OH | $R_2$=O | $R_3$=H | $R_4$=OH | $R_5$=H | $R_6$=H | $R_7$=OH | |
| 13 | $R_1$=H | $R_2$=O | $R_3$=H | $R_4$=OH | $R_5$=H | $R_6$=OAc | $R_7$=H | |
| 14 | $R_1$=H | $R_2$=O | $R_3$=H | $R_4$=H | $R_5$=H | $R_6$=OH | $R_7$=OH | |
| 15 | $R_1$=H | $R_{2\beta}$=OAc | $R_{2\alpha}$=H | $R_3$=H | $R_4$=OAc | $R_5$=H | $R_6$=OH | $R_7$=H |
| 16 | $R_1$=H | $R_{2\beta}$=OAc | $R_{2\alpha}$=H | $R_3$=H | $R_4$=OAc | $R_5$=H | $R_6$=H | $R_7$=OH |
| 17 | $R_1$=OH | $R_2$=O | $R_3$=H | $R_4$=H | $R_5$=H | $R_6$=H | $R_7$=OH | |
| 18 | $R_1$=H | $R_{2\beta}$=OH | $R_{2\alpha}$=H | $R_3$=H | $R_4$=H | $R_5$=H | $R_6$=H | $R_7$=H |
| 19 | $R_1$=H | $R_{2\beta}$=OAc | $R_{2\alpha}$=H | $R_3$=H | $R_4$=H | $R_5$=H | $R_6$=H | $R_7$=H |
| 20 | $R_1$=H | $R_{2\beta}$=OAc | $R_{2\alpha}$=H | $R_3$=H | $R_4$=H | $R_5$=H | $R_6$=H | $R_7$=OH |

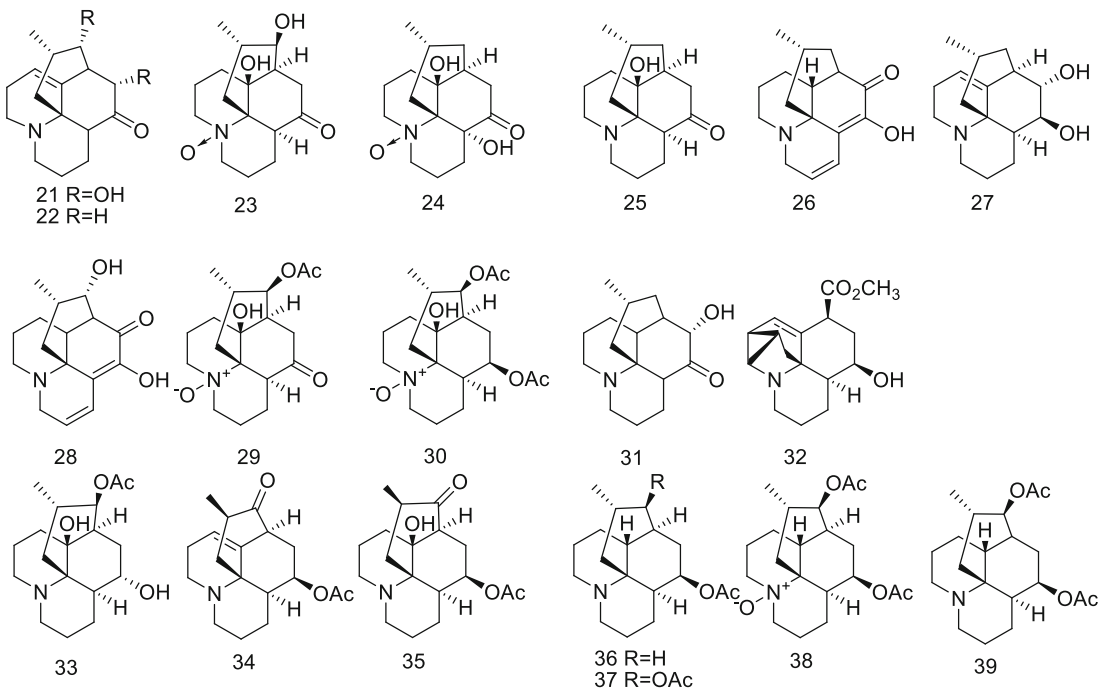



**Fig. 1** The structures of secondary metabolites isolated from *Lycopodium* species

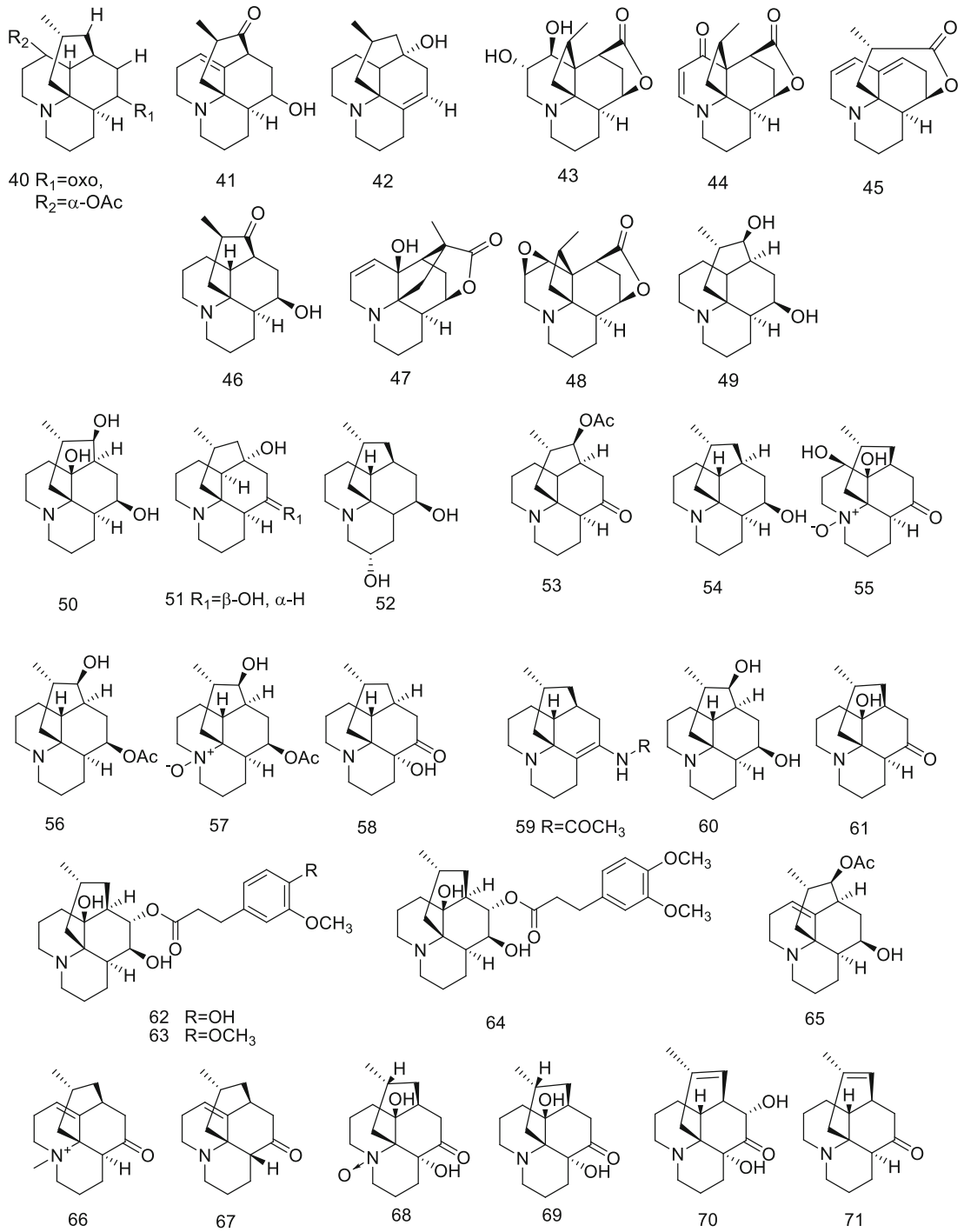



**Fig. 1** continued

new skeleton alkaloids, named lycojaponicumins A (**297**), B (**298**) and C (**277**), were isolated from *L. japonicum*. They represented a unique heterocyclic skeleton formed by the new linkage C4-C9. Notably,

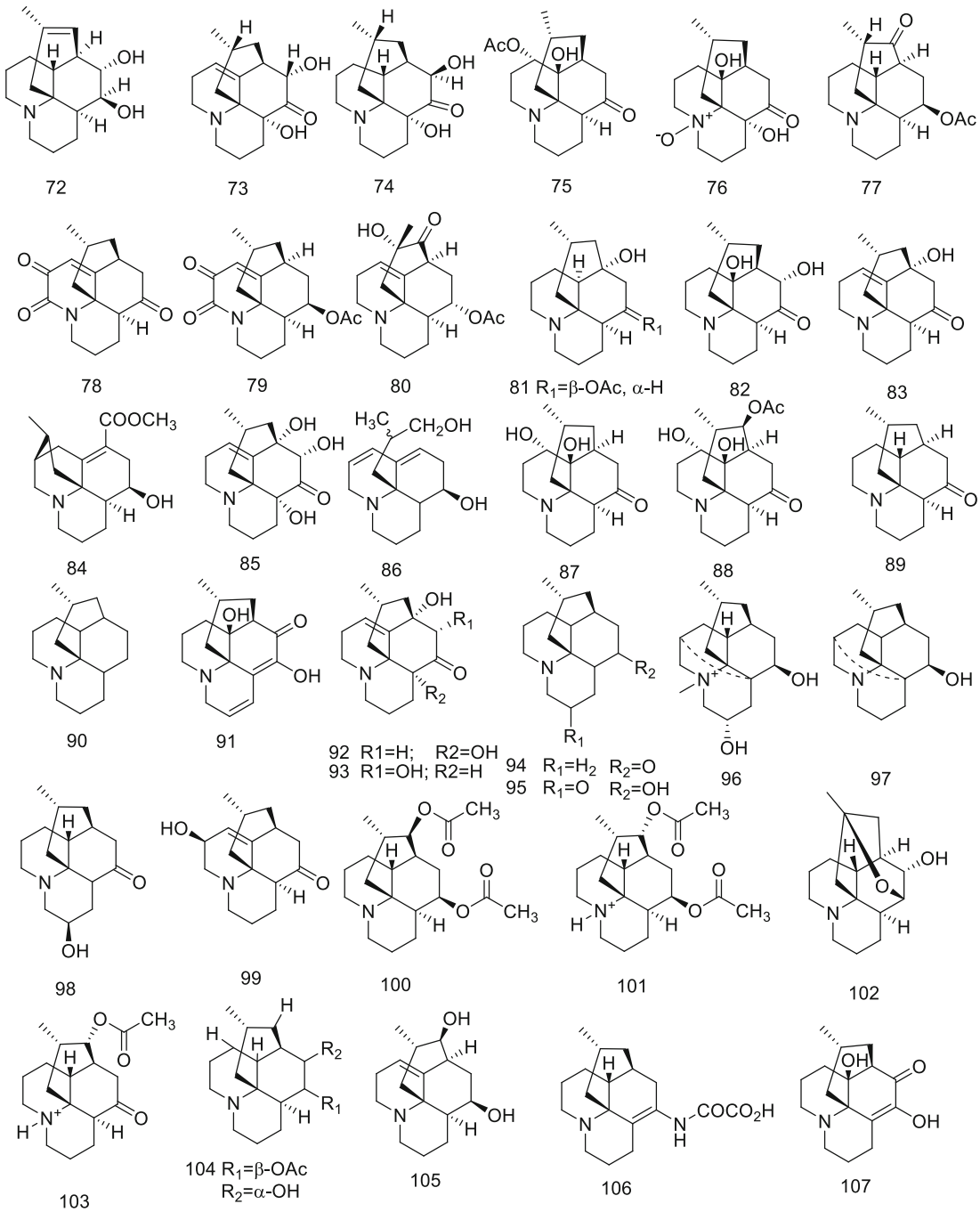



**Fig. 1** continued

lycojaponicumins A and B are the first examples of natural products possessing a 5/5/5/5/6 pentacyclic ring system with a 1-*aza*-7-oxabicyclo[2.2.1]heptane moiety. Lycojaponicumin C is composed of a 6/5/5/6 tetracyclic skeleton, except that C-3 is connected to C-13. Biological testing in vitro showed that lycojaponicumins A-C inhibited lipopolysaccharide (LPS)-induced pro-inflammatory factors in BV2

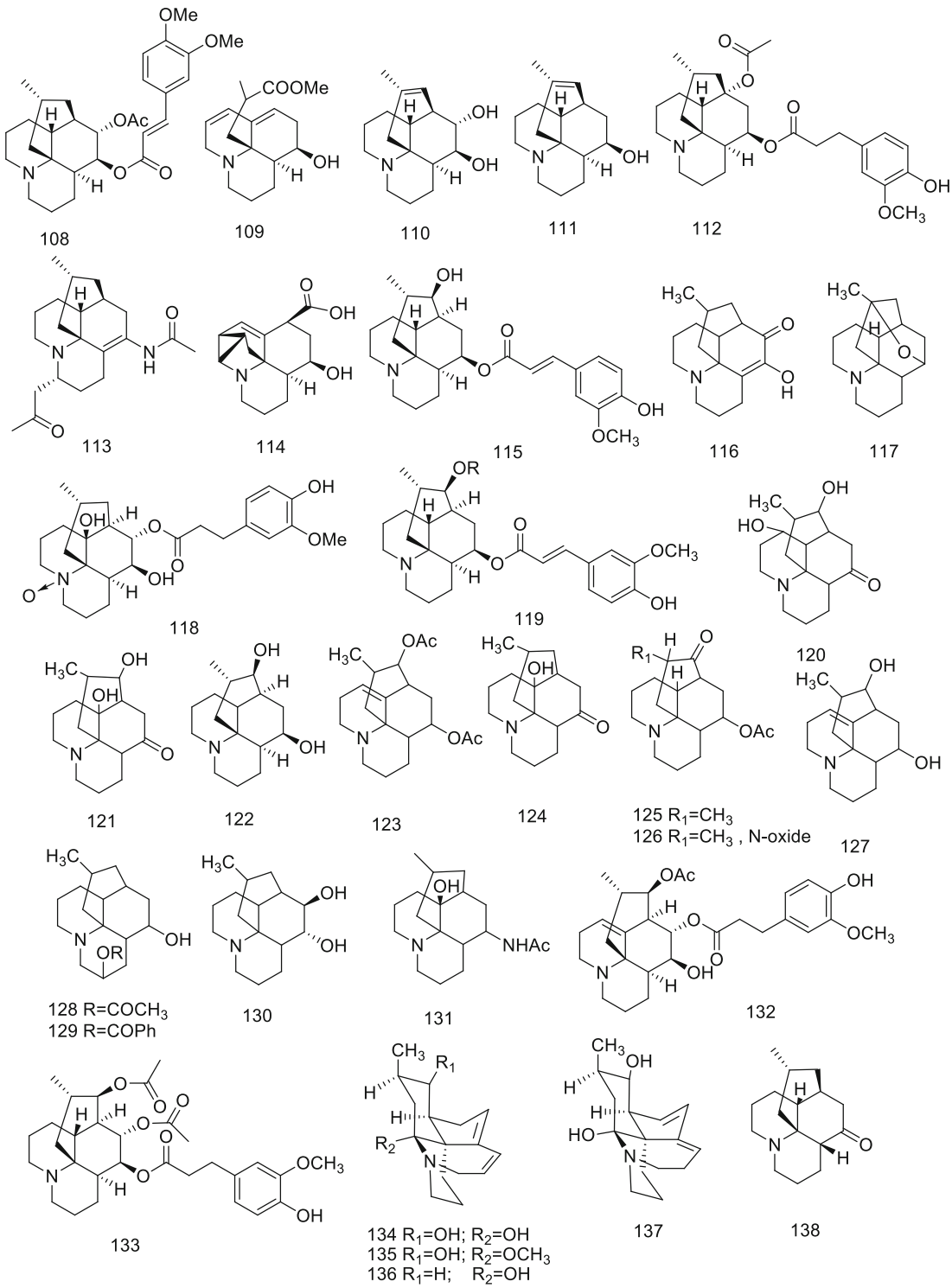



**Fig. 1** continued

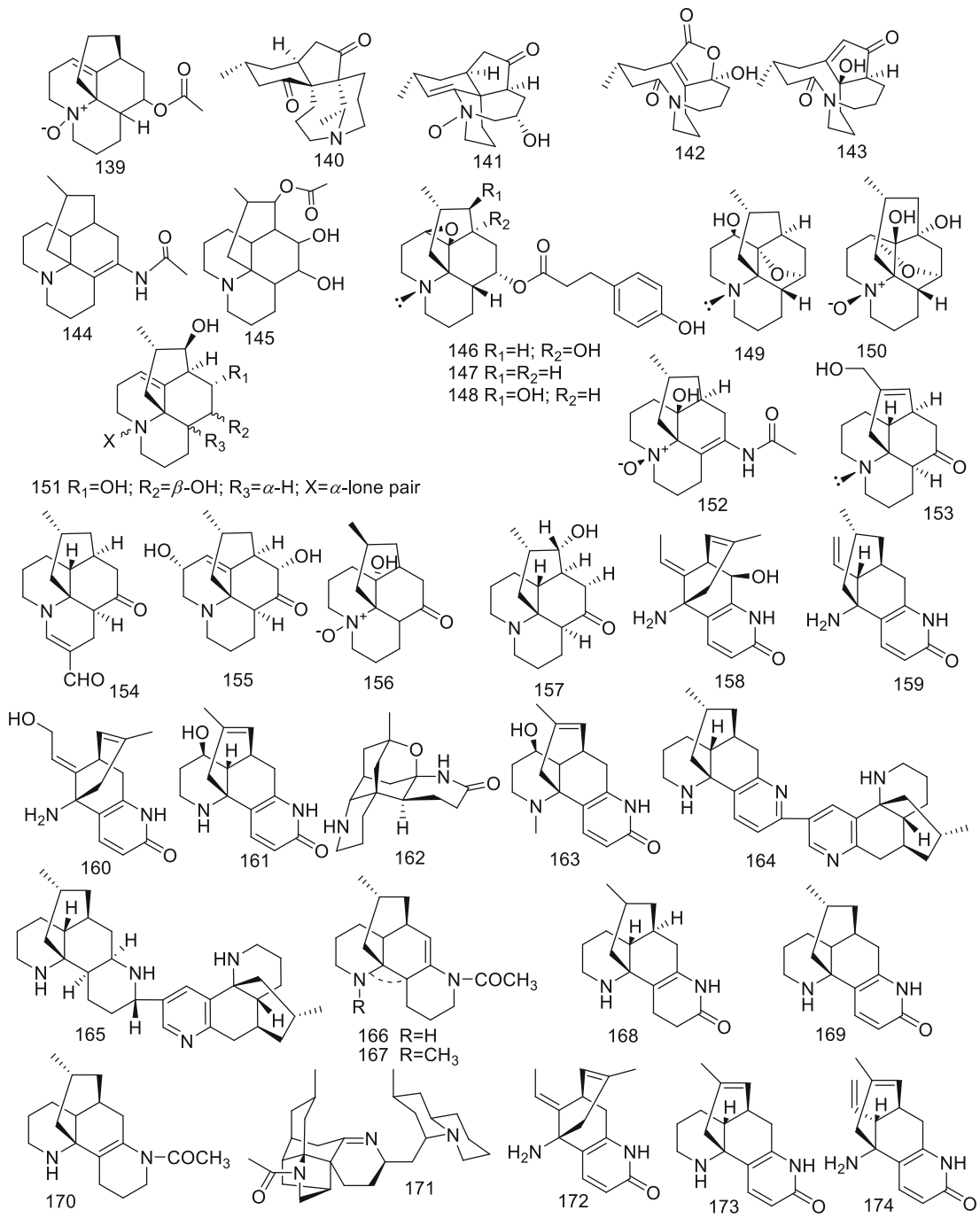



**Fig. 1** continued

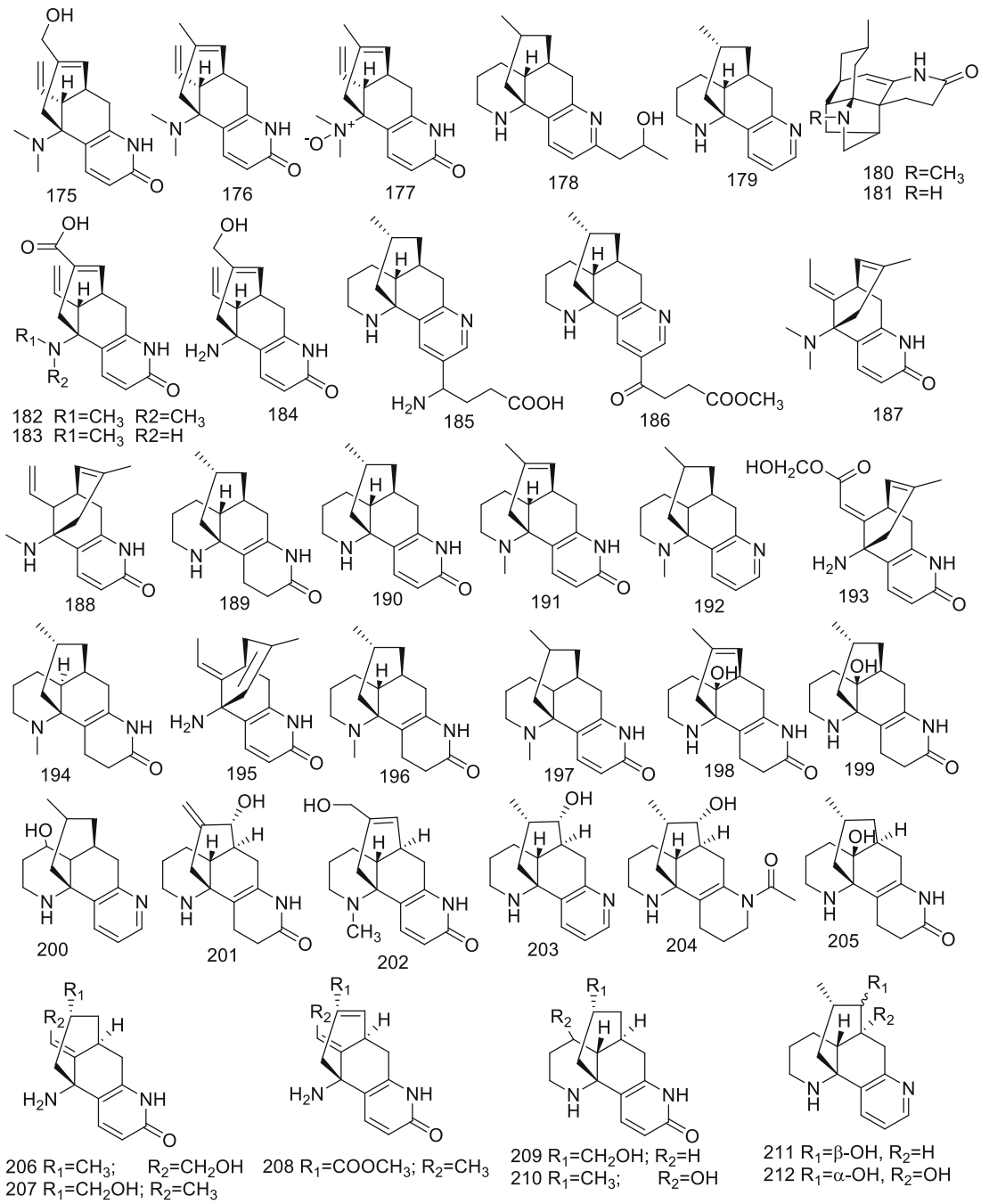



**Fig. 1** continued

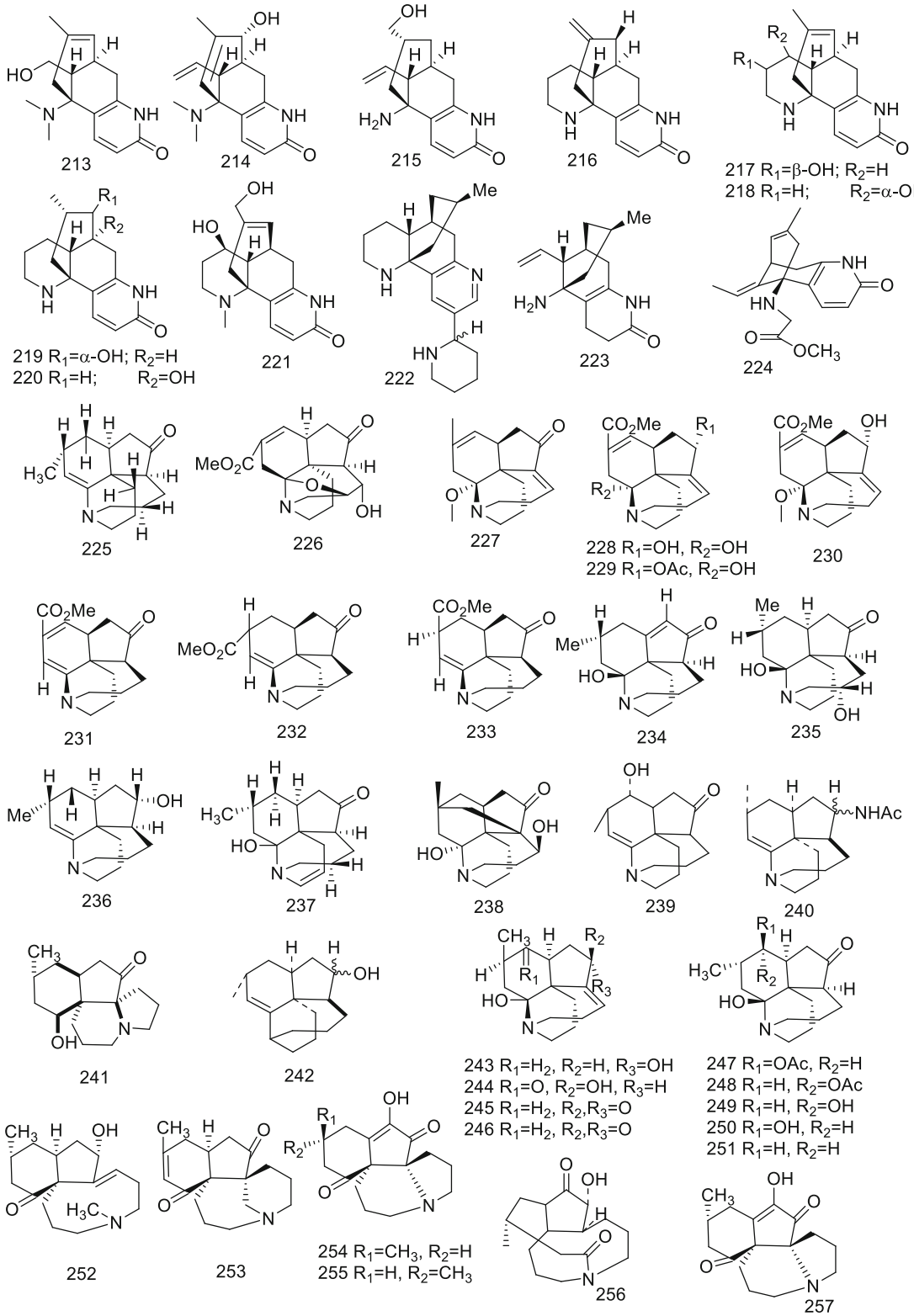



**Fig. 1** continued

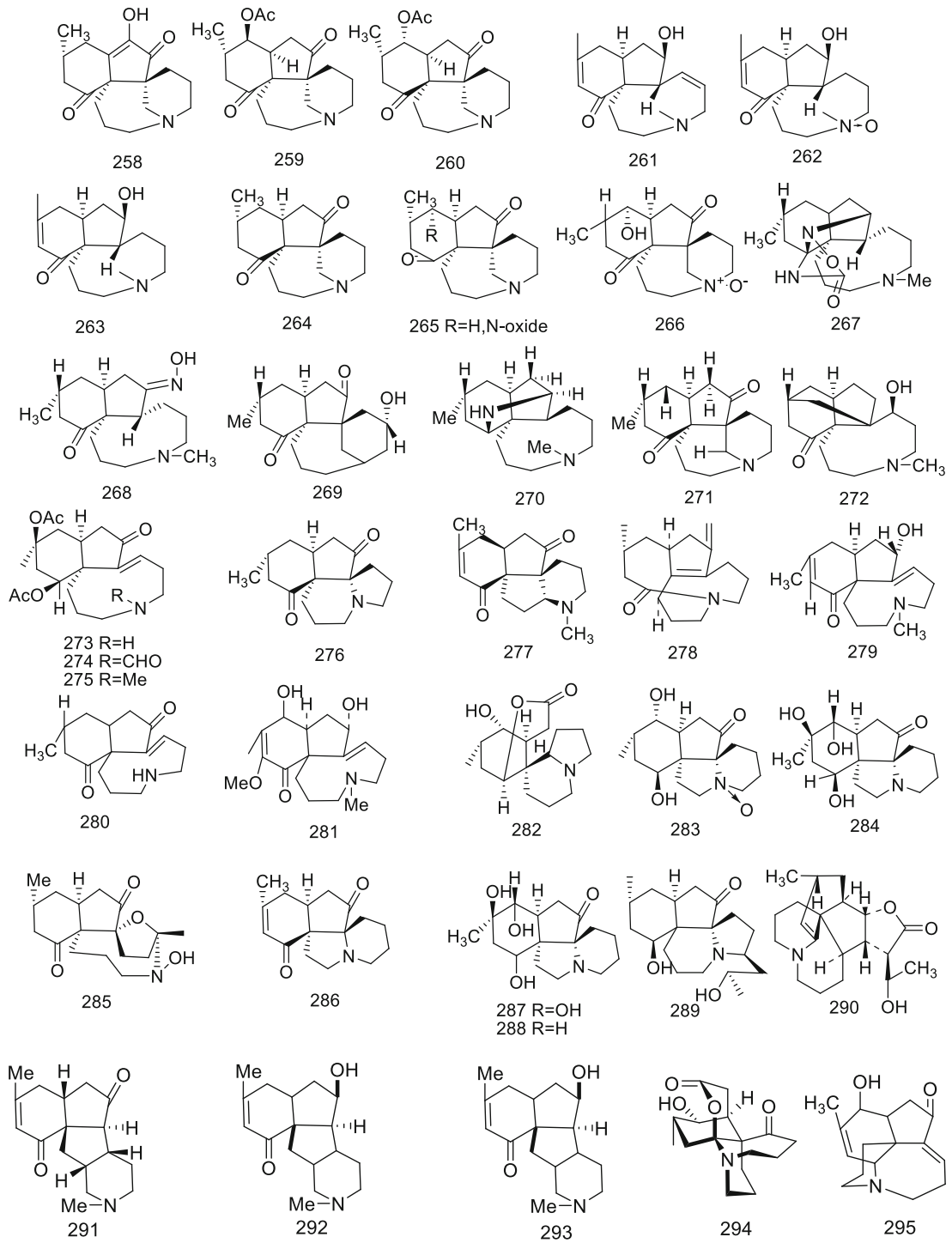



**Fig. 1** continued

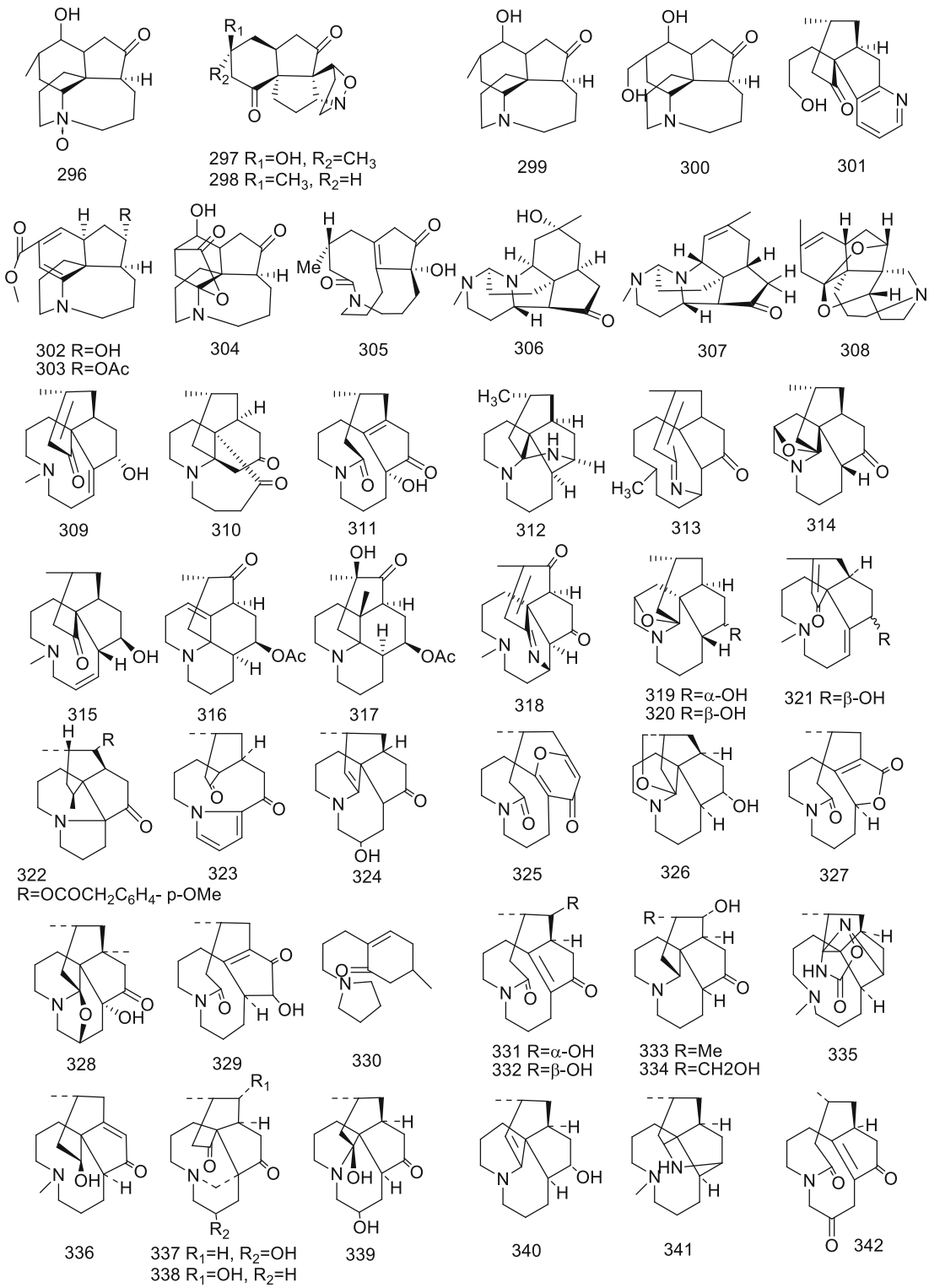



**Fig. 1** continued

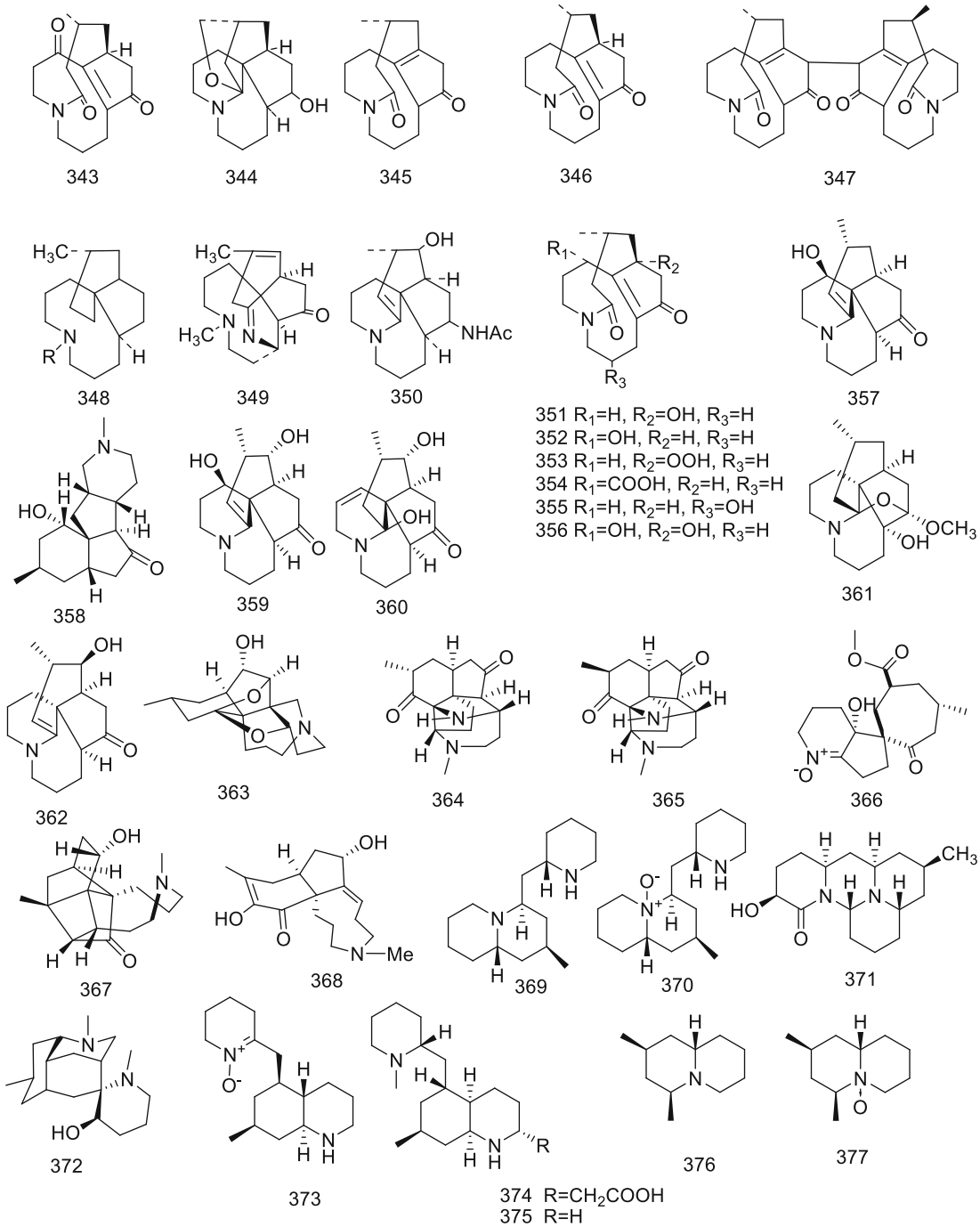



**Fig. 1** continued

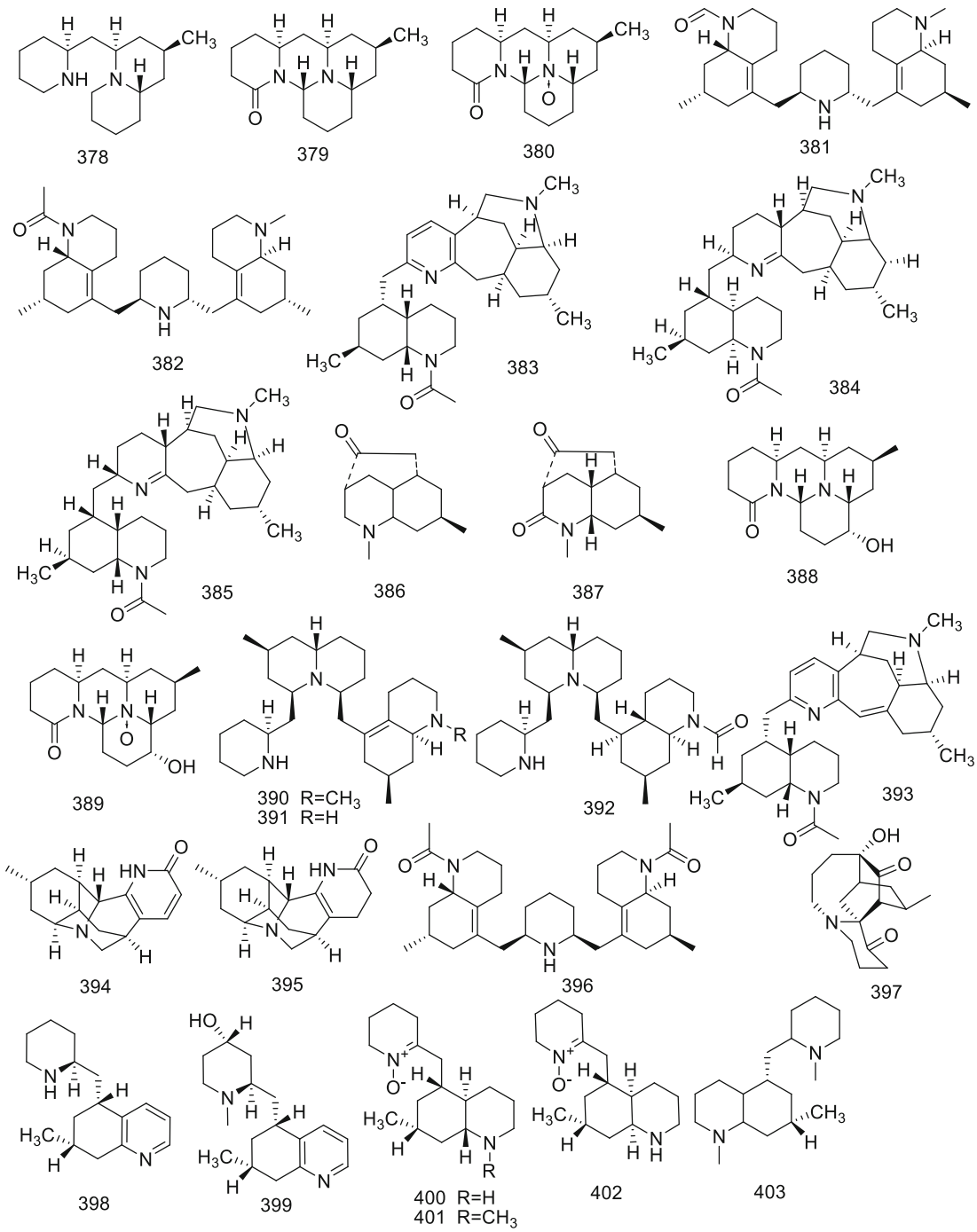



**Fig. 1** continued

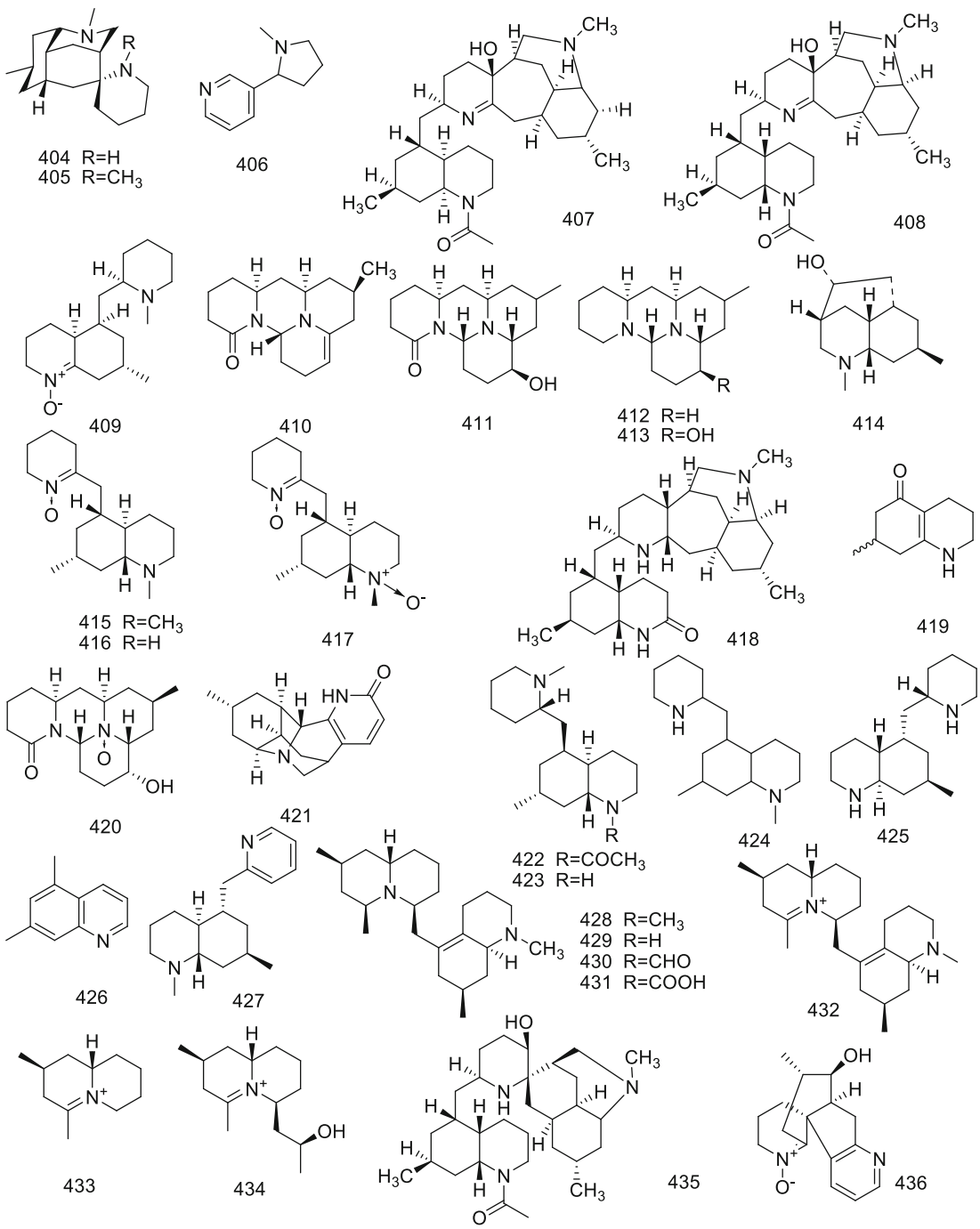



**Fig. 1** continued

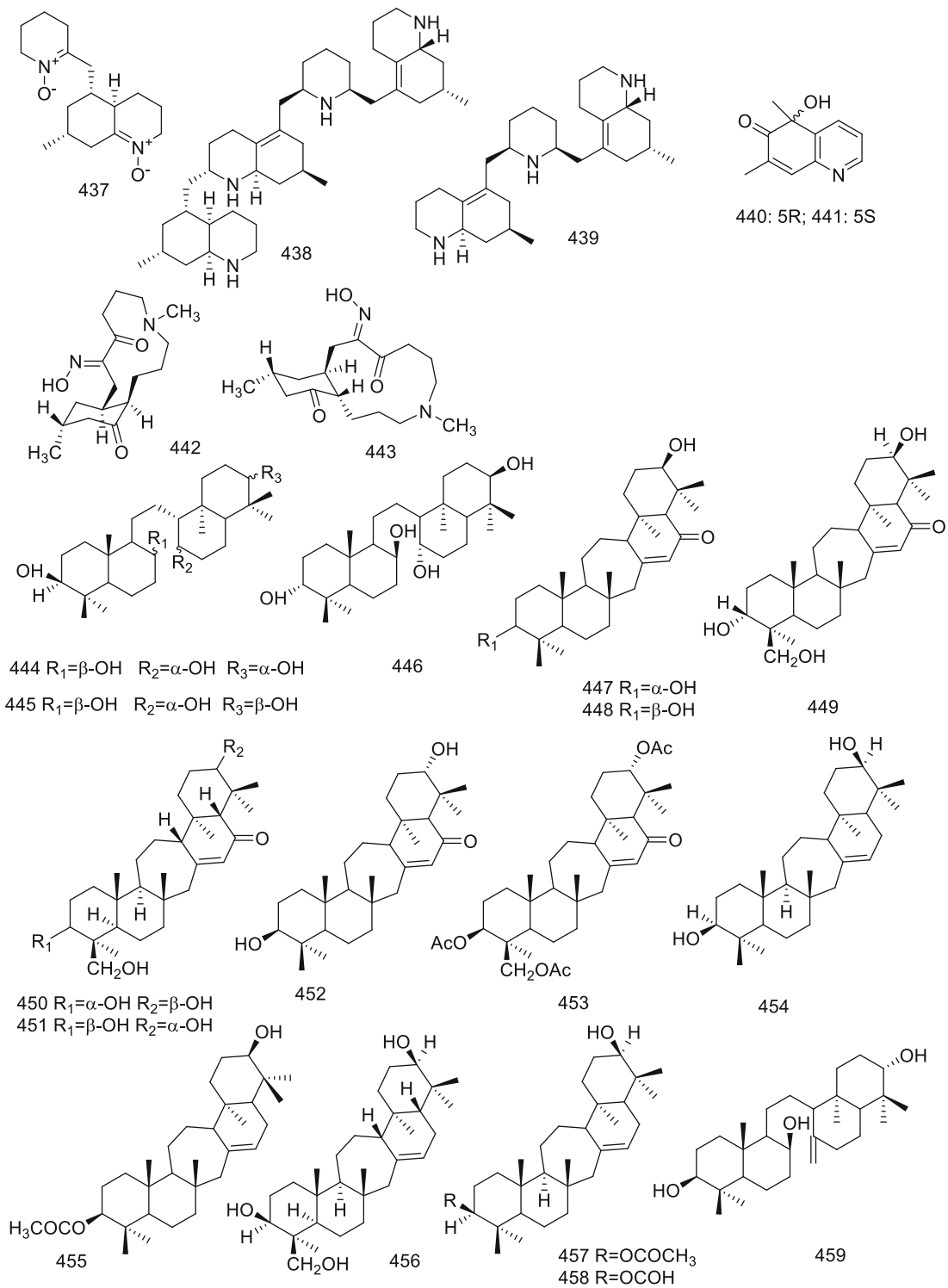



**Fig. 1** continued

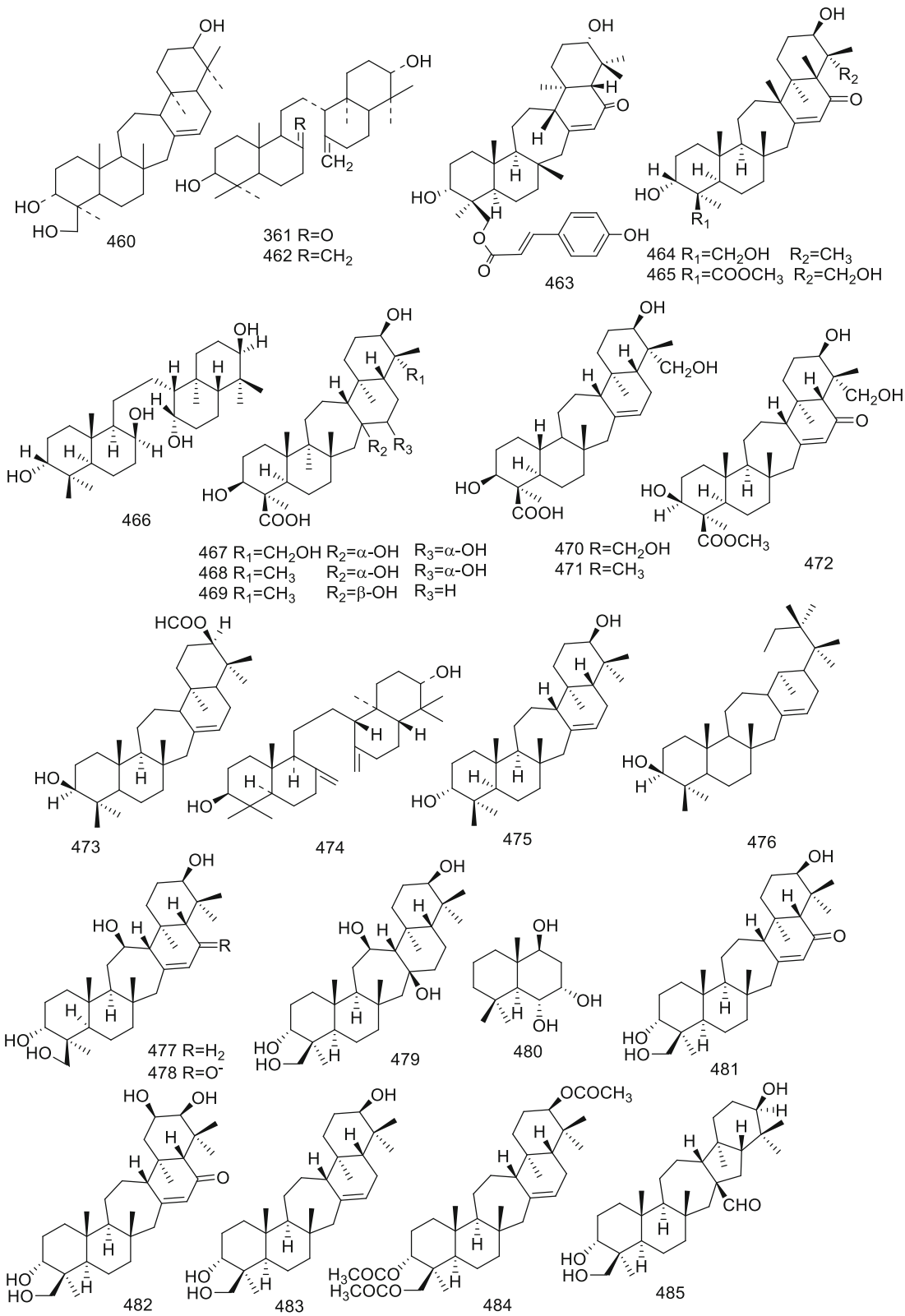



**Fig. 1** continued

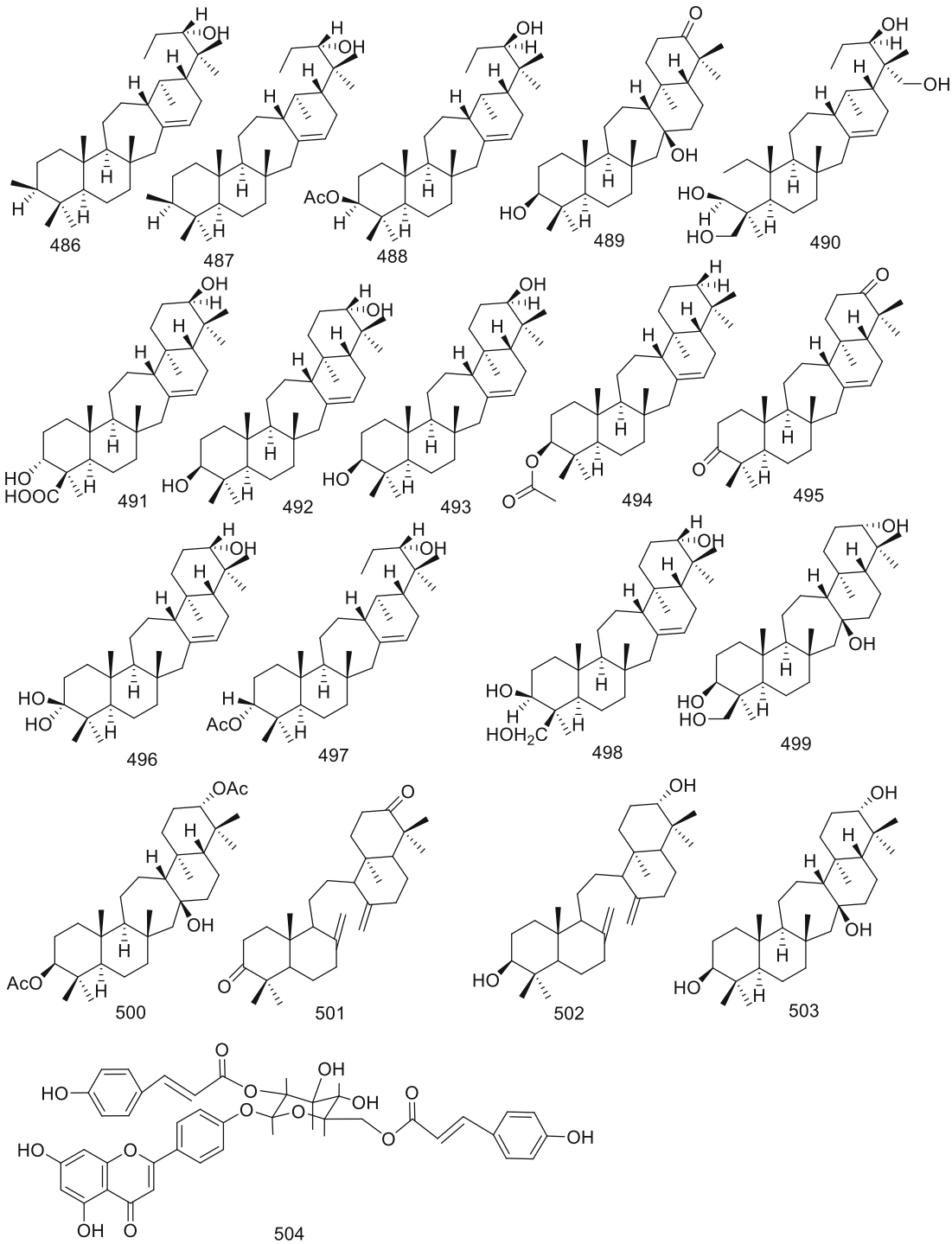



**Fig. 1** continued

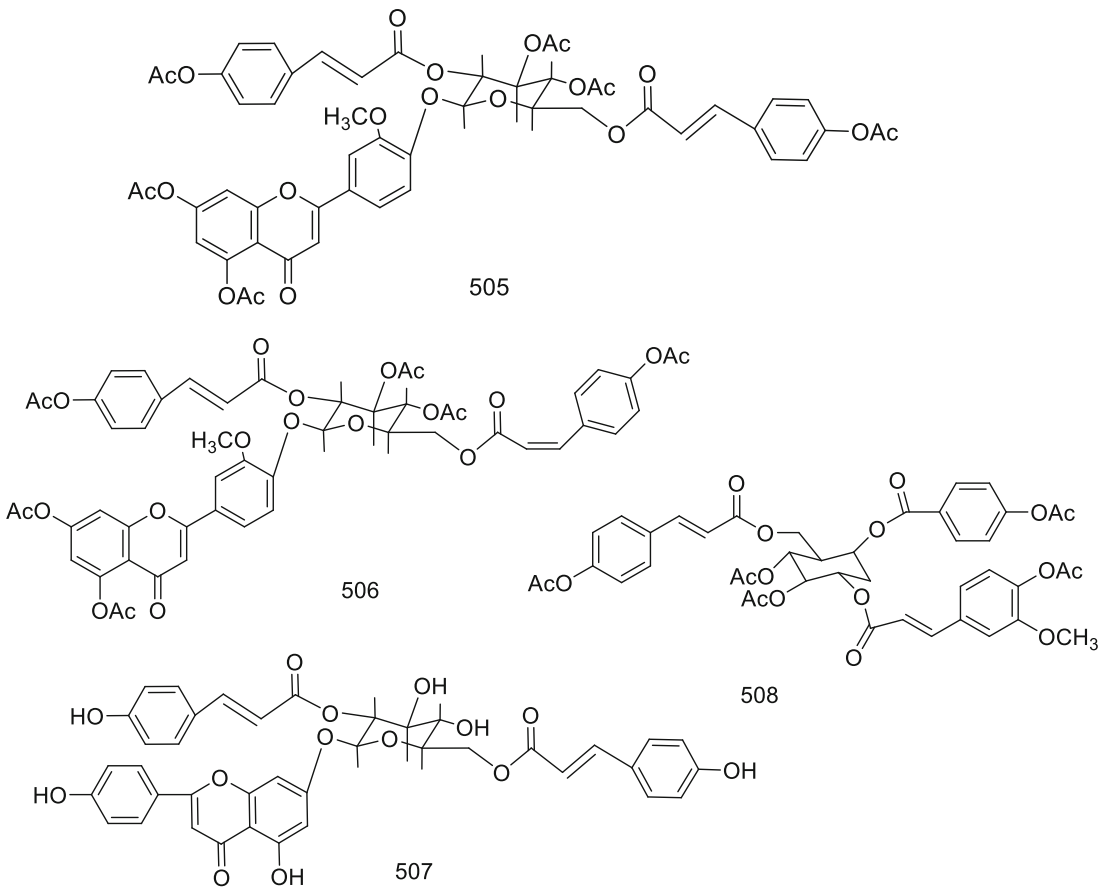



**Fig. 1** continued

microglia and macrophages (Wang et al. 2012a, b). Interestingly, lycojapodine A (**310**), a novel alkaloid with an unprecedented 6/6/6/7 tetracyclic ring system, was also isolated from the club moss *L. japonicum*. Meanwhile, it exhibited anti-human immunodeficiency virus (HIV)-1 activity, showing an $EC_{50}$ value of 85 μg/mL (He et al. 2009).

*Miscellaneous group*

There is no fixed uniform skeleton for this group. In addition to the first three classes, the rest of the *Lycopodium* alkaloids can be classified into this group, and represent quite a diversity of structural motifs. 75 *Lycopodium* alkaloids (**369–443**) are included in this group. Among these, phlegmarine type have the largest number of this group. In all of the miscellaneous group compounds, the C-4 is unconnected to C-12 or C-13. The C-4 of phlegmarine (**425**) always forms a C–C bond with either C-13 or C-12 during the C–C coupling reaction, which leads to the formation of the other three classes. So phlegmarine (**425**) can be regarded as the precursor of the first three kinds of alkaloids.

It was reported that lyconadin B (**395**) is a novel type of alkaloid consisting of five fused rings (one five-membered and four six-membered rings), were able to enhance NGF mRNA expression and production in human glial cells (Ishiuchi et al. 2006a). Zhang et al. found a new $C_{16}N$ skeleton molecule, lycopladine A (**301**), from *L. complanatum* in 2017. The structure of this compound was characterized as 6/9/5 tricyclic skeleton with a *γ*-lactone ring. And the skeleton is constructed from an unusual 1-*oxa*-6-

**Table 2** Secondary metabolites from *Lycopodium* species

| No | Name | Source plants | Plant part | References |
|---|---|---|---|---|
| 1 | Lycopodine | *L. obscurum* | Whole plant | Chen et al. (2014) |
| | | *L. japonicum* | | Halldorsdottir et al. (2013) |
| | | *L. tristachyum* | | Zhu et al. (2018) |
| | | *L. alopecuroides* | | Ayer et al. (1990) |
| | | | | Ayer et al. (1968a) |
| | | *L. clavatum* | | Morale et al. (1979) |
| | | *L. paniculatum* | | Halldorsdottir et al. (2013) |
| | | *L. magellanicum* | | |
| | | | | Wang et al. (2013) |
| | | *L. lucidulum* | | Loyola et al. (1979) |
| | | | | Jiang et al. (2016) |
| | | | | Ayer et al. (1962) |
| | | | | Burnell et al. (1961a, b) |
| 2 | 12β-hydroxyacetylfawcettiine | *L. japonicum* | Whole plant | Cai et al. (2015) |
| 3 | 8β-acetoxy-12β-hydroxy-lycopodine | *L. japonicum* | Whole plant | Wang et al. (2013) |
| 4 | 8β-acetoxy-11α-hydroxy-lycopodine | *L. japonicum* | Whole plant | Cai et al. (2015) |
| 5 | Lycoposerramine M | *L. japonicum* | Whole plant | Wang et al. (2013) |
| 6 | Acetylfawcettiine | *L. japonicum* | Whole plant | Wang et al. (2013) |
| | | *L. fawcettii* | | Burnell et al. (1960) |
| | | *L. obscurum* | | Zhang et al. (2013) |
| | | | | Jiang et al. (2016) |
| 7 | Clavolonine | *L. alpinum* | Whole plant | Halldorsdottir et al. (2013) |
| | | *L. alopecuroides* | | Zhu et al. (2018) |
| | | *L. obscurum* | | Wang et al. (2013) |
| | | | | Ayer et al. (1968a) |
| | | | | Hu et al. (1987) |
| | | | | Pan et al. (2013b) |
| | | *L. clavatum* | | Laemmerhold et al. (2010) |
| | | | | Ayer et al. (1962b) |
| | | | | Burnell et al. (1961) |
| 8 | α-lofoline | *L. japonicum* | Whole plant | Wang et al. (2013) |
| | | *L. annotinum* | | Cai et al. (2015) |
| | | | | Anet et al. (1959) |
| 9 | 6α,8β-Dihydroxylycopodine | *L. japonicum* | Whole plant | Wang et al. (2013) |
| 10 | 4α,8β-Dihydroxylycopodine | *L. japonicum* | Whole plant | Wang et al. (2013) |
| 11 | 8β-hydroxylycodoline | *L. japonicum* | Whole plant | Cai et al. (2015) |
| 12 | 4α,8β,12β-Trihydroxylycopodine | *L. japonicum* | Whole plant | Wang et al. (2013) |
| 13 | 8β-hydroxy-11α-acetoxylycopodine | *L. japonicum* | Whole plant | Wang et al. (2013) |
| 14 | 11β-hydroxy-12-epilycodoline | *L. japonicum* | Whole plant | Yang et al. (2015) |
| | | | | Wang et al. (2013) |
| 15 | 11α-Hydroxy-acetylfawcettine | *L. japonicum* | Whole plant | Wang et al. (2013) |

**Table 2** continued

| No | Name | Source plants | Plant part | References |
|---|---|---|---|---|
| 16 | Acetyllycofawcine | *L. japonicum* | Whole plant | Wang et al. (2013) |
| 17 | Lycoposerramine G | *L. japonicum* | Whole plant | Wang et al. (2013) |
| 18 | Deacetylfawcettiine | *L. japonicum* | Whole plant | Cai et al. (2015) |
| 19 | Fawcettiine (β-lofoline) | *L. japonicum* | Whole plant | Yang et al. (2016a) |
| | | | | Chen et al. (2014) |
| | | *L. obscurum* | | Wang et al. (2013) |
| | | *L. annotinum* | | Anet et al. (1959) |
| | | *L. clavatum* | | Burnell et al. (1961) |
| 20 | Lycofawcine | *Japonicum* | Whole plant | Wang et al. (2013) |
| | | | | Ayer (1965) |
| 21 | 8β-hydroxylycoposerramine K | *L. japonicum* | Whole plant | Wang et al. (2013) |
| 22 | Anhydrolycodoline | *L. obscurum* | Whole plant | Zhang et al. (2013) |
| | | *L. alpinum* | | Halldorsdottir et al. (2013) |
| | | *L. alopecuroides* | | Ayer et al. (1968a) |
| | | *L. japonicum* | | Wang et al. (2013) |
| | | *L. inundatum* | | Morita et al. (2005a, b) |
| 23 | Miyoshianine C | *L. japonicum* | Whole plant | Sun et al. (2008) |
| 24 | Miyoshianine A | *L. japonicum* | Whole plant | Sun et al. (2008) |
| 25 | Lycodoline | *L. annotinum* | Whole plant | Koyama et al. (2004) |
| | | *L. annotinurn* var. *acrifoliurn* | | Chen et al. (2014) |
| | | *L.obscurum* | | Halldorsdottir et al. (2013) |
| | | *L. alpinum* | | Sun et al. (2008) |
| | | *L. alopecuroides* | | Ayer et al. (1990) |
| | | | | Ayer et al. (1968a) |
| | | *L. japonicum* | | Ayer et al. (1962b) |
| | | *L. selago* | | Maclean (1963) |
| | | | | Ayer et al. (1964b) |
| | | *L. lucidulum* | | Manske et al. (1947) |
| | | *L. prostratum* | | Ayer et al. (1963) |
| | | *L. obscurum* | | Jiang et al. (2016) |
| 26 | Huperzine E | *L. serratum* | | Wang et al. (2001) |
| 27 | Lucidioline | *L. serratum* | Whole plant | Zhou et al. (1992) |
| | | *L. japonicum* | | Sun et al. (2008) |
| | | *L. lucidulum* | | Ayer et al. (1969b) |
| 28 | 8β-hydroxyhuperzine E | *L. japonicum* | Whole plant | Wang et al. (2013) |
| 29 | (8β)-8-(acetyloxy)obscurumine A | *L. obscurum* | Whole plant | Pan et al. (2013b) |
| 30 | 12β-hydroxy-acetylfawcettiine *N*-oxide | *L. japonicum* | Whole plant | Yang et al. (2015) |
| 31 | 6α-hydroxylycopodine | *L. lucidulum* | Whole plant | Ayer et al. (1963) |
| 32 | Lannnotinidine A | *L. annotinum* | Whole plant | Koyama et al. (2004) |

**Table 2** continued

| No | Name | Source plants | Plant part | References |
|---|---|---|---|---|
| 33 | 8β-acetoxy-12β-hydroxyepidihydrolycopodine | *L. squarrosum* | Whole plant | Liu et al. (2014) |
| 34 | Acetylacrifoline | *L. obscurum* | Whole plant | Chen et al. (2014) |
| | | | | Ayer et al. (1990) |
| 35 | Acetylannofoline | *L. obscurum* | Whole plant | Chen et al. (2014) |
| | | | | Ayer et al. (1990) |
| 36 | Acetyldihydrolycopodine | *L. obscurum* | Whole plant | Chen et al. (2014) |
| | | | | Zhang et al. (2013) |
| | | *L. paniculatum* | | Morale et al. (1979) |
| | | | | MacLean (1963) |
| | | *L. magellanicum* | | Loyola et al. (1979) |
| | | *L. clavatum* | | Burnell et al. (1961) |
| 37 | Acetylfawcettine | *L. obscurum* | Whole plant | Chen et al. (2014) |
| | | *L. japonicum* | | Zhu et al. (2018) |
| | | | | Loyola et al. (1979) |
| 38 | Acetylfawcettine N-oxide | *L. japonicum* | Whole plant | Zhu et al. (2018) |
| 39 | Acetyllofoline | *L. annotinum* | Whole plant | Ayer et al. (1990) |
| 40 | Acetyllycoposerramin M | *L. japonicum* | Whole plant | Yang et al. (2015) |
| 41 | Acrifoline | *L. annotinum* | Whole plant | Manske et al. (1947) |
| 42 | Anhydrodeacetylpaniculine | *L. paniculatum* | | Southon et al. (1989) |
| | | | | Castillo et al. (1976) |
| | | | | Morale et al. (1979) |
| 43 | Lannnotinidine E | *L. annotinum* | Whole plant | Koyama et al. (2004) |
| 44 | Lannnotinidine F | *L. annotinum* | Whole plant | Koyama et al. (2004) |
| 45 | LannnotinidineG | *L. annotinum* | Whole plant | Koyama et al. (2004) |
| 46 | Annofoline | *L. annotinum* | Whole plant | Anet et al. (1959) |
| 47 | Annotine | *L. annotinum* | Whole plant | Szarek et al. (1964) |
| 48 | Annotinine | *L. annotinum* | Whole plant | Koyama et al. (2004) |
| | | *L. annotinum* | | |
| | | | | Betts et al. (1958) |
| 49 | Deacetylfawcettiine | *L. obscurum* | Whole plant | Jiang et al. (2016) |
| | | | | Laemmerhold et al. (2010) |
| | | *L. fawcettii* | | Pan et al. (2013a) |
| | | *L. japonicum* | | Burnell et al. (1960) |
| | | | | Wang et al. (2013) |
| 50 | Deacetyllycofawcine | *L. obscurum* | Whole plant | Pan et al. (2013b) |
| | | | | Ayer et al. (1965) |
| 51 | Deacetylpaniculine | *L. paniculatum* | | Morale et al. (1979) |
| 52 | Debenzoylalopecurine (2α-hydroxylycopecurine) | *L. inundatum* | Whole plant | Morita et al. (2005a, b) |
| 53 | Dehydroisofawcettiine | *L. obscurum* | Whole plant | Pan et al. (2013a) |

**Table 2** continued

| No | Name | Source plants | Plant part | References |
|---|---|---|---|---|
| 54 | Dihydrolycopodine | *L. paniculatum* | Whole plant | Morale et al. (1979) |
| | | *L. clavatum* | | Ayer et al. (1962b) |
| | | | | Burnell et al. (1961) |
| | | *L. obscurum* | | Johns et al. (1969) |
| | | | Leaves and stems | Hu et al. (1987) |
| 55 | Acetyllycoclavine | *L. fawcettii* | Whole plant | Burnell et al. (1960) |
| 56 | Fawcettine | *L. japonicum* | Whole plant | Zhu et al. (2018) |
| 57 | Fawcettine N-oxide | *L. japonicum* | Whole plant | Zhu et al. (2018) |
| 58 | Flabelliformine | *L. obscurum* | Whole plant | Chen et al. (2014) |
| | | *L. tristachyum* | | Ayer et al. (1990) |
| | | *L. obscurum* | | Jiang et al. (2016) |
| 59 | Flabelline | *L. flabelliforme* | Whole plant | Young et al. (1963) |
| 60 | Isofawcettiine | *L. obscurum* | Whole plant | Pan et al. (2013a) |
| 61 | Isolycopodine | *L. lucidulum* | Whole plant | Ayer et al. (1990) |
| 62 | Lycopocarinamine A | *L. carinatum* | Whole plant | Kogure et al. (2016) |
| 63 | Lycopocarinamine B | *L. carinatum* | Whole plant | Kogure et al. (2016) |
| 64 | Lycopocarinamine C | *L. carinatum* | Whole plant | Kogure et al. (2016) |
| 65 | Lycopocarinamine F | *L. carinatum* | Whole plant | Kogure et al. (2016) |
| 66 | Lycopodatine B | *L. inundatum* | Whole plant | Morita et al. (2005a, b) |
| 67 | Lycopodatine C | *L. inundatum* | Whole plant | Morita et al. (2005a, b) |
| 68 | Lycoposerramine F | *L. serratum* | Whole plant | Takayama et al. (2003) |
| 69 | Lycoposerramine G | *L. serratum* | Whole plant | Takayama et al. (2003) |
| 70 | Lycoposerramine H | *L. serratum* | Whole plant | Takayama et al. (2003) |
| 71 | Lycoposerramine I | *L. serratum* | Whole plant | Takayama et al. (2003) |
| 72 | Lycoposerramine J | *L. serratum* | Whole plant | Takayama et al. (2003) |
| 73 | Lycoposerramine K | *L. serratum* | Whole plant | Takayama et al. (2003) |
| 74 | Lycoposerramine L | *L. serratum* | Whole plant | Takayama et al. (2003) |
| 75 | Lycoposerramine N | *L. serratum* | Whole plant | Takayama et al. (2003) |
| | | *L. carinatum* | | Kogure et al. (2016) |
| 76 | Obscurumine A | *L. obscurum* | Whole plant | Morita et al. (2004) |
| | | | | Morita et al. (2005a, b) |
| 77 | Obscurumine B | *L. obscurum* | Whole plant | Morita et al. (2005a, b) |
| | | | | Jiang et al. (2016) |
| | | | | Chen et al. (2014) |
| 78 | Obscurumine C | *L. obscurum* | Whole plant | Zhang et al. (2013) |

**Table 2** continued

| No | Name | Source plants | Plant part | References |
|---|---|---|---|---|
| 79 | Obscurumine O | *L. obscurum* | Whole plant | Jiang et al. (2016) |
| 80 | Obscurumine P | *L. obscurum* | Whole plant | Jiang et al. (2016) |
| 81 | Paniculine | *L. paniculatum* | | Morale et al. (1979) |
| 82 | Serratezomine C | *L. serratum* | Whole plant | Morita et al. (2000) |
| | | | | Takayama et al. (2003) |
| | | | | Ma et al. (2004) |
| 83 | Serratidine | *L. serratum* | | Takayama et al. (2001) |
| | | | | Ayer et al. (1994) |
| | | | | Ayer (1991) |
| | | | | Takayama et al. (2003) |
| 84 | Annopodine | *L. annottinum* | | Ayer et al. (1973) |
| 85 | 4α,6α-Dihydroxyserratidine | *L. serratum* | | Ma et al. (2004) |
| 86 | lyconnotinol | *L.obscurum* | Whole plant | Ayer et al. (1991) |
| 87 | Lycopocarinamine D | *L. carinatum* | Whole plant | Kogure et al. (2016) |
| 88 | 12-Epilycodoline (isolycodoline or pseudoselagine) | *L. lucidulum* | | Ayer and Altenkirk (1969c) |
| | | | | Southon et al. (1989) |
| | | *L. selago* | | Ayer and Altenkirk (1969c) |
| 89 | Complanadine B | *L. complanatum* | Whole plant | Morita et al. (2005a) |
| 90 | Gnidioidine ($\Delta^{11,12}$,8β-hydroxylycopodine) | *L. gnidioides* | | Nyembo et al. (1978) |
| | | *L. phlegmaria* | | Southon et al. (1989) |
| 91 | Huperzine F | *L. serratum* | | Wang et al. (2001) |
| 92 | 4α-Hydroxyserratidine | *L. serratum* | | Ma et al. (2004) |
| 93 | 6α-Hydroxyserratidine | *L. serratum* | | Ma et al. (2004) |
| 94 | Dehydrolycopecurine (5-ketone-lycopecurine) | *L. alopecuroides* | | Southon et al. (1989) |
| | | *L. inundatum* | | Ayer et al. (1971) |
| 95 | Isoinundatine (2-oxolycopecurine 5-ketone) | *L. inundatum* | | Southon et al. (1989) |
| 96 | Lycopodatine A | *L. inundatum* | Whole plant | Morita et al. (2005a, b) |
| 97 | lycopecurine | *L. alopecuroides* | Whole plant | Ayer et al. (1971) |
| 98 | Inundatine | *L. inundatum* | Whole plant | Morita et al. (2005a, b) |
| 99 | Lycophlegmine (10β-hydroxyanhydrolycodoline) | *L. phlegmaria* | | Southon et al. (1989) |
| | | | | Ma et al. (2004) |
| 100 | 5R,8R-O-acetylfawcettiine | *L. alpinum* | Whole plant | Halldorsdottir et al. (2013) |

**Table 2** continued

| No | Name | Source plants | Plant part | References |
|---|---|---|---|---|
| 101 | 5R,8S-O-acetyllofoline | *L. alpinum* | Whole plant | Halldorsdottir et al. (2013) |
| 102 | 6α-Hydroxy-5,15-oxide-lycopodane | *L.serratum* | Whole plant | Yang et al. (2010) |
| 103 | 8S-O-acetylepiclavolonine | *L. alpinum* | Whole plant | Halldorsdottir et al. (2013) |
| 104 | Lycoclavine | *L. japonicum* | Whole plant | Yang et al. (2016a) |
| | | *L. alpinum* | | Halldorsdottir et al. (2013) |
| 105 | Lycofoline(base H) | *L. annotinum* | Whole plant | Anet et al. (1962) |
| 106 | Huperzine G | *L. serratum* | | Wang et al. (1998) |
| 107 | Huperzine O | *L. serratum* | | Ma et al. (2004) |
| 108 | Lyconesidine C | *L. chinense* | Whole plant | Hirasawa et al. (2002) |
| 109 | Lyconnotine | *L. annotinum* | Whole plant | Anet et al. (1964) |
| | | | | Koyama et al. (2004) |
| 110 | Miyoshianine B (lycoposerramine J) | *L. serratum* | | Takayama et al. (2003) |
| 111 | Selagoline | *L. selago* | | Staerk et al. (2004) |
| 112 | Lycoposerramine O | *L. serratum* | | Takayama et al. (2003) |
| 113 | Lannotinidine H | *L. annotinum* | | Ishiuchi et al. (2009a, b) |
| 114 | Lannotinidine J | *L. annotinum* | | Ishiuchi et al. (2009a, b) |
| 115 | Lannnotinidine C | *L. annotinum* | Whole plant | Koyama et al. (2004) |
| 116 | Lycocarinatine A | *L. carinatum* | Whole plant | Sakornrat et al. (2014) |
| | | | | Kogure et al. (2016) |
| | | | | Thorroad et al. (2014) |
| 117 | Lannotinidine I | *L. annotinum* | | Ishiuchi et al. (2009a, b) |
| 118 | 12-deoxyhuperzine O | *L. complanatum* | Whole plant | Cheng et al. (2013) |
| | | *L. serratum* | | Yang et al. (2010) |
| 119 | 5,15-Oxidolycopodane | *L. annotinum* | Whole plant | Ayer et al. (1990) |
| 120 | 8β,11α-dihydroxylycopodine | *L. clavatum* | Aerial part | Pongpamorn et al. (2016) |
| 121 | Anhydrodihydrolycopodine | *L. tristachyum* | Whole plant | Ayer et al. (1990) |
| 122 | Deacetyllycoclavine | *L. paniculatum* | | Morale et al. (1979) |
| 123 | Diacetyllycofoline | *L. fawcettii* | Whole plant | Burnell et al. (1960) |
| | | *L. japonicum* | | Zhu et al. (2018) |
| 124 | Pseudoselagine | *L. lucidulum* | Whole plant | Ayer et al. (1969c) |
| 125 | Strictumine A | *L. obscurum* | Whole plant | Wang et al. (2016) |
| 126 | Strictumine B | *L. obscurum* | Whole plant | Wang et al. (2016) |

**Table 2** continued

| No | Name | Source plants | Plant part | References |
|---|---|---|---|---|
| 127 | Acrifolinol | *L. annotinum* | | Perry et al. (1956) |
| | | *L. obscurum* | | Ayer et al. (1989a) |
| 128 | Acetyldebenzoylalopecurine | *L. alopecuroides* | Whole plant | Ayer et al. (1969d) |
| 129 | Alopecurine | *L. alopecuroides* | Whole plant | Ayer et al. (1969d) |
| 130 | Lycognidine<br>(5β-*O*-[3-(3,4-dimethoxyphenyl)propionyl]-6α-hydroxydihydro-lycopodine) | *L. gnidioides* | | Southon et al. (1989)<br>Nyembo et al. (1978) |
| 131 | Lycoverticine<br>(12-hydroxy flabelline) | *L. verticillatum* | | Southon et al. (1989) |
| 132 | Malycorin B | *L. carinatum* | Whole plant | Kogure et al. (2016) |
| | | *L. phlegmaria* | | Hirasawa et al. (2008a) |
| 133 | Malycorin C | *L. phlegmaria* | Whole plant | Hirasawa et al. (2008a) |
| 134 | Huperserine A | *L. serratum* | Whole plant | Jiang et al. (2014a, b) |
| 135 | Huperserine B | *L. serratum* | Whole plant | Jiang et al. (2014a, b) |
| 136 | Huperserine C | *L. serratum* | Whole plant | Jiang et al. (2014a, b) |
| 137 | Huperserine D | *L. serratum* | Whole plant | Jiang et al. (2014a, b) |
| 138 | 4-epilycopodine | *L. nummularifolium* | Whole plant | Nilsu et al. (2018) |
| 139 | Acetyllycophlegmarianol | *L. phlegmaria* | Whole plant | Nilsu et al. (2018) |
| 140 | 17α-methyllycoflexine | *L. japonicum* | Whole plant | Yang et al. (2018) |
| 141 | Huperzine Y1 | *L. serratum* | Whole plant | Jiang et al. (2019) |
| 142 | Huperzine Y2 | *L. serratum* | Whole plant | Jiang et al. (2019) |
| 143 | Huperzine Y3 | *L. serratum* | Whole plant | Jiang et al. (2019) |
| 144 | Phlenumdine D | *L. nummularifolium* | Aerial part | Nakayama et al. (2019) |
| 145 | Phlenumdine E | *L. nummularifolium* | Aerial part | Nakayama et al. (2019) |
| 146 | Lycosquarrine A | *L. squarrosum* | Aerial part | Zhu et al. (2020) |
| 147 | Lycosquarrine B | *L. squarrosum* | Aerial part | Zhu et al. (2020) |
| 148 | Lycosquarrine C | *L. squarrosum* | Aerial part | Zhu et al. (2020) |
| 149 | Lycosquarrine D | *L. squarrosum* | Aerial part | Zhu et al. (2020) |
| 150 | Lycosquarrine E | *L. squarrosum* | Aerial part | Zhu et al. (2020) |
| 151 | Lycosquarrine F | *L. squarrosum* | Aerial part | Zhu et al. (2020) |
| 152 | Lycosquarrine G | *L. squarrosum* | Aerial part | Zhu et al. (2020) |
| 153 | Lycosquarrine H | *L. squarrosum* | Aerial part | Zhu et al. (2020) |
| 154 | Lycoplanine B | *L. complanatum* | Whole plant | Zhang et al. (2018a, b) |
| 155 | Lycoplanine C | *L. complanatum* | Whole plant | Zhang et al. (2018a, b) |
| 156 | 12-epilycodoline *N*-oxide | *L. phlegmaria* | Whole plant | Thu et al. (2019) |
| 157 | Lycofargesiine E | *L. fargesii* | Whole plant | Xiong et al. (2019) |

**Table 2** continued

| No | Name | Source plants | Plant part | References |
|---|---|---|---|---|
| 158 | 6β-hydroxyhuperzine A | *L. selago* | Whole plant | Ayer et al. (1991) |
| | | | | Ayer et al. (1989b) |
| 159 | 8,15-dihydrohuperzinine | *L. casuarinoides* | Whole plant | Yin et al. (2006) |
| 160 | Carinatumin A | *L. carinatumm* | Whole plant | Choo et al. (2007) |
| | | *L. carinatum* | | |
| 161 | Carinatumin B | *L. carinatumn* | Whole plant | Choo et al. (2007) |
| | | *L. carinatum* | | |
| 162 | Casuarine A | *L. casuarinoides* | Whole plant | Liu et al. (2013) |
| 163 | Casuarine B | *L. casuarinoides* | Whole plant | Liu et al. (2013) |
| 164 | Complanadine A | *L. complanatum* | Whole plant | Morita et al. (2005a) |
| | | | | Kobayashi et al. (2000) |
| 165 | Complanadine E | *L. complanatum* | Whole plant | Ishiuchi et al. (2011) |
| 166 | Fastigiatine | *L. fastigiatum* | Whole plant | Gerard et al. (1986) |
| | | | | Ayer et al. (1991) |
| 167 | Des-N-methyl-fastigiatine | *L. fastigiatum* | Whole plant | Gerard et al. (1986) |
| | | | | Ayer et al. (1991) |
| 168 | Des-N-methyl-α-obscurine | *L. obscurum* | Whole plant | Chen et al. (2014) |
| | | *L. alpinum* | | Halldorsdottir et al. (2013) |
| | | *L. fawcettii* | | Burnel et al. (1963) |
| 169 | Des-N-methyl-β-obscurine | *L. obscurum* | Whole plant | Pan et al. (2013a) |
| | | | | Ayer et al. (1989a) |
| 170 | Flabellidine | *L. paniculatum* | | Morale et al. (1979) |
| 171 | Himeradine A | *L. chinense* | Whole plant | Morita et al. (2003) |
| 172 | Huperzine A | *L. serratum* | Whole plant | Ayer et al. (1989b) |
| | | | | Ayer et al. (1990) |
| | | | | Ayer et al. (1991) |
| | | | | Ayer et al. (1994) |
| | | | | Liu et al. (1994) |
| | | | | Takayama et al. (2001) |
| 173 | Huperzine B | *L. casuarinoides* | Whole plant | Yin et al. (2006) |
| | | | | Takayama et al. (2001) |
| | | *L. serratum* | | Ayer et al. (1991) |
| 174 | Huperzine C | *L. casuarinoides* | Whole plant | Liu et al. (1994) |
| 175 | Huperzine D | *L. casuarinoides* | Whole plant | Yin et al. (2006) |
| | | | | Liu et al. (1994) |
| 176 | Huperzinine | *L. casuarinoides* | Whole plant | Liu et al. (1994) |
| | | *L. serratum* | | Ayer et al. (1991) |
| 177 | Huperzinine *N*-oxide | *L. casuarinoides* | Whole plant | Yin et al. (2006) |
| 178 | Hydroxypropyllycodine | *L. obscurum* | | Ayer et al. (1989) |

**Table 2** continued

| No | Name | Source plants | Plant part | References |
|---|---|---|---|---|
| 179 | Lycodine | *L. complanatum* | Whole plant | Kobayashi et al. (2000) |
| | | | | Katakawa et al. (2009) |
| | | *L. serratum* | | Wang et al. (2013) |
| | | | | Loyola et al. (1979) |
| | | *L. japonicum* | | Takayama et al. (2001) |
| | | | | Ayer et al. (1994) |
| | | *L. magellanicum* | | Ayer et al. (1991) |
| | | *L. annotinum* | | Anet et al. (1958) |
| | | *L. obscurum* | | Pan et al. (2013b) |
| | | *L. fawcettii* | | Burnel et al. (1963) |
| 180 | Lyconadin D | *L. complanatum* | Whole plant | Ishiuchi et al. (2011) |
| 181 | Lyconadin E | *L. complanatum* | Whole plant | Ishiuchi et al. (2011) |
| 182 | Lycoparin A | *L. casuarinoides* | Whole plant | Hirasawa et al. (2008b) |
| 183 | Lycoparin B | *L. casuarinoides* | Whole plant | Hirasawa et al. (2008b) |
| 184 | Lycoparin C | *L. casuarinoides* | Whole plant | Hirasawa et al. (2008b) |
| 185 | Lycopladine F | *L. complanatum* | Whole plant | Ishiuchi et al. (2009b) |
| 186 | Lycopladine G | *L. complanatum* | Whole plant | Ishiuchi et al. (2009b) |
| 187 | *N, N*-dimethylhuperzine A | *L. serratum* | | Hu et al. (1992) |
| 188 | *N*-demethylhuperzinine | *L. casuarinoides* | Aerial parts | Shen et al. (1994) |
| 189 | N-demethyl-α-obscurine | *L. obscurum* | Whole plant | Jiang et al. (2016) |
| | | | | Braekman et al. (1974) |
| | | | | Zhang et al. (2013) |
| 190 | N-demethyl-β-obscurine | *L. obscurum* | Whole plant | Jiang et al. (2016) |
| | | | | Katakawa et al. (2009) |
| | | | | Zhang et al. (2013) |
| 191 | N-methyl-huperzine B | *L. serratum* | Whole plant | Ayer et al. (1991) |
| 192 | N-methyl-lycodine | *L. magellanicum* | | Loyola et al. (1979) |
| 193 | Phlemariuine M (Phlegmariurine M) | *L. fordii* | Whole plant | Ayer et al. (1991) |
| 194 | Sauroxine | *L. saururus* | Aerial parts | Vallejo et al. (2013) |
| | | | | Ayer et al. (1965) |
| 195 | Selagine | *L. selago* | Whole plant | Ayer et al. (1994) |
| | | | | Ayer et al. (1989b) |
| | | | | Ayer et al. (1991) |

**Table 2** continued

| No | Name | Source plants | Plant part | References |
|---|---|---|---|---|
| 196 | α-obscurine | *L. obscurum* | Whole plant | Ayer et al. (1961) |
| | | *L. japonicum* | | Sun et al. (2008) |
| 197 | β-obscurine | *L. obscurum* | | Ayer et al. (1961) |
| 198 | Huperzine U (2,3-dihydro-12-hydroxyhuperzine B) | *L. serratum* | | Ma et al. (2004) |
| 199 | Hydroxy-des-*N*-methyl-α-obscurine (12-OH) | *L. flabelliforme* | | Southon et al. (1989) |
| 200 | 11-Hydroxylycodine | *L. complanatum* | | Kobayashi et al. (2001) |
| 201 | Lycofargesiine A | *L. fargesii* | Whole plant | Xiong et al. (2019) |
| 202 | Lycofargesiine B | *L. fargesii* | Whole plant | Xiong et al. (2019) |
| 203 | Lycofargesiine C | *L. fargesii* | Whole plant | Xiong et al. (2019) |
| 204 | Lycofargesiine D | *L. fargesii* | Whole plant | Xiong et al. (2019) |
| 205 | Lycoplanine D | *L. complanatum* | Whole plant | Zhang et al. (2018a, b) |
| 206 | Lycosquarrine I | *L. squarrosum* | Aerial part | Zhu et al. (2020) |
| 207 | Lycosquarrine J | *L. squarrosum* | Aerial part | Zhu et al. (2020) |
| 208 | Lycosquarrine K | *L. squarrosum* | Aerial part | Zhu et al. (2020) |
| 209 | Lycosquarrine L | *L. squarrosum* | Aerial part | Zhu et al. (2020) |
| 210 | Lycosquarrine M | *L. squarrosum* | Aerial part | Zhu et al. (2020) |
| 211 | Lycosquarrine N | *L. squarrosum* | Aerial part | Zhu et al. (2020) |
| 212 | Lycosquarrine O | *L. squarrosum* | Aerial part | Zhu et al. (2020) |
| 213 | Lycocasuarine I | *L. casuarinoides* | Aerial part | Zhu et al. (2019) |
| 214 | Lycocasuarine J | *L. casuarinoides* | Aerial part | Zhu et al. (2019) |
| 215 | Lycocasuarine K | *L. casuarinoides* | Aerial part | Zhu et al. (2019) |
| 216 | Lycocasuarine L | *L. casuarinoides* | Aerial part | Zhu et al. (2019) |
| 217 | Lycocasuarine M | *L. casuarinoides* | Aerial part | Zhu et al. (2019) |
| 218 | Lycocasuarine N | *L. casuarinoides* | Aerial part | Zhu et al. (2019) |
| 219 | Lycocasuarine O | *L. casuarinoides* | Aerial part | Zhu et al. (2019) |
| 220 | Lycocasuarine P | *L. casuarinoides* | Aerial part | Zhu et al. (2019) |
| 221 | Lycocasuarine Q | *L. casuarinoides* | Aerial part | Zhu et al. (2019) |
| 222 | Lycoplatyrine A | *L. platyrhizoma* | Whole plant | Yeap et al. (2019) |
| 223 | Lycoplatyrine B | *L. platyrhizoma* | Whole plant | Yeap et al. (2019) |
| 224 | Huperserine E | *L. serratum* | Whole plant | Jiang et al. (2014a, b) |
| 225 | Fawcettidine (base F) | *L. alopecuroides* | Whole plant | Ayer et al. (1969d) |
| 226 | Lycogladine A | *L. complanatum* | Whole plant | Zhang et al. (2018a, b) |
| 227 | Lycogladine B | *L. complanatum* | Whole plant | Zhang et al. (2018a, b) |
| 228 | Lycogladine C | *L. complanatum* | Whole plant | Zhang et al. (2018a, b) |
| 229 | Lycogladine E | *L. complanatum* | Whole plant | Zhang et al. (2018a, b) |
| 230 | Lycogladine D | *L. complanatum* | Whole plant | Zhang et al. (2018a, b) |

**Table 2** continued

| No | Name | Source plants | Plant part | References |
|---|---|---|---|---|
| 231 | Lycogladine F | *L. complanatum* | Whole plant | Zhang et al. (2018a, b) |
| 232 | Lycogladine G | *L. complanatum* | Whole plant | Zhang et al. (2018a, b) |
| 233 | Lycogladine H | *L. complanatum* | Whole plant | Zhang et al. (2018a, b) |
| 234 | Lycoposerramine C | *L. serratum* | Whole plant | Takayama et al. (2002) |
| 235 | Lycoposerramine P | *L. serratum* | Whole plant | Takayama et al. (2002) |
| 236 | Lycoposerramine Q | *L. serratum* | Whole plant | Takayama et al. (2002) |
| 237 | Lycothunine | *L. serratum* | Whole plant | Katakawa et al. (2007) |
| 238 | Palhinine B | *L. japonicum* | Whole plant | Wang et al. (2013) |
| 239 | Anhydroaposerratinine | *L. verticillatum* | | Ma et al. (2004) |
| 240 | 8-Deoxyserratinidine | *L. phlegmaria* | | Ma et al. (2004) |
| 241 | 8-Deoxyserratinine | *L. serratum* | | Ma et al. (2004) |
| 242 | Epidihydrofawcettidine | *L. phlegmaria* | | Ma et al. (2004) |
| 243 | Dihydrolycopoclavamine A | *L. serratum* | Whole plant | Katakawa et al. (2011) |
| 244 | Lycoposquarrosamine A | *L. squarrosum* | Whole plant | Katakawa et al. (2011) |
| 245 | Lycopoclavamine A | *L. clavatum* | Whole plant | Katakawa et al. (2011) |
| 246 | Lycopoclavamine B | *L. clavatum* | Whole plant | Katakawa et al. (2011) |
| 247 | 8β-acetoxyfawcettimine | *L. squarrosum* | Whole plant | Katakawa et al. (2011) |
| 248 | Acetylaposerratinine | *L. squarrosum* | Whole plant | Katakawa et al. (2011) |
| 249 | 8α-hydroxyfawcettimine | *L. squarrosum* | Whole plant | Katakawa et al. (2011) |
| 250 | 8β-hydroxyfawcettimine | *L. squarrosum* | Whole plant | Katakawa et al. (2011) |
| 251 | Fawcettimine | *L. clavatum* | Whole plant | Katakawa et al. (2011) |
| | | *L. squarrosum* | | Katakawa et al. (2009) |
| | | *L. serratum* | | Zhu et al. (2018) |
| | | *L. japonicum* | | He et al. (2009) |
| | | *L. fawcetti* | | Burnell et al. (1961) |
| 252 | (15R)-14,15-Dihydroepilobscurinol | *L. japonicum* | Whole plant | Wang et al. (2013) |
| 253 | 14,15-Dehydrolycoflexine | *L. japonicum* | Whole plant | Wang et al. (2013) |
| 254 | 15-epi-6-hydroxy-6,7-dehydro-8-deoxy-13-dehydroserratinine | *L. japonicum* | Whole plant | Zhu et al. (2018) |
| 255 | 6-hydroxy-6,7-dehydro-8-deoxy-13-dehydroserratinine | *L. japonicum* | Whole plant | Zhu et al. (2018) |
| 256 | 5α-hydroxy-6-oxodihydrophlegmariurine A | *L. japonicum* | Whole plant | Zhu et al. (2018) |
| 257 | 6-hydroxyl-6,7-dehydro-8-deoxy-13-dehydroserratinine | *L. japonicum* | Whole plant | Wang et al. (2013) |

**Table 2** continued

| No | Name | Source plants | Plant part | References |
|---|---|---|---|---|
| 258 | 6-hydroxyl-6,7-dehydrolycoflexine | *L. japonicum* | Whole plant | Wang et al. (2013) |
| 259 | 8β-acetyllycoposerramine U | *L. squarrosum* | Whole plant | Liu et al. (2014) |
| 260 | Acetyllycoposerramine U | *L. squarrosum* | Whole plant | Katakawa et al. (2011) |
| 261 | Lycobscurine A | *L. obscurum* | Whole plant | Pan et al. (2013a) |
| 262 | Lycobscurine B | *L. obscurum* | Whole plant | Pan et al. (2013a) |
| 263 | Lycobscurine C | *L. obscurum* | Whole plant | Pan et al. (2013a) |
| 264 | lycoflexine | *L. obscurum* | Whole plant | Zhang et al. (2013) |
| | | | | Chen et al. (2014) |
| | | *L. japonicum* | | Wang et al. (2013) |
| | | *L. squarrosum* | | Katakawa et al. (2011) |
| 265 | Lycoflexine N-oxide | *L. squarrosum* | Whole plant | Katakawa et al. (2011) |
| 266 | Lycoposerramine U N-oxide | *L. squarrosum* | Whole plant | Sakornrat et al. (2014) |
| 267 | Lycoposerramine A | *L. serratum* | Whole plant | Takayama et al. (2001) |
| 268 | Lycoposerramine B | *L. serratum* | Whole plant | Katakawa et al. (2004) |
| 269 | Lycoposerramine D | *L. serratum* | Whole plant | Takayama et al. (2002) |
| 270 | Lycoposerramine S | *L. serratum* | Whole plant | Takayama et al. (2002) |
| 271 | Lycoposerramine U | *L. serratum* | Whole plant | Takayama et al. (2002) |
| 272 | Palhinine A | *L. japonicum* | Whole plant | Wang et al. (2013) |
| | | | | Zhu et al. (2018) |
| 273 | Lycoposerramine T | *L. serratum* | Whole plant | Katakawa et al. (2009) |
| 274 | N-Formyllycoposerramine T | *L. serratum* | Whole plant | Katakawa et al. (2009) |
| 275 | N-Methyllycoposerramine T | *L. serratum* | Whole plant | Katakawa et al. (2009) |
| 276 | 8-deoxy-13-dehydro-serratinine | *L. japonicum* | Whole plant | Wang et al. (2013) |
| 277 | Lycojaponicumin C | *L. japonicum* | Whole plant | Wang et al. (2012a, b) |
| | | *L. japonicum* | | |
| | | | | Zhu et al. (2018) |
| 278 | Plegmariurine B | *L. japonicum* | Whole plant | Zhu et al. (2018) |
| 279 | Acetyllobscurinol | *L. ophioglossoides* | | Ayer et al. (1989a) |
| 280 | Alopecuridine | *L. alopecuroides* | | Ayer et al. (1968a) |
| 281 | Lycophlegmarine | *L. phlegmaria* | | Ma et al. (2004) |
| 282 | Serratezomine A | *L. serratum* | Whole plant | Morita et al. (2000) |
| 283 | Serratezomine B | *L. serratum* | Whole plant | Morita et al. (2000) |
| 284 | Serratinine | *L. serratum* | Whole plant | Zhou et al. (1992) |
| 285 | Sieboldine A | *L. sieboldii* | Whole plant | Hirasawa et al. (2003) |
| 286 | 8-deoxy-13-dehydroserratinine | *L. japonicum* | Whole plant | Cai et al. (2015) |

**Table 2** continued

| No | Name | Source plants | Plant part | References |
|---|---|---|---|---|
| 287 | Serratanidine | *L. serratum* | Whole plant | Katakawa et al. (2007) |
| 288 | Serratine | *L. serratum* | Whole plant | Katakawa et al. (2007) |
| 289 | Malycorin A | *L. phlegmaria* | Whole plant | Hirasawa et al. (2008a) |
| 290 | Megastachine | *L. megastachyum* | Whole plant | Braekman et al. (1979) |
| 291 | 5-dehydromagellanine | *L. magellanicum* | | Loyola et al. (1979) |
| 292 | Magellanine | *L. magellanicum* | Whole plant | Castillo et al. (1976) |
| 293 | Magellaninone | *L. magellanicum* | Whole plant | Loyola et al. (1979) |
| 294 | 8α-hydroxylycojapodine A | *L. squarrosum* | Whole plant | Liu et al. (2014) |
| 295 | Alolycopine | *L. alopecuroides* | Whole plant | Ayer et al. (1969ad) |
| 296 | Lannnotinidine B | *L. annotinum* | Whole plant | Koyama et al. (2004) |
| 297 | Lycojaponicumin A | *L. japonicum* | Whole plant | Wang et al. (2012a, b) |
| 298 | Lycojaponicumin B | *L. japonicum* | Whole plant | Wang et al. (2012a, b) |
| 299 | Lyconesidine A | *L. chinense* | Whole plant | Hirasawa et al. (2002) |
| 300 | Lyconesidine B | *L. chinense* | Whole plant | Hirasawa et al. (2002) |
| 301 | Lycopladine A | *L. complanatum* | Whole plant | Ishiuchi et al. (2006b) |
| 302 | Lycopladine B | *L. complanatum* | | Ishiuchi et al. (2006a) |
| 303 | Lycopladine C | *L. complanatum* | | Ishiuchi et al. (2006a) |
| 304 | Lycopladine D | *L. complanatum* | | Ishiuchi et al. (2006a) |
| 305 | Lycoposerramine E | *L. serratum* | Whole plant | Takayama et al. (2002) |
| 306 | Obscurumine H | *L. obscurum* | Whole plant | Jiang et al. (2016) |
| 307 | Obscurumine I | *L. obscurum* | Whole plant | Jiang et al. (2016) |
| 308 | Obscurumine K | *L. obscurum* | Whole plant | Jiang et al. (2016) |
| 309 | Lobscurinol | *L. phlegmaria* | Whole plant | Wang and Wu et al. (2015) |
| 310 | Lycojapodine A | *L. japonicum* | Whole plant | He et al. (2009) |
| | | | | Zhu et al. (2018) |
| 311 | Lycoposerramine E | *L. phlegmaria* | Whole plant | Wang and Wu (2015) |
| 312 | Macleanine | *L. serratum* | Whole plant | Ayer et al. (1994) |
| 313 | Obscurinine | *L. obscurum* | Whole plant | Jiang et al. (2016) |
| | | | | Ayer et al. (1989a) |
| | | *L. japonicum* | | Hu et al. (1987) |
| | | | | Zhu et al. (2018) |
| 314 | Obscurumine D | *L. obscurum* | Whole plant | Zhang et al. (2013) |

**Table 2** continued

| No | Name | Source plants | Plant part | References |
|---|---|---|---|---|
| 315 | Obscurumine E | *L. obscurum* | Whole plant | Zhang et al. (2013) |
| 316 | Obscurumine F<br>=(5β,15S)-15-Methyl-8-oxolycopod-11-en-5-yl Acetate | *L. obscurum* | Whole plant | Chen et al. (2014) |
| 317 | Obscurumine G<br>=(5β,15R)-15-Hydroxy-15-methyl-8-oxolycopodan-5-yl Acetate | *L. obscurum* | Whole plant | Chen et al. (2014) |
| 318 | Obscurumine J | *L. obscurum* | Whole plant | Jiang et al. (2016) |
| 319 | Obscurumine L | *L. obscurum* | Whole plant | Jiang et al. (2016) |
| 320 | Obscurumine M | *L. obscurum* | Whole plant | Jiang et al. (2016) |
| 321 | Epilobscurinol | *L. ophioglossoides* | | Ayer et al. (1989a) |
| 322 | Huperserratinine | *L. serratum* | | Zhu et al. (1994) |
| 323 | Huperzine H | *L. serratum* | | Ma et al. (2004) |
| 324 | Huperzine I<br>(2*a*-hydroxyfawcettidine) | *L. serratum* | | Ma et al. (2004) |
| 325 | Huperzine P | *L. serratum* | | Ma et al. (2004) |
| 326 | Huperzine Q | *L. serratum* | | Ma et al. (2004) |
| 327 | Huperzine R | *L. serratum* | | Ma et al. (2004) |
| 328 | Huperzine S (2*b*,13*b*-epoxyalopecuridine) | *L. serratum* | | Ma et al. (2004) |
| 329 | Huperzine T (5*a*-hydroxy-6-oxodihydrophlegmariurine A) | *L. serratum* | | Ma et al. (2004) |
| 330 | Huperzine W | *L. serratum* | | Ma et al. (2004) |
| 331 | 8*a*-Hydroxyphlegmariurine B | *L. serratum* | | Ma et al. (2004) |
| 332 | 8*b*-Hydroxyphlegmariurine B | *L. serratum* | | Yuan et al. (2003) |
| 333 | Lyconesidine A | *L. chinense* | | Anet et al. (1962) |
| 334 | Lyconesidine B | *L. chinense* | | Anet et al. (1962) |
| 335 | Lycoposerramine A | *L. serratum* | | Takayama et al. (2001) |
| 336 | Lycoposerramine C | *L. serratum* | | Takayama et al. (2002) |
| 337 | Lycoposerramine D | *L. serratum* | | Takayama et al. (2002) |
| 338 | Lycoposerramine U | *L. serratum* | | Takayama et al. (2002) |
| 339 | Lycoposerramine P | *L. serratum* | | Takayama et al. (2002) |
| 340 | Lycoposerramine Q | *L. serratum* | | Takayama et al. (2002) |
| 341 | Lycoposerramine S | *L. serratum* | | Takayama et al. (2002) |
| 342 | 2-Oxophlegmariurine B | *L. serratum* | | Ma et al. (2004) |
| 343 | 11-Oxophlegmariurine B | *L. serratum* | | Ma et al. (2004) |
| 344 | *N*-Oxyhuperzine Q | *L. serratum* | | Ma et al. (2004) |
| 345 | Phlegmariurine A | *L. fordii*<br>*L. serratum* | | Ma et al. (2004) |
| 346 | Phlegmariurine B | *L. fordii*<br>*L. serratum* | | Ma et al. (2004) |
| 347 | Phlegmariurine C | *L. fordii* | | Ma et al. (2004) |

**Table 2** continued

| No | Name | Source plants | Plant part | References |
|---|---|---|---|---|
| 348 | Fawcettimane | *L. obscurum* | Whole plant | Ayer et al. (1991) |
| 349 | Isoobscurinine | *L. obscurum* | Whole plant | Jiang et al. (2016) |
| | | | | Ayer et al. (1989a) |
| | | *L. japonicum* | | Zhu et al. (2018) |
| 350 | Serratinidine (5*a*-NHAc,8*a*-OH-fawcettidine) | *L.serratum* | | Ma et al. (2004) |
| 351 | 7*a*-Hydroxyphlegmariurine B | *L. serratum* | | Ma et al. (2004) |
| 352 | 11*a*-Hydroxyphlegmariurine B | *L. serratum* | | Ma et al. (2004) |
| 353 | 7-Hydroperoxy-phlegmariurine B | *L. serratum* | | Ma et al. (2004) |
| 354 | 11*a*-Hydroperoxy-phlegmariurine B | *L. serratum* | | Ma et al. (2004) |
| 355 | 2*a*-Hydroxyphlegmariurine B | *L. serratum* | | Ma et al. (2004) |
| 356 | 7*a*,11*a*-Dihydroxy-phlegmariurine B | *L. serratum* | | Ma et al. (2004) |
| 357 | 11α-hydroxyfawcettidine | *L. serratum* | Whole plant | Katakawa et al. (2007) |
| 358 | Paniculatine | *L. paniculatum* | Whole plant | Castillo et al. (1976) |
| 359 | 8α,11α-dihydroxyfawcettidine | *L. serratum* | Whole plant | Katakawa et al. (2007) |
| 360 | 8α-hydroxylycothunine | *L. serratum* | Whole plant | Katakawa et al. (2007) |
| 361 | Lycosquarrine P | *L. squarrosum* | Aerial part | Zhu et al. (2020) |
| 362 | Lycosquarrine Q | *L. squarrosum* | Aerial part | Zhu et al. (2020) |
| 363 | Lycoplatyrine C | *L. platyrhizoma* | Whole plant | Yeap et al. (2019) |
| 364 | Phlegmadine B | *L. phlegmaria* | | Zhang et al. (2020) |
| 365 | Phlegmadine C | *L. phlegmaria* | | Zhang et al. (2020) |
| 366 | Squarrosinoxide | *L. squarrosum* | Whole plant | Nilsu et al. (2018) |
| 367 | Phlegmadine A | *L. phlegmaria* | Whole plant | Zhang et al. (2019) |
| 368 | 14-hydroxylobscurinol | *L. phlegmaria* | Whole plant | Zhang et al. (2019) |
| 369 | (+)-cermizine D | *L. obscurum* | Whole plant | Pan et al. (2013b) |
| 370 | (+)-cermizine D N-oxide | *L. obscurum* | Whole plant | Pan et al. (2013b) |
| 371 | 2-hydroxycernuine | *L. cernuum* | Aerial parts | Morel et al. (2012) |
| 372 | 4β-hydroxynankakurine B | *L. phlegmaria* | Whole plant | Wang and Wu et al. (2015) |
| 373 | Carinatumin C | *L. carinatumn* | Whole plant | Choo et al. (2007) |
| | | *L. carinatum* | | Choo et al. (2007) |
| 374 | Cermizine A | *L. cernuum* | Whole plant | Morita et al. (2005a) |
| 375 | Cermizine B | *L. cernuum* | Whole plant | Morita et al. (2004) |
| 376 | Cermizine C | *L. cernuum* | Whole plant | Morita et al. (2004) |
| 377 | Cermizine C N-oxide | *L. cernuum* | Whole plant | Morita et al. (2004) |
| 378 | Cermizine D | *L. cernuum* | Whole plant | Morita et al. (2004) |
| 379 | Cernuine | *L. cernuum* | Whole plant | Ayer et al. (1967ab) |
| | | | | Morita et al. (2004) |
| 380 | Cernunine N-oxide | *L. cernuum* | Whole plant | Morita et al. (2004) |
| 381 | Cryptadine A | *L. cryptomerinum* | Whole plant | Koyama et al. (2007) |
| 382 | Cryptadine B | *L. cryptomerinum* | Whole plant | Koyama et al. (2007) |
| 383 | Dihydrolycolucine | *L. lucidulum* | Whole plant | Ayer et al. (1979) |

**Table 2** continued

| No | Name | Source plants | Plant part | References |
|---|---|---|---|---|
| 384 | Lucidine A | *L. lucidulum* | | Tori et al. (2000) |
| 385 | Lucidine B | *L. lucidulum* | Whole plant | Tori et al. (2000) |
| | | | | Ayer et al. (1979) |
| 386 | Luciduline | *L. lucidulum* | Whole plant | Ayer et al. (1968b) |
| 387 | Lucidulinone (9-ketoluciduline) | *L. lucidulum* | Whole plant | Tori et al. (2000) |
| 388 | Lycocernuine (12α-hydroxycernuine) | *L. cernuum* | Whole plant | Ayer et al. (1967ab) Morita et al. (2004) |
| 389 | Lycocernunie N-oxide | *L. cernuum* | Whole plant | Morita et al. (2004) |
| 390 | Lycochinine A | *L. chinense* | Whole plant | Hirasawa et al. (2009) |
| 391 | Lycochinine B | *L. chinense* | Whole plant | Hirasawa et al. (2009) |
| 392 | Lycochinine C | *L. chinense* | Whole plant | Hirasawa et al. (2009) |
| 393 | Lycolucine (10,11,14,15,16, 17-hexadehydro-lucidine B) | *L. lucidulum* | Whole plant | Ayer et al. (1979) |
| 394 | Lyconadin A | *L. complanatum* | Whole plant | Kobayashi et al. (2001) |
| 395 | Lyconadin B | *L. complanatum* | Whole plant | Ishiuchi et al. (2006b, c, a) |
| 396 | Lycoperine A | *L. hamiltonii* | Whole plant | Hirasawa et al. (2006) |
| 397 | Lycopladine H | *L. complanatum* | Whole plant | Sacher et al. (2012) Ishiuchi et al. (2009a) |
| 398 | Lycoposerramine V | *L. serratum* | Whole plant | Shigeyama et al. (2007) |
| 399 | Lycoposerramine W | *L. serratum* | Whole plant | Shigeyama et al. (2007) |
| 400 | Lycoposerramine X | *L. serratum* | Whole plant | Katakawa et al. (2006) |
| 401 | Lycoposerramine Y | *L. serratum* | Whole plant | Katakawa et al. (2006) |
| 402 | Lycoposerramine Z | *L. serratum* | Whole plant | Katakawa et al. (2006) |
| 403 | *N, N*-dimethylphlegmarine | *L. clavatum* | Whole plant | Ayer et al. (1990) |
| 404 | Nankakurine A | *L. hamiltonii* | Whole plant | Hirasawa et al. (2004) |
| 405 | Nankakurine B | *L. phlegmaria* | Whole plant | Wang and Wu et al. (2015) |
| 406 | Nicotine | *L. cernuum* | Whole plant | Marion et al. (1948) |
| 407 | Oxolucidine A | *L. lucidulum* | | Tori et al. (2000) |
| 408 | Oxolucidine B (or serratanine B, 14β-hydroxy-lucidine B) | *L. lucidulum* | | Tori et al. (2000) |
| 409 | $\Delta^{13,N}$,$N_{\alpha}$-methylphlegmarine-$N_{\beta}$-oxide | *L. phlegmaria* | Whole plant | Wang and Wu et al. (2015) |
| 410 | Anhydrolycocernuine (deoxy-$\Delta^{12,13}$-lycocernuine) | *cernuum* | | Ma et al. (2004) |
| | | *L. inundatum* | | |
| | | *L. carolinianum* | | Braekman et al. (1974) |

**Table 2** continued

| No | Name | Source plants | Plant part | References |
|---|---|---|---|---|
| 411 | Carolinianine (14,15-didehydrolycocernuine) | *L. carolinianum* | | Ma et al. (2004) |
| 412 | Dihydrodeoxycernuine (deoxy-deoxolycocernuine) | *L. carolinianum* | | Ma et al. (2004) |
| | | | | Braekman et al. (1974) |
| 413 | Dihydrodesoxy lycocernuine (deoxolycocernuine) | *L. carolinianum* | | Ma et al. (2004) |
| | | | | Braekman et al. (1974) |
| 414 | Dihydroluciduline (5α-OH) | *L. lucidulum* | | Ma et al. (2004) |
| 415 | Huperzine J | *L. serratum* | | Ma et al. (2004) |
| 416 | Huperzine K | *L. serratum* | | Ma et al. (2004) |
| 417 | Huperzine L | *L. serratum* | | Ma et al. (2004) |
| 418 | Huperzine V | *L. serratum* | | Ma et al. (2004) |
| 419 | Huperzinine B | *L. serratum* | | Ma et al. (2004) |
| 420 | Lycocernuine *N*-oxide | *L. cernuum* | | Ma et al. (2004) |
| 421 | Lyconadine A | *L. complanatum* | | Ma et al. (2004) |
| 422 | $N_{\alpha}$-Methyl-$N_{\beta}$-acetyl-phlegmarine | *L. clavatum* | | Ma et al. (2004) |
| | | | | Nyembo et al. (1978) |
| 423 | $N_{\alpha}$-Methylphlegmarine | *L. phlegmaria* | | Ma et al. (2004) |
| 424 | $N_{\beta}$-Methylphlegmarine | *L. phlegmaria* | | Ma et al. (2004) |
| 425 | Phlegmarine | *L. phlegmaria* | | Ma et al. (2004) |
| 426 | Phlegmariurine N | *L. serratum* | | Ma et al. (2004) |
| 427 | Serralongamine A | *L. serratum* var. *longipetiolatum* | Whole plant | Jiang et al. (2014a, b) |
| 428 | Senepodine A | *L. chinense* | Whole plant | Morita et al. (2001) |
| 429 | Senepodine B | *L. chinense* | | Hirasawa et al. (2003) |
| 430 | Senepodine C | *L. chinense* | | Hirasawa et al. (2003) |
| 431 | Senepodine D | *L. chinense* | | Hirasawa et al. (2003) |
| 432 | Senepodine E | *L. chinense* | | Hirasawa et al. (2003) |
| 433 | Senepodine G | *L. chinense* | | Morita et al. (2004) |
| 434 | Senepodine H | *L. chinense* | | Morita et al. (2004) |
| 435 | Spirolucidin | *L. lucidulum* | Whole plant | Ayer et al. (1984) |
| 436 | Lycosquarrine R | *L. squarrosum* | Aerial part | Zhu et al. (2020) |
| 437 | Lycofargesiine F | *L. fargesii* | Whole plant | Xiong et al. (2019) |
| 438 | Hupercumine A | *L. cunninghamioides* | | Hirasawa et al. (2018) |
| 439 | Hupercumine B | *L. cunninghamioides* | | Hirasawa et al. (2018) |
| 440 | (+)-Huperzine Z | *L. serratum* | Whole plant | Jiang et al. (2019) |
| 441 | (-)-Huperzine Z | *L. serratum* | Whole plant | Jiang et al. (2019) |
| 442 | Huperserratine A | *L. serratum* | Whole plant | Wu et al. (2020) |

**Table 2** continued

| No | Name | Source plants | Plant part | References |
|---|---|---|---|---|
| 443 | Huperserratine B | *L. serratum* | Whole plant | Wu et al. (2020) |
| 444 | (3β,8β,14α,21α)-dinoronocerane-3,8,14,21-tetrol | *L. japonicum* | Whole plant | Yan et al. (2005a, b) |
| 445 | (3β,8β,14α,21β)-dinoronocerane-3,8,14,21-tetrol | *L. japonicum* | Whole plant | Yan et al. (2005a, b) |
| 446 | (3α,8β,14α,21β)-26,27-dinoronocerane-3,8,14,21-tetrol | *L. obscurum* | Whole plant | Zhao et al. (2010) |
| 447 | 16-Oxodiepiserratenediol | *L. clavatum* | Whole plant | Tsuda et al. (1969) |
| 448 | 16-Oxoepiserratenediol | *L. clavatum* | Whole plant | Tsuda et al. (1969) |
| 449 | 16-Oxolycoclavanol | *L. clavatum* | Whole plant | Tsuda et al. (1969) |
| 450 | 16-oxoserrat-14-en-3α,21β,-24-triol | *L. clavatum* | Whole plant | Tsuda et al. (1970) |
| 451 | 16-oxoserrat-14-en-3β,21α,24-triol | *L. serratum* | Whole plant | Tsuda et al. (1970) |
| 452 | 16-oxoserratenediol | *L. clavatum* | Whole plant | Tsuda et al. (1969) |
| 453 | 16-oxoserratriol | *L. lucidulum* | Whole plant | Orito et al. (1972) |
| 454 | 21-episerratenediol | *L. megastachyum* | Stems | Miller et al. (1972) |
| | | *L. japonicum* | | Wang et al. (2014) |
| 455 | 21-epi-serratenediol-3-acetate | *L. megastachyum* | Stems | Miller et al. (1972) |
| 456 | 21-Episerratriol(serrat-14 ene-3β,21β,24-triol) | *L. clavatum* | Whole plant | Tsuda et al. (1969) |
| 457 | 21β-hydroxyserrat-14-en-3β-yl-acetate | *L. japonicum* | | Wang et al. (2014) |
| 458 | 21β-hydroxyserrat-14-en-3β-yl-formate | *L. japonicum* | | Wang et al. (2014) |
| 459 | 26-nor-8β-hydroxy-α-onocerin | *L. obscurum* | Whole plant | Zhao et al. (2010) |
| 460 | 3α,21β,24-trihydroxyserrat-14-ene | *L. clavatum* | Whole plant | Trofimova et al. (1996) |
| 461 | 3β,21α-dihydroxy-26-nor-8,14-sekogammaser-14(27)-en-8-one | *L. clavatum* | Whole plant | Trofimova et al. (1996) |
| 462 | 3β,21α-dihydroxy-8,14-sekogammasera-8(26),14(27)-diene | *L. clavatum* | Whole plant | Trofimova et al. (1996) |
| 463 | 3α,21α-dihydroxy-16-oxoserrat-14-en-24-yl *p*-coumarate | *L. japonicum* | Whole plant | Sun et al. (2017) |
| 464 | 3α,21β,24-trihydroxyserrat-14-en-16-one (lycernuic ketone C) | *L. cernuum* | A mixture of root-stem-leaf | Zhang et al. (2002a) |
| 465 | 3α,21β,29-trihydroxy-16-oxoserrat-14-en-24-methyl ester (lycernuic ketone B) | *L. cernuum* | A mixture of root-stem-leaf | Zhang et al. (2002a) |
| 466 | 3α,8β,14α,21β-tetrahydroxy-26,27-bisnoronocerane | *L. clavatum* | Whole plant | Sano et al. (1970a) |
| 467 | 3β,14α,15α,21β,-29-pentahydroxyserratane-24-oic acid (lycernuic acid C) | *L. cernuum* | A mixture of root-stem-leaf | Zhang et al. (2002a) |
| 468 | 3β,14α,15α,21β-tetrahydroxyserratane-24-oic acid (lycernuic acid D) | *L. cernuum* | A mixture of root-stem-leaf | Zhang et al. (2002a) |
| 469 | 3β,14β,21β-trihydroxyserratane-24-oic acid (lycernuic acid E) | *L. cernuum* | A mixture of root-stem-leaf | Zhang et al. (2002a) |
| 470 | 3β,21β,29-dihydroxyserrat-14-en-24-oic acid (lycernuic acid A) | *L. cernuum* | A mixture of root-stem-leaf | Zhang et al. (2002a) |
| 471 | 3β,21β,29-trihydroxy-16-oxoserrat-14-en-24-methyl ester (lycernuic ketone A) | *L. cernuum* | A mixture of root-stem-leaf | Zhang et al. (2002a) |
| 472 | 3β,21β-dihydroxyserrat-14-en-24-oic acid (lycernuic acid A) | *L. cernuum* | A mixture of root-stem-leaf | Zhang et al. (2002a) |
| 473 | 3β-hydroxyserrat-14-en-21β-yl-formate | *L. japonicum* | | Wang et al. (2014) |
| 474 | Diepiserratenediol | *L. clavatum* | Whole plant | Tsuda et al. (1969) |
| 475 | Episerratenediol | *L. lucidulum* | Whole plant | Orito et al. (1972) |
| 476 | Hydroxyserratenone | *L. phlegmaria* | Leaves and stems | Inubushi et al. (1971) |

**Table 2** continued

| No | Name | Source plants | Plant part | References |
|---|---|---|---|---|
| 477 | Japonicumin A | *L. japonicum* | Whole plant | Li et al. (2006a) |
| 478 | Japonicumin B | *L. japonicum* | Whole plant | Li et al. (2006a) |
| 479 | Japonicumin C | *L. japonicum* | Whole plant | Li et al. (2006a) |
| 480 | Japonicumin D | *L. japonicum* | Whole plant | Li et al. (2006a) |
| 481 | Lycernuic ketone C | *L. japonicum* | Whole plant | Sun et al. (2017) |
| 482 | Lycoclavanin | *L. clavatum* | Whole plant | Tsuda et al. (1970) |
| | | | | Tsuda et al. (1969) |
| 483 | Lycoclavanol | *L. megastachyum* | Stems | Miller et al. (1972) |
| | | *L. clavatum* | | Tsuda et al. (1969) |
| | | *L. japonicum* | Whole plant | Wang et al. (2014) |
| 484 | Lycoclavanol triacetate | *L. megastachyum* | Stems | Miller et al. (1972) |
| 485 | Lycopodiin A | *L. japonicum* | Whole plant | Yan et al. (2005a, b) |
| 486 | Phlegmanol D | *L. megastachyum* | Stems | Miller et al. (1972) |
| | | *L. phlegmaria* | Leaves and stems | Inubushi et al. (1971) |
| 487 | Phlegmanol A | *L. phlegmaria* | Leaves and stems | Inubushi et al. (1971) |
| 488 | Phlegmanol B | *L. phlegmaria* | Leaves and stems | Inubushi et al. (1971) |
| 489 | Phlegmanol C | *L. phlegmaria* | Leaves and stems | Inubushi et al. (1971) |
| 490 | Phlegmanol E | *L. phlegmaria* | Leaves and stems | Inubushi et al. (1971) |
| 491 | Phlegmaric acid | *L. phlegmaria* | Leaves and stems | Inubushi et al. (1971) |
| 492 | Serrat-14-en-3β,21α-diol | *L. cernuum* | A mixture of root-stem-leaf | Zhang et al. (2002a) |
| 493 | Serrat-14-en-3β,21β-diol | *L. cernuum* | A mixture of root-stem-leaf | Zhang et al. (2002a) |
| 494 | Serrat-14-en-3β-yl-acetate | *L. japonicum* | | Wang et al. (2014) |
| 495 | Serrate-14-en-3,21-dione | *L. japonicum* | | Wang et al. (2014) |
| 496 | Serratenediol | *L. phlegmaria* | Leaves and stems | Inubushi et al. (1971) |
| | | *L. serratum* | | Inubushi et al. (1967a) |
| | | *L. complanatum* | | Wang et al. (2014) |
| | | *L. japonicum* | Whole plant | |
| 497 | Serratenediol-3-acetate | *L. phlegmaria* | Leaves and stems | Inubushi et al. (1971) |
| | | *L. megastachyum* | Stems | Miller et al. (1972) |
| 498 | Serratriol | *L. phlegmaria* | Leaves and stems | Inubushi et al. (1971) |
| 499 | Tohogeninol | *L. lucidulum* | Whole plant | Orito et al. (1972) |
| 500 | Tohogenol | *L. phlegmaria* | Leaves and stems | Inubushi et al. (1971) |
| | | | | Orito et al. (1972) |

**Table 2** continued

| No | Name | Source plants | Plant part | References |
|---|---|---|---|---|
| | | *L. japonicum* | Whole plant | Sun et al. (2017) |
| | | *L. complanatum* | | Inubushi et al. (1967a) |
| 501 | Tohogenol diacetate | *L. megastachyum* | Stems | Miller et al. (1972) |
| 502 | α-onoceradienedione | *L. japonicum* | | Wang et al. (2014) |
| 503 | α-onocerin | *L. japonicum* | Whole plant | Wang et al. (2014) |
| | | *L. clavatum* | | Tsuda et al. (1969) |
| 504 | Apigenin-4′-O-(2,6-di-O-*p*-coumaroyl-β-D-glucopyranoside) | *L. clavatum* | Leaves | Ansari et al. (1979) |
| | | *L. cernuum* | Leaves and stems | Tori et al. (2005) |
| | | | A mixture of root-stem-leaf | Zhang et al. (2002a) |
| 505 | 1b | *L. clavatum* | Leaves and stems | Tori et al. (2005) |
| 506 | 2b | *L. clavatum* | Leaves and stems | Tori et al. (2005) |
| 507 | Apigenin-7-O-β-D-(2,6-di-O-*p*-coumaroyl)glucoside | *L. clavatum* | Leaves and stems | Tori et al. (2005) |
| | | | | Rao et al. (1983) |
| 508 | 3b | *L. clavatum* | Leaves and stems | Tori et al. (2005) |

*Lycopodium casuarinoides* Spring is a synonym of *Lycopodiastrum casuarinoides* (Spring) Holub; *Lycopodium phlegmaria* L. is a synonym of *Phlegmariurus phlegmaria* (L.) Holub; *Lycopodium saururus* Lam. is a synonym of *Phlegmariurus saururus* (Lam.) B. Øllg; *Lycopodium serratum* Thumb. is a synonym of *Huperzia serrata* (Thunb.) Trev; *Lycopodium nummularifolium* Blume is a synonym of *Phlegmariurus nummularifolius* (Blume) Ching; *Lycopodium cunninghamioides* Hayata is a synonym of *Huperzia cunninghamioides* (Hayata) Holub; *Lycopodium fargesii* Herter is a synonym of *Huperzia fargesii* (Herter) Holub; *Lycopodium platyrhizoma* J.H. Wilce is a synonym of *Diphasiastrum platyrhizoma* (J.H. Wilce) Holub; *Lycopodium squarrosum* G. Forst. is a synonym of *Huperzia squarrosa* (G. Forst.) Trevis. and *Phlegmariurus squarrosus* (G. Forst.) Á. Löve & D. Löve

azaspiro[4.4]nonane moiety and an unprecedented 3-azabicyclo[6.3.1]dodecane unit. As an aside, it is interesting to note that the inhibitory activity of the $Ca_v3.1$ T-type calcium channel of lycoplanine A was comparable to that of Mibefradil, which approved by the FDA for the treatment of hypertension (Zhang et al. 2017). It may be a lead compound for the treatment of diseases associated with T-type calcium channel, such as Parkinson's disease, pain, tumor, sleep disorder, epilepsy, and other central or peripheral neurological diseases. This discovery broadens the understanding of the activity of *Lycopodium* alkaloids and opens new research fields.

## Triterpenoids

A total of 59 triterpenoids (**444–479,481–503**) have been found in *Lycopodium* species. Serratene triterpenoids, the most common terpenoids isolated from the extracts of *Lycopodium* plants, are the widely concerned chemical constituents in addition to alkaloids of genus *Lycopodium*. Moreover, triterpenoids of the serratane type appear to be characteristic of this genus, which could be used as a valuable chemotaxonomical criterion to distinguish from the related genera such as *Selaginella* and *Isoetes*. (Miller et al. 1972). Serratenes, a kind of pentacyclic triterpenoids which come from single protonation of α-onocerin (**503**) that rich in genus *Lycopodium* (Zhao et al. 2010), possess unusual skeletons with a seven-membered C-ring, seven tertiary methyl groups (one or two may be oxygenated), as well as usually a double bond between C-14 and C-15 and oxygen functionalities at C-3 and C-21. Further, there should be an existing singly protonated enzyme so that α-onocerin triterpenoid could be converted to serratenediol triterpenoid, and both belong to serratenes (Inubushi et al. 1967b). In recent years, the bioactivity of serratenediol (**496**) that first isolated from the Japanese club moss, *L. serratum* has been examined. It can induce apoptosis via regulating the ratio of Bax/Bcl-xL in HL-60 cell

**Table 3** Anti-AD activity of Lycopodium

| Tested substance | Model | Effect | Doses or concentrations tested | References |
|---|---|---|---|---|
| Lycoparins C | Method of Ellman (in vitro) | Lycoparin C could inhibit acetylcholinesterase (from bovine erythrocyte) with $IC_{50}$=25 μM<br>PC: None. NC: None | | Hirasawa et al. (2008a, b) |
| Huperzine C | In vitro screening for anti-acetylcholinester-ase activity | Huperzine C showed markedly inhibitory activity against acetylcholinesterase. PC: huperzine A. NC: None | | Liu et al. (1994) |
| Carinatumins A and B | Method of Ellman<br>(in vitro) | Carinatumins A and B could inhibit acetylcholinesterase (from bovine erythrocyte) with $IC_{50}$=4.6 and 7.0 μM, respectively<br>PC: huperzine A ($IC_{50}$=0.8 μM) and huperzine B ($IC_{50}$=8 μM). NC: None | | Choo et al. (2007) |
| Lycosquarosine A and acetylaposerratinine | Ellman's spectrophotometric method with minor modifications (in vitro) | Dose dependent manner. Lycosquarosine A could inhibit AChE activity with $IC_{50}$=54.3 μg/ml, acetylaposerratinine could inhibit AChE activity with $IC_{50}$=15.2 μg/ml<br>PC: berberine ($IC_{50}$=0.09 μg/ml). NC: None | | Chuong et al. (2014) |
| Lycojapodine A | Method of Ellman<br>(in vitro) | Lycojapodine A could inhibit acetycholinesterase with an $IC_{50}$ value of 90.3 μM<br>PC: (-)-huperzine A. NC: None | | He et al. (2009) |
| Sieboldine A | The fluorometric determination<br>(in vitro) | Sieboldine A could inhibit acetylcholinesterase (from electric eel) with $IC_{50}$=2.0 μM<br>PC: (±)-huperzine A ($IC_{50}$=1.6 μM). NC: None | | Hirasawa et al. (2003) |
| Lycoperine A | Method of Ellman<br>(in vitro) | Lycoperine A could inhibit acetylcholinesterase (from bovine erythrocyte) with $IC_{50}$=60.9 μM<br>PC: None. NC: None | | Hirasawa et al. (2006) |
| Casuarine B | Method of Ellman<br>(in vitro) | Casuarine B exhibited moderate anti-AChE activity with $IC_{50}$= 46.40 μM<br>PC: huperzine A ($IC_{50}$=0.03 μM). NC: None | | Liu et al. (2013) |
| Huperserine E | The spectrophotometric Ellman method (in vitro) | Huperserine E exhibited moderate anti-AChE activity with $IC_{50}$= 6.71 μM<br>PC: huperzine A ($IC_{50}$=0.03 μM). NC: None | | Jiang et al. (2014a, b) |
| Obscurumine L | Method of Ellman<br>(in vitro) | Obscurumine L exhibited weak anti-AChE activity with $IC_{50}$=81.0 μM<br>PC: tacrine ($IC_{50}$=0.33 μM). NC: None | | Jiang et al. (2016) |
| 2α, 11α-Dihydroxyfawcettidine | Method of Ellman<br>(in vitro) | 2α, 11α-Dihydroxyfawcettidine could inhibit acetylcholinesterase with $IC_{50}$=27.9 μM<br>PC: None. NC: None | | Katakawa et al. (2007) |

**Table 3** continued

| Tested substance | Model | Effect | Doses or concentrations tested | References |
|---|---|---|---|---|
| Serratezomine D | Method of Ellman (in vitro) | Serratezomine D could inhibit acetylcholinesterase (from electric eel) with $IC_{50}$=0.6 mM<br>PC: galanthamine ($IC_{50}$=6.4 μM). NC: NC | | Kubota et al. (2009) |
| Annotinolides A, B and C | Thiosulfonate fluorescence analysis (in vitro) | Annotinolides A, B and C exhibited considerable inhibitory effects against the aggregation of Aβ 1−42 peptide<br>PC: epigallocatechin-3-gallate ($IC_{50}$=10 μM). NC: None | 50 μM | Tang et al. (2016) |
| Huperzine A | Postoperative cognitive dysfunction model by performing the splenectomy in aged rats. (in vivo) | Huperzine A attenuated postoperative cognitive dysfunction by increasing the serum IL-10 and decreasing the serum TNF-α and IL-6 and the expression of β-protein<br>PC: None. NC: vehicle and model groups | 0.15 mg/kg/day for 3 weeks (*i.g.*) | Deng et al. (2018) |
| N-demethyl-sauroxine | Method of Ellman (in vitro) | N-demethyl-sauroxine could inhibit acetylcholinesterase with $IC_{50}$= 54.5 μg/mL (209.6 ± 1.1 μM)<br>PC: physostigmine salicylate ($IC_{50}$=0.079 μg/mL). NC: None | | Vallejo et al. (2013); Ortega et al. (2004a) |
| 6-hydroxylycopodine and sauroxine | Method of Ellman (in vitro) | 6-hydroxylycopodine and sauroxine could inhibit acetylcholinesterase (from erythrocyte membranes) with $IC_{50}$=296.8 and 32.3 μM<br>PC: physostigmine salicylate. NC: None | 2–700 μM | Puiatti et al. (2013) |
| Lycoclavanol and α-onocerin | Method of Ellman (in vitro) | Lycoclavanol and α-onocerin could inhibit acetylcholinesterase<br>PC: galanthamine (0.6 mg/mL). NC: None | 0.6 mg/mL | Yan et al. (2005a, b) |
| Lycopodine, obscurumine F, 5-acetyllycofoline | Ellman's spectrophotometric method with minor modifications (in vitro) | Lycopodine, obscurumine F, 5-acetyllycofoline could inhibit acetylcholinesterase (from the rat cortical) slightly<br>PC: huperzine A ($1.7 \times 10^{-7}$ mol/L). NC: None | $4.0 \times 10^{-5}$ mol/L | Wang et al. (2016) |
| 8, 15-Dihydrohyperzine A, 12-epilycodine N-oxide, gnidioidine | Method of Ellman (in vitro) | 8, 15-Dihydrohyperzine A, 12-epilycodine N-oxide, gnidioidine could inhibit acetylcholinesterase (from electric eel) with $IC_{50}$=2.626, 0.591 and 3.442 μM<br>PC: huperzine A ($IC_{50}$=0.016 μM). NC: None | | Thorroad et al. (2014) |
| N-demethylhuperzinine | Cholinesterase activity tested on isolated mouse skeletal muscle (in vitro) | N-demethylhuperzinine could inhibit cholinesterase<br>PC: neostigmine (0.3 μM/mL). NC: None | 2 μM/mL | Shen et al. (1994) |
| Lyclavatol | Method of Ellman (in vitro) | Concentration dependent manner. Lyclavatol could inhibit acetylcholinesterase with $IC_{50}$=673.4 μg/mL<br>PC: galanthamine. NC: None | | Rollinger et al. (2005) |
| α-onocerin | Method of Ellman (in vitro) | Concentration dependent manner. α-onocerin could inhibit acetylcholinesterase with $IC_{50}$=5.2 μM<br>PC: galanthamine and donepezil. NC: None | 1, 3, 5 mg/mL | Orhan et al. (2003) |

**Table 3** continued

| Tested substance | Model | Effect | Doses or concentrations tested | References |
|---|---|---|---|---|
| Squarrosine A, pyrrolehuperzine A | Ellman's method with minor modifications (in vitro) | Squarrosine A and pyrrolehuperzine A could inhibit acetylcholinesterase (from Electrophorus electricus) with $IC_{50}$=7.30 ±0.12 and 8.91±0.83 μM<br>PC: donepezil ($IC_{50}$=0.021±0.0002 μM). NC: methanol | | Nilsu et al. (2016) |
| Huperphlegmines A and B | Method of Ellman (in vitro) | Huperphlegmines A and B could inhibit acetylcholinesterase with $IC_{50}$ =25.95±0.67 and 29.14±0.77 μg/mL<br>PC: galanthamine ($IC_{50}$=0.33±0.01 μg/mL). NC: None | | Nguyen et al. (2018) |
| Four serratene-type triterpenoids | The β-secretase 1 fluorescence resonance energy transfer assay (in vitro) | Four triterpenoids showed β-secretase 1 inhibition with $IC_{50}$=2.79± 0.28 μM for 21β, 24-dihydroxyserrat-14-en-3α-yl acetate, 2.49± 0.12 μM for 16-oxo-21β-hydroxyserrat-14-en-3α-yl acetate, 17.82± 0.61 μM for 16-oxo-21β, 24-dihydroxyserrat-14-en-3α-yl acetate and 19.58±0.63 μM for 21β-hydroxyserrat-14-en-3α-yl acetate<br>PC: quercetin ($IC_{50}$=6.75±0.54 μM). NC: None | | Nguyen et al. (2017) |
| Squarrosinoxide | Method of Ellman (in vitro) | Squarrosinoxide possessed a moderate anti-acetylcholinesterase activity ($IC_{50}$=3.12±0.028 μM)<br>PC: huperzine A ($IC_{50}$=0.034±0.0005 μM). NC: None | | Nilsu et al. (2018) |
| Huperzine Y2 and Y3 | Method of Ellman (in vitro) | Huperzine Y2 and Huperzine Y3 exhibited inhibitory activities against acetylcholinesterase with $IC_{50}$ values of 57.1±1.6 and 32.7±1.0 μM, respectively<br>PC: huperzine A ($IC_{50}$=0.45±0.02 μM). NC: None | | Jiang et al. (2019) |
| 12-epilycodoline *N*-oxide | Method of Ellman (in vitro) | Dose dependent manner. 12-epilycodoline *N*-oxide showed moderately AChE inhibitory effect with $IC_{50}$ value of 64.56 μg/mL<br>PC: donepezil ($IC_{50}$=2.57 μg/mL). NC: None | | Thu et al. (2019) |
| Lycosquarrine K | Method of Ellman (in vitro) | Lycosquarrine K exhibited inhibitory activity against acetylcholinesterase with $IC_{50}$ value of 4.2 μM<br>PC: huperzine A ($IC_{50}$=0.1 μM). NC: None | | Zhu et al. (2020) |

lines. Therefore, serratane triterpenoids might be potential candidates for the development of anti-cancer drugs (Ham et al. 2012). Besides, according to Zhang et al. (2014), regarding the serratenediol derivatives, the introduction of a polar hydroxyl and carboxyl group at C-24 led to the increase in the antitumor activity. The presence of the carbonyl group in ring B was also more favorable for enhancing the antitumor activity among the α-onocerin (**503**) derivatives. In addition, a variety of significant biological activities including anti- AChE, inhibition of aspartate protease secreted by *Candida albicans* and DNA anti-topoisomerase II of serratane triterpenoids have been found in many *Lycopodium* plants, especially *L. japonicum* (Yan et al. 2005a, b). Lately, Wang et al. (2014) isolated two new triterpenoids, named 3β-hydroxyserrat-14-en-21β-yl-formate (**473**) and 21β-hydroxyserrat-14-en-3β-yl-formate (**458**), for the first time from an ethanol extract of the entire plant of *L. japonicum*. Their structures were elucidated by means of spectroscopic analysis to be both the formates of serratenediols, which were reported rarely in serratene-type terpenoids.

Glycosides

In the continual search for biologically active substances active substance, Tori et al. (2005) investigated Japanese *L. clavatum*, and have isolated three new glycosides (**505, 506, 508**) as well as known apigenin-4′-O-(2″,6″-di-O-*p*-coumaroyl)-β-D-glucopyranoside (**504**) and apigenin-7-O-β-D-(2,6-di-O-*p*-coumaroyl)glucoside (**507**) (Rao et al. 1983). Notably, all belong to flavones glycosides except compound **508**, a new class of glucoside from *Lycocpodium* species so far, having a benzoate group instead of the flavone unit. Additionally, in the *Candida*-secreted aspartic proteases (SAP) inhibition assay of an ethanol extract of *L. cernuum*, apigenin-4′-O-(2″,6″-di-O-*p*-coumaroyl)-β-D-glucopyranoside (**504**) was identified and found to be active with $IC_{50}$ of 8.4 µg/mL (Zhang et al. 2002a). Reports on glycosides in *Lycopodium* are very rare, making them an interesting topic for further studies.

Others

A small amount of other compounds including one monoterpene (**480**), aliphatic alcohol, anthraquinone and two phytosterols have been found in *Lycopodium* species (Li et al. 2006b; Cai et al. 2015; Teng et al. 2010). Insufficiently, few reports of biological and pharmacological activity are available on these compounds of genus *Lycopodium.*

## Biological and pharmacological activities of drugs made from *Lycopodium* species

Secondary metabolites from plants of genus of *Lycopodium* have many pharmacological effects, including anti-AD, neuroprotection, anti-tumor, anti-inflammatory and so on. Details of biological and pharmacological activities are shown in Tables 3, 4, 5, 6 and 7. Triterpenoids mainly showed anti-tumor effect, and alkaloids possess pharmacological effect on cholinesterase inhibition, neuroprotection and anti-inflammatory. Among them, Hup A is commonly used to improve memory and mental function in people with Alzheimer's disease, other types of dementia, age-related memory loss, and other conditions.

*Anti-AD* activity

AD is a neurodegenerative disease and the most frequent and predominant cause of dementia among the elderly. Although the pathogenesis of AD is complicated and involves numerous pathways, two major hypotheses are currently under consideration regarding the molecular mechanism: the cholinergic hypothesis and the amyloid cascade hypothesis (Chuong et al. 2014). There is considerable evidence that the memory deficits associated with AD are due to impairment of cholinergic neurotransmission in the central nervous system (Ma et al. 2004). As a consequence, the enhancement of cholinergic neurotransmission has been considered as one potential therapeutic approach against AD. The inhibition of cholinesterase may be related to the traditional use of *Lycopodium* in the treatment of mental disorders such as memory impairment and anxiety. At the same time, the curative effect on mild nausea caused by stimulation of the central nervous system may be the

**Table 4** Neuroprotective activity of Lycopodium

| Tested substance | Model | Effect | Doses or concentrations tested | References |
|---|---|---|---|---|
| Lyconadins A and B | 1321N1 human astrocytoma cells (in vitro) | The mRNA expressions for nerve growth factor were enhanced by Lyconadins A and B<br>PC: None. NC: None | 1–10 μM | Ishiuchi et al. (2006a) |
| Complanadine A (CA), complanadine B (CB) (2005a, b) | Human astrocytoma cells (glial cell line) (in vitro) | CA and CB could induce secretion of neurotrophic factors from human astrocytoma cells<br>PC: phorbol 12-myristate 13-acetate (PMA) (100 nM)<br>NC: vehicle group | CA: 1–10 μM/day for 2 days, CB: None | Morita et al. |
| Huperzine A | The mouse neuroblastoma N2a cells (in vitro) | Concentration and time dependent manner. Huperzine A could protect N2a cells against Aβ oligomer-induced cell death by downregulation of cellular tumor antigen p53 (Trp53) expression<br>PC: None. NC: vehicle and model group | 10 μM | Tao et al. (2013) |
| EtOAc fraction of aerial part from *L. squarrosum* | Scopolamine-induced cognitive impairment mice (in vivo) | Extract exhibited a strong neuroprotective effect on cognitive impairment<br>PC: ascorbic acid ($IC_{50}$=0.67±0.05 μg/mL) and berberine chloride ($IC_{50}$=0.28±0.06 μg/mL). NC: vehicle group | 150, 300 mg/kg/day for 14 days (*p.o.*) | Tung et al. (2017) |
| Huperzine A | Streptozotocin-injected rat (in vivo) | Does dependent manner. Huperzine A ameliorated diabetes-associated cognitive decline via modulating brain-derived neurotrophic factor, oxidative stress, inflammation and apoptosis<br>PC: donepezil. NC: vehicle and model groups | 0.05, 0.1 mg/kg/day for 7 weeks (*i.p.*) | Mao et al. (2014) |
| Huperzine A | Rat neural stem cells (in vitro) | Concentration and time dependent manner. Huperzine A could protect neural stem cells by acting on microglia cells and reducing the apoptosis rate of neural stem cells<br>PC: None. NC: vehicle and model groups | 1 μmol /L | Zhu et al. (2013) |
| Huperzine A | D-gal-induced presbycusis rats (in vivo) | Huperzine A exhibited protective effect on the nerve fibers of presbycusis induced by D-gal<br>PC: None. NC: vehicle and model groups | 0.1 mg /kg/day for 7 days (*s.c.*) | Li et al. (2014) |
| Huperzine A | Acute hypobaric hypoxic-induced rats (in vivo) | Huperzine A treatment had a protective effect against acute hypobaric hypoxic-induced apoptosis of hippocampal neurons in rats, and it ameliorates spatial learning and memory deficits in rats<br>PC: None. NC: vehicle and model groups | 0.1 mg/kg (*i.g.*) | Shi et al. (2013) |
| Huperzine A | Rat cortical neurons (in vitro) | Does and time dependent manner. Huperzine A attenuated amyloid β-peptide fragment 25–35-induced apoptosis via inhibiting reactive oxygen species formation and caspase-3 activation<br>PC: None. NC: None | 0.01, 0.1, 1, 10 μM | Xiao et al. (2002) |
| Huperzine A | Rat PC12 cells (in vitro) | Does dependent manner. Huperzine A exerted significant protection against $H_2O_2$-induced apoptosis through improving expression of apoptosisrelated genes<br>PC: None. NC: vehicle and model groups | 0.1, 1, 10 μM | Wang et al. (2001) |

**Table 4** continued

| Tested substance | Model | Effect | Doses or concentrations tested | References |
|---|---|---|---|---|
| Huperzine A | Rat pheochromocytoma line PC12 (in vitro) | Does dependent manner. Huperzine A had significant neuroprotective effects against Aβ-caused cell injury possibly through an antioxidative pathway<br>PC: None. NC: vehicle and model groups | 0.01, 0.1, 1, 10 μM | Xiao et al. (2000) |
| Huperzine A | Staurosporine-induced primary cortical neurons (in vitro) | Does dependent manner. Huperzine A could protect neurons against staurosporine-induced apoptosis via regulating the apoptotic related genes and caspase-3 proenzyme<br>PC: None. NC: vehicle and model groups | 0.1–100 μM | Zhang et al. (2003) |
| Huperzine A | 1. Mouse embryonic hippocampal neural stem cells (in vitro)<br>2. 8-week-old C57BL/6 mice<br>(in vivo) | 1. Huperzine A promoted the proliferation of cultured mouse embryonic hippocampal neural stem cells (NSCs)<br>2. Huperzine A increased the newly generated cells in the subgranular zone (SGZ) of the hippocampus in adult mice<br>PC: None. NC: None | 1. 0.01, 0.1, 1, 10, 100 μM<br>2. 0.2 mg/kg/day for 4 weeks (*i.p.*) | Ma et al. (2013) |
| Phlegmadine B | PC12 cells (in vitro) | Phlegmadine B exhibited moderate neurotrophic effects via stimulating NGF-induced neurite outgrowth on PC12 cells with the differentiation rate of 10.86% after 72 h<br>PC: 50 ng/mL NGF (the rate of 18.09%). NC: 5 ng/mL NGF (the rate of 4.39%) | | Zhang et al. (2020) |

reason why people in some regions traditionally use these herbs as expectorants and emetics. Therefore, it is imperative to evaluate the cholinesterase inhibition of secondary metabolites of *Lycopodium* in vitro and in vivo. Until now, nearly 400 *Lycopodium* alkaloids have been reported. As a result, some of them have been proven to be good AChE inhibitors such as Hup A, huperzine B, huperzine C, and *N*-methylhuperzine B belonging to the lycodine class. Among them, Hup A was licensed in China as a drug for the treatment of AD and in the United States as a dietary supplement. It could be seen that the main activity of Hup A is anti-AChE.

Since Hup A was discovered from *L. serratum* in the 1980s, it has been extensively evaluated by the Chinese for its bioactivity, or its inhibitory activity towards cholinesterase and for treatment of AD (Liu et al. 1986). Before 2000, many cholinesterase inhibitory tests have shown that Hup A is the most selective AChE inhibitor, although its activity is not the strongest in vitro and the $IC_{50}$ value of Hup A relative to other AChE inhibitors is: donepezil<Hup A<tacrine<physostigmine<galantamine(Gal) (Wang et al. 1986; Tang et al. 1988; Tang et al. 1999). This result can be illustrated by the specific data below. The ratios of Hup A, E2020 and tacrine for butyrylcholinesterase (BChE) (rat serum): AChE (rat cortex homogenate) determined by a colorimetric method were 884.57, 489.05 and 0.80, respectively. (Cheng et al. 1996). In contrast to the AChE inhibition in vitro, the relative inhibitory effect of oral Hup A on cortical AChE was found to be about 24-fold and 180-fold potent in molar terms than donepezil and tacrine, respectively (Wang et al. 1998). In a later similar experiment, when the effects of Hup A, donepezil and rivastigmine on cortical

**Table 5** Anti-tumor activity of Lycopodium

| Tested substance | Model | Effect | Doses or concentrations tested | References |
|---|---|---|---|---|
| Himeradine A | Murine lymphoma L1210 cells (in vitro) | Himeradine A exhibited cytotoxicity against murine lymphoma L1210 cells with $IC_{50}$=10 μg/ml<br>PC: None. NC: None | | Michael et al. (2004) |
| Lycopodine | Hormone sensitive (LnCaP) and refractory prostate cancer cells (PC3) (in vitro) | Dose-dependent manner. Lycopodine triggered apoptosis by modulating 5-lipoxygenase, and depolarizing mitochondrial membrane potential<br>PC: None. NC: vehicle group | 74, 148, 222 mM | Bishayee et al. (2013) |
| Apigenin | Human malignant melanoma A375 and lung carcinoma A549 cell line (in vitro) | Dose-dependent manner. Apigenin exhibited anticancer potential in A375 and A549 cells mediated through DNA interaction, damage and mitochondrial dysfunction by action on mitochondrial oxidative phosphorylation system<br>PC: None. NC: vehicle group | 20, 50, 80 mg/mL for A375 and 30, 60, 90 mg/mL for A549 | Das et al. (2012) |
| Lycopodine | HeLa human cervical carcinoma cell line<br>(in vitro) | Dose and time dependent manner. Lycopodine could inhibit proliferation of HeLa cells through induction of apoptosis via caspase-3 activation<br>PC: None. NC: vehicle group | 50, 100, 150, 200 μg/mL | Mandal et al. (2010) |
| Cermizine D, senepodines G and H | Murine lymphoma L1210 cells (in vitro) | Cermizine D and senepodines G and H exhibited cytotoxicity against murine lymphoma L1210 cells with $IC_{50}$=7.5, 7.8 and 8.2 μg/ml, respectively<br>PC: None. NC: None | | Michael et al. (2007) |
| Lycophlegmarin | BEL 7402, HL-60, A549 (in vitro) | Lycophlegmarin exhibited modest growth-inhibitory activity against BEL 7402, showed no cytotoxicity against HL-60 and A549. PC: None. NC: None | | Shi et al. (2005) |
| Alcoholic extract of *L. serratum* and serratenediol | HL-60, HCT-15, A549, SK-Hep1<br>(in vitro) | Dose-dependent manner. Inhibitory effects of 100 μg/ml *L. serratum* on SK-Hep1 (75.7%), HT-29 (71.7%), and A549 (53.8%) cells were less profound than that noted for the HL-60 cells (89.2%). HL-60 cells were highly sensitive to growth inhibition and apoptosis induced by *L. seratum* and serratenediol<br>PC: None. NC: vehicle group | 6–100 μg/mL for *L. serratum*; 6.25, 12.5 and 25 μM for serratenediol | Ham et al. (2012) |
| Ethanolic Extract of *L. serratum* (ELS) | LPS-induced C6 glioma cells (in vitro) | ELS could inhibit LPS-induced C6 glioma migration through ROS scavenging activity and suppressing MMP-9 expression<br>PC: None. NC: vehicle group | 5, 10, 25, 50 μg/mL | Park et al. (2018) |

**Table 5** continued

| Tested substance | Model | Effect | Doses or concentrations tested | References |
|---|---|---|---|---|
| Lycopodiin A and 3-epilycoclavanol | Human tumor A549 and K562 cell line assays (in vitro) | Lycopodiin A and 3-epilycoclavanol could indicated moderate antitumor activity<br>PC: None. NC: None | 10–100 μg/mL | Yan et al. (2005a, b) |
| Lycojaponicumin A | Ileocecal cancer cells HCT-8 (in vitro) | Lycojaponicumin A could inhibit the growth of ileocecal cancer cells HCT-8 with $IC_{50}$=1.15±0.17 μM<br>PC: None. NC: vehicle group | 0.00001, 0.0001, 0.001, 0.01, 0.1, 1, 10, 50, 100 μM | Jiang et al. (2013a) |
| Lycojaponicumin B | Ileocecal cancer cells HCT-8 (in vitro) | Lycojaponicumin B could inhibit the growth of ileocecal cancer cells HCT-8 with $IC_{50}$=1.33±0.11 μM<br>PC: None. NC: vehicle group | 0.00001, 0.0001, 0.001, 0.01, 0.1, 1, 10, 50, 100 μM | Jiang et al. (2013b) |
| Lycojaponicumin A | Leukemia HL-60 cells (in vitro) | Lycojaponicumin A could inhibit the proliferation and induce apoptosis of leukemia HL-60 cells<br>PC: None. NC: vehicle group | 0.625, 1.25, 2.5, 5.0, 10.0 μg/ml | Jiang et al. (2013c) |
| Lycojaponicumin C | Ileocecal cancer cells HCT-8 (in vitro) | Lycojaponicumin C could inhibit the growth of ileocecal cancer cells HCT-8 with $IC_{50}$=2.04±0.21 μM<br>PC: None. NC: vehicle group | 0.00001, 0.0001, 0.001, 0.01, 0.1, 1, 10, 50, 100 μM | Wu et al. (2013a) |
| Lycojaponicumin C | gastric cancer cell lines (HGC-27, MGC-803, BGC-823, SGC-7901) (in vitro) | Lycojaponicumin C could inhibit the growth of gastric cancer cell lines (HGC-27, MGC-803, BGC-823, SGC-7901) with $IC_{50}$=3.21±0.33, 1.12±0.17, 0.87 ±0.07 and 1.33±0.19 μM<br>PC: None. NC: vehicle group | 0.001, 0.01, 0.1, 1, 10, 50, 100 μM | Wu et al. (2013b) |
| Lycojaponicumin C | liver cancer cell lines (HepG2, MHCC-LM3, Bel-7402, HuH-7) (in vitro) | Lycojaponicumin C could inhibit the growth of liver cancer cell lines (HepG2, MHCC-LM3, Bel-7402, HuH-7) with $IC_{50}$=2.26±0.32, 1.46±0.21, 2.41± 0.11 and 3.21±0.37 μM<br>PC: None. NC: vehicle group | 0.001, 0.01, 0.1, 1, 10, 50, 100 μM | Wu et al. (2013c) |

acetylcholine levels and AChE activity in rats were compared, Hup A was still the most potent and had longer lasting effect (Liang et al. 2004). In addition, Hup A injected intraperitoneally exerted similar efficacy of AChE inhibition in rats as observed following oral administration (Wang et al. 1998), but the inhibitory potency of it on brain AChE was less than that of donepezil after the intraventricular injection (Cheng et al. 1998). These findings indicated that Hup A has higher bioavailability and penetrates the blood brain barrier more easily. Moreover, repeated doses of Hup A showed no significant difference on the AChE inhibition compared with that of single dose, indicating no tolerance to Hup A (Wang et al. 1998; Laganiere et al. 1991). In 1997, The X-ray crystal structure of the (-)-Hup A-AChE complex showed that the three-carbon bridge, the prerequisite structure for the AChE inhibitor activity in Hup A (Kozikowski et al. 1991), was inserted into the hydrophobic area of

**Table 6** Anti-inflammatory activity of Lycopodium

| Tested substance | Model | Effect | Doses or concentrations tested | References |
|---|---|---|---|---|
| Chloroform extract and the alkaloid fraction of aerial parts of *L. clavatum* | Acetic acid induced albino mice (in vivo) | Chloroform extract and the alkaloid fraction could inhibit acetic acid-induced increasing in capillary permeability<br>PC: indomethacin (10 mg/kg). NC: vehicle group | 500 mg/kg (*p. o.*) | Orhan et al. (2007a) |
| Acetyldihydrolycopodine, methyl *p*-coumarate and stigmastane-3-oxo-21-oic acid | LPS—induced RAW 264.7 cell (in vivo) | Concentration-dependent manner. The three compounds could inhibit NO production. $IC_{50}$ of acetyldihydrolycopodine and methyl *p*-coumarate are 46.84± 9.64, and 10.73±4.12 μM, respectively<br>PC: dexamethasone (10 μM). NC: vehicle and model groups | 6.25, 12.5, 25, 50 μM | Yang et al. (2015) |
| Huperzine A | Presbycusis rats induced by D-galactose (in vivo) | Huperzine A could inhibit the release of inflammatory cytokines by inhibiting the activation of the Schwann cells and NF-κB in cochlear tissue<br>PC: None. NC: vehicle and model groups | 0.1 mg/kg/day for 8 weeks (*s.c.*) | Gu et al. (2014) |
| Huperzine A | Mice models of paw edema induced by egg white (in vivo) | Dose-dependent manner. Huperzine A showed significant anti-inflammatory effect on paw edema induced by egg white<br>PC: None. NC: vehicle and model groups | 0.1, 0.3, 0.9 mg/kg (*i. p.*) | Shi et al. (2014) |
| Huperzine A | LPS—induced rat microglial cells (in vitro) | Does-dependent manner. Huperzine A decreased the releasing of IL-6, TNF-α and NO<br>PC: None. NC: vehicle and model groups | 0.1, 1, 10 μmol/L | Huang et al. (2017) |
| Six alkaloids of *L. japonicum* | LPS—induced BV2 macrophages (in vitro) | The six alkaloids displayed moderate activities against pro-inflammatory factors with $IC_{50}$ =49.03 μM for 8β-Hydroxylycodoline, 44.38 μM for 11β-hydroxy-12-epilycodoline, 35.23 μM for lycopodine, 40.08 μM for deacetylfawcettiine, 4.23 μM for α-lofoline and 38.75 μM for acetyllycofawcine, respectively<br>PC: curcumin ($IC_{50}$=3.12 μM). NC: model group | | Wang et al. (2009) |

**Table 6** continued

| Tested substance | Model | Effect | Doses or concentrations tested | References |
|---|---|---|---|---|
| Obscurumine O | Phytohemagglutinin and phorbol myristate acetate stimulated Jurkat cells<br>(in vitro) | Concentration-dependent manner. Obscurumine O exhibited inhibitory activity for IL-2 production with $IC_{50}$=17.2 μM<br>PC: dexamethasone. NC: None | 1.25, 2.5, 5, 10, 20, 40 μM for 24 h | Jiang et al. (2016) |
| The chloroform extract, *n*-butanol extract and water extract of *L. japonicum* | Acetic acid induced peritonitis mice; dimethyl benzene-induced inflammation on the ear of mice models; rat models of ankle swelling induced by fonmaldehycle<br>(in vivo) | *L. japonicum* showed significant anti-inflammatory effect, and its effective components are concentrated in chloroform extract<br>PC: None. NC: vehicle groups | 40 g/kg (*i.p.*) | Zeng et al. (1999) |
| The alkaloids of *L. japonicum* | Rat models of arthritis induced by Complete Freund's Adjuvant (CFA)<br>(in vivo) | The alkaloids of *L. japonicum* inhibited the swelling of arthritis induced by CFA in rats, and improved the synovial lesions of ankle joint in rats<br>PC: Etoricoxib (1 mg/kg). NC: vehicle and model groups | 30, 60, 120 mg/kg/day for 30 days (*i.g.*) | Liu et al. (2019) |

AChE surrounded by aromatic residues (Raves rt al. 1997). Notably, the other AChE inhibitors function in a similar manner, but the Hup A-AChE complex has a longer half-life than these and other prophylactic agents (Ma et al. 2004). Before this, a Lineweaver-Burke plot for Hup A indicated a pattern of AChE inhibition of the mixed competitive type, as the intersection of the lines occurred in the second quadrant (Cheng et al. 1996). In particular, the AChE activity recovered to 94±(SD)5% of the control after 4 times washing with 5–6 fold volume of 0.01 mol/L pH 7.4 Tris–HCl buffer, indicating the inhibitory manner of Hup A was reversible (Tang et al. 1988). Overall, Hup A is a potent, reversible and selective AChE inhibitor, which has been approved as the drug for treatment of AD in China, and is marketed in USA as a dietary supplement (as powdered *L. serratum* in tablet or capsule format). In addition, Hup A is now used to prevent organophosphorus poisoning and clinically to treat myasthenia gravis due to its AChE inhibitory activity.

Although all of the other *Lycopodium* alkaloids identified to date have either not shown any AChE inhibition activity or possessed activity that is significantly lower than that of Hup A, one interesting thing to note is that there may be a synergistic effect among the alkaloids. For example, *L. saururus*, an important commercial item in Argentina, was widely used as a stimulant and for memory improvement traditionally. Until now, studies on it showed the presence of nine different alkaloids in a purified alkaloid extract, with sauroine (Ortega et al. 2004b), being the predominant one. According to the reported by Ortega et al., the purified alkaloid extract of *L. saururus* was evaluated in relation to its effect on the AChE and exhibited a strong inhibitory effect ($IC_{50}$= 0.58 μg/mL) (Ortega et al. 2004a). However, hitherto evaluations of purified alkaloids showed that the major alkaloid (sauroine) showed no inhibitory effect and sauroxine had the strongest inhibition with an $IC_{50}$=8.9±0.4 μg/mL (Vallejo et al. 2013), that is, no compound has similar inhibitory activity to the alkaloid extract.

**Table 7** Others pharmacological activity of *Lycopodium*

| Pharmacological effects | Tested substance | Model | Effect | Doses or concentrations tested | Reference |
|---|---|---|---|---|---|
| *Anti-microbial* | Different extracts of *L. clavatum* | Microdilution test (in vitro) | All the extracts possessed noteworthy activity against ATCC strain of *S. aureus* (4 μg/mL) and antifungal effect (16 and 32 μg/mL)<br>PC: ampicilline (<0.12–2 μg/mL), ofloxacine (<0.12–1 μg/mL), ketoconazole (1 μg/mL), and fluconazole (4 μg/mL). NC: None | 0.25–512 μg/mL | Orhan et al. (2007b) |
| | MeOH: $H_2O$ (9:1) extract of a mixture of rootstem-leaf, two compounds of *L. cernuum* | Candidasecreted aspartic proteases inhibition assay (in vitro) | There were inhibitory effects against *C.albicans* secreted aspartic proteases with $IC_{50}$= 30 μg/mL for the extract, 8.5 μg/mL for apigenin-4′-*O*-(2′′, 6′′-di-*O*-*p*-coumaroyl)-β-D-glucopyranoside and 20 μg/mL for 3β, 14α, 15α, 21β, -29-pentahydroxyserratane-24-oic acid respectively<br>PC: pepstatin A ($IC_{50}$=0.0015 μg/mL). NC: None | 2, 10, 50 μg/mL | Zhang et al. (2002a) |
| | Different extracts of *L. clavatum and L. complanatum* subsp. *chamaecyparissus* | Microdilution test (in vitro) | Both fern species showed anti-protozoan activity ($IC_{50}$=2.7-> 90 μg/mL)<br>PC: melarsoprol ($IC_{50}$=0.003 μg/mL), benznidazole ($IC_{50}$=0.35 μg/mL), miltefosine ($IC_{50}$=0.20 μg/mL), chloroquine ($IC_{50}$=0.056 μg/mL)<br>NC: None | 0.123–90 μg/mL | Orhan et al. (2013) |
| *Antiviral* | Different extracts from *L. clavatum* | Viruses treated vero cell line and MDBK cell (in vitro) | Only the chloroform extract was active against *Herpes simplex* (8–16 μg/ml), while petroleum ether and alkaloid extracts inhibited potently *Parainfluenza* (4–16 μg/ml and 4–32 μg/ml, respectively)<br>PC: acyclovir (<0.25–16 μg/mL) and oseltamivir (<0.25–32 μg/mL). NC: None | 0.25–512 μg/mL | Orhan et al. (2007b) |
| *Cardiovascular protection* | Huperzine A | Methylglyoxal—induced injured human brain microvascular endothelial cells (in vitro) | Does-dependent manner. Huperzine A could protect human brain microvascular endothelial cells by decreasing caspase-3 activity increasing and increasing (1, 10 μmol/L) the superoxide dismutase activity<br>PC: None. NC: vehicle and model groups | 0.01, 0.1, 1, 10 μmol/L | Jiang et al. (2015) |

**Table 7** continued

| Pharmacological effects | Tested substance | Model | Effect | Doses or concentrations tested | Reference |
|---|---|---|---|---|---|
| | Serralongamines B and D | Human monocyte-derived macrophages incubated acetylated LDL (in vitro) | Serralongamines B and D exhibited the inhibitory activity against foam cell formation in human macrophages<br>PC: None. NC: vehicle group | 30 μM | Ishiuchi et al. (2016) |
| *Anti-diabetes* | 95% ethanol extract of *L. clavatum* | Microtiter fluorometric assays (in vitro) | Time-dependent manner. The ethanol extract decreased the metabolism of CYP3A4 substrates by inhibiting cytochrome P450 3A4 through mechanism-based inactivation<br>PC: None. NC: vehicle and model groups | 10, 50 μg/mL | Tam et al. (2011) |
| *Protection of auditory function* | Huperzine A | Presbycusis rats induced by D - galactose (in vivo) | Huperzine A shortened the time of hearing signal from peripheral to central axis, improved the sensitivity of temporal resolution, and decreased the number of senile cells in the inferior colliculus<br>PC: None. NC: vehicle and model groups | 0.1 mg/kg | Kong et al. (2013) |
| *Wound healing activity* | Aqueous and 70% ethanol leaf extracts of *L. serratum* | Excision, incision and dead space wound models on rats (in vivo) | The ethanol extract possessed significant wound healing promoting activity compared to aqueous extract<br>PC: framycetin sulphate cream<br>NC: vehicle group | 50 mg of ointment once a day<br>30 mg/kg aqueous and 20 mg/kg ethanol extracts (*p.o.*) | Manjunatha et al. (2007) |

*PC* positive control; *NC* negative control

The residues responsible for the catalytic activity of AChE, the catalytic triad (Ser203, His447, Glu334), are found at the bottom of a 20 Å deep gorge or cavity that constitutes the active site (AS). Outside the gorge, next to the "entrance", there is another site called the peripheral anionic site (PAS), where the precursors of the amyloid β (Aβ) are proposed to deposit before aggregation (Ferrari et al. 2001; Giacobini et al. 2000). Previous studies have shown that molecules able to interact with both sites of AChE could prevent the aggregating activity of AChE toward Aβ as well as the hydrolysis of acetylcholine (Bartolini et al. 2003). On this basis, the fact is that alkaloids with different degrees of affinity for the AS and the PAS exhibit different inhibitory abilities. The molecular dynamics simulation for the AChE complexes with *Lycopodium* alkaloids highlighted that the compounds like Hup A and sauroxine with higher AChE inhibition activity presented higher affinities for the AS than the PAS, but sauroine had no activities due to similar binding energy for the AS and the PAS (Puiatti et al. 2013).

Except to alkaloids, triterpenoids from plants of this genus are also found to be active against AD. For

example, the inhibitory activity of α-onocerin, a well-known serratene-type triterpenoid isolated from the chloroform extract of *L. clavatum*, was determined by the Ellman method at 1, 3 and 5 mg/mL. Surprisingly, in a dose-independent manner, α-onocerin ($IC_{50}$= 5.2 μM) inhibited AChE better than donepezil at 1 and 3 mg/mL concentrations and almost the same inhibition rate at 5 mg/mL (Orhan et al. 2003). In the same way, only lycoclavanol and α-onocerin showed inhibition activities (20.0 and 39.0%, resp) among seven triterpenoids isolated from *L. japonicum*. Gal was used as the standard drug (inhibition 63.3%) (Yan et al. 2005a, b). These findings could suggest that α-onocerin may be a candidate compound in the treatment of AD for further research. In addition, it is worth noting that most of the literature we collected used Ellman's reagent to determine the anti-AChE activity of secondary metabolites or extracts. Although Elman's method is still an appropriate method for the determination of cholinesterase activity, it is prone to false-positive. To solve this problem, Rhee developed a method using thin layer chromatography (TLC) assay based on Ellman's method, and the true enzyme inhibition could be distinguished from the false-positive chemical inhibition (Rhee et al. 2003). In further, anti-AChE activity of secondary metabolites should be tested by Ellman based TLC assay.

The amyloid hypothesis for the pathogenesis of AD was proposed, by which the accumulation of Aβ aggregates triggers a cascade of neurotoxic events in the brain eventually leading to a widespread neuronal degeneration and hence to dementia (Inestrosa et al. 1996; Alvarez et al. 1995). Accordingly, new anti-Alzheimer drug candidates focused on this problem, in order to modify the stage of the diseases (Muñoz-Torrero et al. 2008). In an in vitro study, lycopodine alkaloids annotinolides A-C were evaluated for their inhibitory effects against the aggregation of $Aβ_{1-42}$ peptide, a key factor in AD's pathogenesis, using thioflavin T fluorescence. All exhibited considerable antiaggregating activities at 50 μM with inhibitory ratios of 42.4, 38.1, and 36.1%, respectively. Epigallocatechin-3-gallate was used as a positive control (inhibitory ratio: 86.6% at 10 μM). Additionally, they were also tested for their anti-AChE but showed no activities. As an initial protease that processes APP in the pathway leading to the production of Aβ, β-site amyloid precursor protein-cleaving enzyme 1 (BACE1) has long been regarded as a therapeutic target for the reduction of Aβ formation (Ghosh et al. 2008). In recent years, ten diterpenes from *L. complanatum* were assessed for their cholinesterase and BACE1 inhibitory potential. All of them did not inhibit AChE and BChE, but did inhibit BACE1. Based on fluorescence resonance energy transfer, an in vitro study showed that compounds (21β,24-dihydroxyserrat-14-en-3α-yl acetate, 16-oxo-21β-hydroxyserrat-14-en-3α-yl acetate, 16-oxo-21β,24-dihydroxyserrat-14-en-3α-yl acetate, 21β-hydroxyserrat-14-en-3α-yl acetate) could be interesting leads for BACE1–inhibiting molecules, thanks to the α-acetoxy moiety at C-3 that is one of the key factors of inhibition ability. Among them, 21β,24-dihydroxyserrat-14-en-3α-yl acetate and 16-oxo-21β-hydroxyserrat-14-en-3α-yl acetate showed a potent effect with $IC_{50}$ values of 2.79±0.28 and 2.49± 0.12 μM, respectively, indicating higher potency than quercetin, the positive control ($IC_{50}$ value of 6.75± 0.54 μM). Notably, 16-oxo-21β-hydroxyserrat-14-en-3α-yl acetate was found to be a mixed-type inhibitor by using the Lineweaver–Burk and Dixon plot, and had the lowest BACE1 inhibition Ki values of 5.4. Therefore, these results revealed that 16-oxo-21β-hydroxyserrat-14-en-3α-yl acetate may be a promising BACEl inhibitor and a promising lead for further research on compounds for AD treatment (Nguyen et al. 2017).

### *Neuroprotective* activity

The *Lycopodium* alkaloids dominated by Hup A have been recently found to exert versatile neuroprotective effects in cell and animal models under various pathological conditions by antagonizing neurotoxicity, inhibiting oxidative stress injury and apoptosis, inducing secretion of neurotrophic factors and hippocampal neurogenesis other than affecting the hydrolysis of synaptic acetylcholine (ACh) and the aggregation of Aβ described directly above. Notably, these multiple neuroprotective effects of Hup A are important in AD treatment.

A series of studies was launched investigating the link between Aβ toxicity and oxidation, which demonstrated that the production of free radicals and oxidative stress were involved in Aβ insults (Behl et al. 1994). Some antioxidants have been proved to rescue cells from Aβ toxicity. Fragment 25–35 of Aβ

is the functional part that mediates the toxicity of whole-length Aβ (Pike et al. 1993). An in vitro study showed that Hup A (0.01–1.0 μM) protected rat pheochromocytoma line PC12 cells against $A\beta_{25–35}$ (1 μM) insult through an antioxidant pathway. Compared with no Hup A treatment, an elevation in activities of catalase and glutathione peroxidase, the enhanced cell survival as well as a decrease in the level of malondialdehyde and superoxide dismutase (SOD) activity were observed (Xiao et al. 2000). Interestingly, SOD activity increased after the exposure of the cells to $A\beta_{25–35}$, which might be a direct induction or otherwise a compensatory reaction against Aβ insult (Pappolla et al. 1998). Subsequently, Xiao et al. provided the first direct evidence that the protection of Hup A against $A\beta_{25-35}$-induced apoptosis is related to inhibiting reactive oxygen species (ROS) formation and caspase-3 activation in primary rat cortical cultures. In this study, ROS-based fluorescence, caspase-3-like fluorogenic cleavage, and Western blot analysis demonstrated that Hup A (0.01–10 μM) reduced $A\beta_{25-35}$-induced (20 μM) ROS formation in a dose-dependent manner, and 1 μM of Hup A attenuated caspase-3 activity at 6, 12, 24, and 48 h posttreatment (Xiao et al. 2002). Moreover, the concentration required to produce maximal attenuation in ROS formation was not quite correlated with its neuroprotective dose, possibly because ROS formation is a very early event in the Aβ cascade (Mattson et al. 1995). Dahlgren et al. reported that Aβ (1–42) oligomers inhibit neuronal viability tenfold more than fibrils and approximately 40-fold more than unaggregated peptide (Dahlgren et al. 2002). In an in vitro study, Hup A was added with a concentration of 10 μM for a 2-h preincubation before exposure to 5 μM Aβ (1–42) oligomer. The direct protein–protein interaction network analysis showed that Hup A protects neuroblastoma N2a cells against Aβ oligomer-induced cell death by downregulation of cellular tumor antigen p53 expression (Tao et al. 2013).

It is known that glutamate is the most toxic excitatory amino acid in the brain, which can induce degeneration of hippocampal neurons and cause damage to neurons. Previous studies have suggested that Hup A act on glutamate receptors to exert its neuroprotective effects and reckoned antagonism of Hup A at *N*-methyl-D-aspartate (NMDA) receptor as one of mechanisms for ameliorating abnormal lipid peroxidation (Ved et al. 1997; Shang et al. 1999; Wang et al. 1999). Pretreatment of cultured brain neurons with Hup A (100 μM) reduced glutamate-induced neuronal cell death and calcium mobilization, but did not affect the increase in intracellular free calcium channel induced by exposure to high KCl or a calcium activator Bay-K-8644 (Ved et al. 1997). Further, in another in vitro study, Hup A (0.1–300 μM) reversibly inhibited NMDA (100 μM)-induced current in acutely dissociated hippocampus pyramidal neurons in a concentration-dependent manner with $IC_{50}$ of 0.49 μM (Wang et al. 1999). These results demonstrated that Hup A acted directly on NMDA receptor to achieve a neuroprotective effect.

The neuroprotective effect of Hup A was also realized by preventing apoptosis of neuron cells. An in vitro study showed that Hup A can attenuate staurosporine-induced apoptosis of primary cortical neurons by upregulation of bcl-2, downregulation of bax and blockade of decrease in immunoreactive caspase-3 proenzyme. MTT-reduction was decreased to 68% of the control level after 24 h exposure of the primary cortical neurons to 0.5 μM staurosporine. This effect was significantly attenuated by incubation with Hup A (0.1–100 mM) starting 2 h before staurosporine. Hup A had the maximal neuroprotective effect at a concentration of 1 μM, where it increased MTT signal to 84% of the control (Zhang et al. 2003). Similarly, Hup A (1 μM) exerted significant protection against $H_2O_2$-induced (100 μM) apoptosis through improving expression of apoptosis related genes (Wang et al. 2001). In addition, an in vivo study was performed to explore the effects of Hup A on relieving the acute hypobaric hypoxic-induced apoptosis of hippocampal neurons in rats. Compared with high altitude group, lower rate of hippocampal neurons apoptosis, down-regulated expression of Bax and up-regulated expression of Bcl-2 in the hippocampus tissues were found in the high altitude + Hup A group rats that given intragastrically with Hup A suspension (10 mg/mL) in a dose of 0.1 mg/kg before one day of the decompression simulation experiment (Shi et al. 2013). However, the positive group were absent in above studies.

Although Hup A has been shown to exert multiple beneficial effects in brain, few of its actions on adult hippocampal neurogenesis have been established. Hup A can activate mitogen-activated protein

kinase/extracellular signal-regulated kinase (MAPK/ERK) signaling pathway, which is a well-known regulator of biological processes including cell proliferation and differentiation. Recent studies have shown the modulating role of the MAPK/ERK pathway in neurogenesis (Lu et al. 2011; Hao et al. 2004). In vivo and in vitro studies carried out by Ma et al. suggested that Hup A enhances neurogenesis through promoting cell proliferation by a MAPK/ERK-dependent mechanism in cultured hippocampal neural stem cells (NSCs). An in vitro study showed that Hup A (0.01–100 μM) promoted the proliferation of cultured mouse embryonic hippocampal NSCs. Besides, intraperitoneal injection of Hup A (0.2 mg/kg/day for 4 weeks) increased the newly generated cells in the subgranular zone (SGZ) of the hippocampus in adult mice (Ma et al. 2013).

Alkaloids (complanadine A, complanadine B, lyconadin A, lyconadin B) isolated from *L. complanatum* have been detected to induce secretion of neurotrophic factors from human astrocytoma cells. In an in vitro study, human astrocytoma cells (glial cell line) were incubated for 2 days with 1–10 μM complanadine A, and then rat pheochromocytoma (PC-12) cells were cultivated for 2 days in the conditioned 1321N1 culture medium. Phorbol 12-myristate 13-acetate (100 μM), an activator of neurotrophic factor biosynthesis, was used as a positive control. As a result, the culture medium showed to contain neurotrophic factors synthesized in 1321N1 cells, which promote the differentiation of PC-12 cells in a does dependent manner (Morita et al. 2005a). Additionally, releasing activities of neurotrophic factors from 1321N1 human astrocytoma cells by complanadine B, lyconadins A and B were examined in a subsequent study using a semiquantitative RT-PCR method, in which enhancement of the mRNA expression for NGF was observed (Ishiuchi et al. 2006a). However, according to the organized Table 4, almost all the experiments did not set up a positive control. Therefore, it is necessary to add positive controls to verify the neuroprotective activity of the extracts or secondary metabolites of plants of genus *Lycopodium*.

*Anti-tumor* activity

Traditional herbal medicines have attracted a great deal of attention as alternative cancer therapy due to their low toxicity and costs. Many plant-derived bioactive constituents, such as camptothectin (from *Camptotheca acuminata*), paclitaxel (from *Taxus brevifolia*), and vinblastine (from *Catharanthus roseus*), or plant-based semisynthetic compounds (*e.g.*, cabazitaxel, docetaxel, vinorelbine), have been discovered and commercialized as cancer therapeutics (Vickers et al. 2002). Extracts and secondary metabolites from plants of genus *Lycopodium* also show obvious antitumor effects, even though their antitumor effects are rarely recorded in traditional usage. The mechanisms include reducing migration and inducing apoptosis of tumor cells. Detailed information about these activities is listed in Table 5.

The results of an in vitro study clearly showed that ethanol extract of *L. serratum* (ELS) (5, 10, 25, 50 μg/mL) could decrease the ability of wound healing of LPS-treated C6 glioma cells in a dose-dependent manner, compared with the untreated control. It also indicated that the mechanisms of ROS scavenging and suppressing matrix metalloproteinase-9 (MMP-9) expression are involved (Park et al. 2018). However, there was no positive group in this study, and anti-tumor activity in vivo was not evaluated either. At present, few studies on the reduction of tumor cell migration of *Lycopodium* species have been reported, which is worthy of further investigation in the future.

Another major mechanism of antitumor effect of *Lycopodium* species is the induction of tumor cells apoptosis. It was reported that the crude ethanol extract of *L. clavatum* contains certain alkaloids, in which lycopodine is the major active principle. In an in vitro study, the effect of lycopodine on viability of HeLa cells was measured by MTT assay. Lycopodine (50, 100, 150, 200 μg/mL) reduces the viability of HeLa cells in a dose-dependent manner and time-dependent. However, $IC_{50}$ value was not presented. Further studies have shown that lycopodine can inhibit the proliferation of HeLa cells through induction of apoptosis via caspase-3 activation (Mandal et al. 2010). Lycopodine also had a good inhibitory effect on hormone sensitive (LnCaP) and refractory prostate cancer cells (PC3). Lycopodine (74, 148, 222 mM) could down-regulate the expression of 5-lipoxygenase and the 5-oxo-ETE receptor (OXE receptor1) and epidermal growth factor (EGF) receptor, thus effectively causing up-regulation of cytochrome c with depolarization of mitochondrial

inner membrane potential, eventually leading to cell apoptosis. However, the tested three doses of lycopodine are too large, and the $IC_{50}$ value is not specified. Concomitantly, circular dichroism (CD) spectroscopic analysis showed that lycopodine could be inserted into DNA molecules to inhibit the synthesis and replication of DNA (Bishayee et al. 2013). An overall analysis of results showed that lycopodine is a promising candidate suitable for therapeutic use as an anti-tumor drug. But these studies lack positive controls and data from in vivo studies, which is a concern for subsequent studies of lycopodine. Lycopodine also has anti-AChE activity and anti-inflammatory activity, but less research has been done. The main effect of lycopodine is still anti-tumor activity, and other pharmacological activities of lycopodine could be further studied.

In another in vitro study, *L. serratum* (6–100 μg/ml) significantly inhibited cell viability, in which 100 μg/ml was found to be the most active dose. At this dose, *L. serratum* induced apoptosis of SK-Hep1 (75.7%), HT-29 (71.7%), A549 (53.8%) and HL-60 (89.2%) cell. Among these, HL-60 cells were highly sensitive to growth inhibition and apoptosis induced by *L. serratum*. Subsequent investigations indicated that serratenediol, a triterpenoid obtained from the methylene chloride fraction of *L. serratum*, strongly inhibited the proliferation of HL-60 cells with $IC_{50}$= 12.9 μM. An analysis of the mechanism indicated that serratenediol (6.25, 12.5 and 25 μM) treated HL-60 cells had hallmarks of apoptotic events, including increased ratio of Bax/Bcl-xL, released the cytochrome c, activated caspase-9, -3, and cleaved poly-ADP-ribose polymerase (PARP) (Ham et al. 2012). Nevertheless, the $IC_{50}$ values of *L. serratum*-induced apoptosis in these cells were not presented, preventing comparison of the sensitivities among different cells.

As reports show, the new skeleton secondary metabolites including lycojaponicumin A, lycojaponicumin B and lycojaponicumin C all had significant inhibitory effects on the growth of ileocecal cancer cells HCT-8 with $IC_{50}$=1.15±0.17, 1.33±0.11 and 2.04±0.21 μM, respectively (Jiang et al. 2013a; b; Wu et al. 2013a). Meanwhile, lycojaponicumin A (0.625, 1.25, 2.5, 5.0, 10.0 μg/ml) can inhibit the proliferation and induce apoptosis of leukemia HL-60 cells in a dose-dependent manner (Jiang et al. 2013c), and lycojaponicumin C significantly inhibited the growth of gastric cancer cell lines (HGC-27, MGC-803, BGC-823, SGC-7901) with $IC_{50}$=3.21±0.33, 1.12±0.17, 0.87±0.07 and 1.33±0.19 μM and liver cancer cell lines (HepG2, MHCC-LM3, Bel-7402, HuH-7) with $IC_{50}$=2.26±0.32, 1.46±0.21, 2.41± 0.11 and 3.21±0.37 μM, respectively. (Wu et al. 2013b; Wu et al. 2013c). In addition, lycophlegmarin, a serratane-type triterpene, exhibited modest growth-inhibitory activity in vitro against human hepatoma (BEL-7402) cells (Shi et al. 2005). Therefore, several of the secondary metabolites mentioned above may be used to prepare as anti-tumor drugs and have great prospects for development and application. However, none of these secondary metabolites have been evaluated for their antitumor activity in vivo, and their detailed mechanism of action has not been reported either.

However, positive control was lack in all of the experiments (Table 5), and positive controls should be added to confirm the anti-tumor activity of these secondary metabolites.

### *Anti-inflammatory* activity

Secondary metabolites from plants of genus *Lycopodium* have shown notable anti-inflammatory activities. More information related to these activities is present in Table 6. The main effective substances associated with this effect are demonstrated to be Hup A and the extract of *Lycopodium japonicum* Thunb. *L. japonicum* has been used as a TCM, which has a long history of treating the inconvenient flexing and stretching, wind dampness arthralgia syndrome, bruises, and other diseases with definitely curative effects. In addition, it has been used in traditional medicine around the world to treat inflammation related diseases such as dermatitis, enteritis and hepatitis, which also strongly relate to the anti-inflammatory activity of *Lycopodium* plants.

LPS-induced rat microglial cells were treated with various doses of Hup A (0.1, 1, 10 μmol/L) in vitro, and the results suggested that this secondary metabolite decreased the releasing of major inflammatory factors such as IL-6, TNF-α and NO (Huang et al. 2017). But the information of positive control group was absent in this study. An in vivo investigation revealed that different doses of Hup A (0.1, 0.3, 0.9 mg/kg, *i.p.*) had certain inhibitory effects on foot swelling caused by egg white in mice (Shi et al.

2014). Nevertheless, the study did not establish a positive control group. Before this study, Gu et al. intended to establish the model of presbycusis rats by subcutaneous injection of D-galactose to simulate the aging mechanism of the body. The result showed that Hup A (0.1 mg/kg) blocked Schwann cells, inhibited the activation of NF-κB, and then inhibited the release of inflammatory factors (such as IL-1β, IL-6, TNF-α), which played a local anti-inflammatory effect on cochlear tissue (Gu et al. 2014). However, there was only one dose in the study that could not adequately reflect its anti-inflammatory strength and the benefit of Hup A for the treatment of presbycusis needs to be confirmed by further clinical research.

In an in vivo study, Zeng et al. compared the anti-inflammatory effect of different extracts (chloroform extract, *n*-butanol extract and water extract) of *L. japonicum* (40 g/kg) by using rat ear dimethyl benzene-induced inflammation method, acetic acid induced abdominal inflammation method and rat metatarsal edema method. The result showed that *L. japonicum* has significant anti-inflammatory pharmacological effects, and its effective components are concentrated in chloroform extract (Zeng et al. 1999). However, there was no analysis of phytochemical composition and positive control. Furthermore, another study showed that the alkaloids of *L. japonicum* (30, 60, 120 mg/kg) significantly inhibited the swelling of arthritis induced by Complete Freund's Adjuvant (CFA) in rats, and improved the synovial lesions of ankle joint in rats with a positive control (etoricoxib, 1 mg/kg) and a vehicle group. The mechanism may be related to the decrease of IL-1β and TNF- α levels in vivo (Liu et al. 2019). Besides, Orhan et al., from Turkey, found that chloroform extract of *L. clavatum* (LC) and the alkaloid fraction could inhibit acetic acid induced increasing in capillary permeability and had an obvious anti-inflammatory effect at a dose of 500 mg/kg having percentage of inhibition 24.3 and 32.1, respectively. Indomethacin (10 mg/kg) was used as the positive control. Among them, the anti-inflammatory activity of the aerial parts of LC are primarily due to the alkaloidal components, which might most probably be lycopodine (84.5%) as the major compound (Orhan et al. 2007a). However, only one dose was tested in above study.

In addition, acetyldihydrolycopodine and stigmastane-3-oxo-21-oic acid isolated from *L. obscurum* and methyl *p*-coumarate isolated from *L. japonicum* could significantly inhibit nitric oxide production in dose-dependent manner (6.25, 12.5, 25, 50 μM), using dexamethasone (10 μM) as a positive control. It was suggested that they had potential anti-inflammatory activities with $IC_{50}$=46.84±9.64 for acetyldihydrolycopodine and 10.73±4.12 μM for methyl *p*-coumarate, respectively. (Yang et al. 2015). Nevertheless, the $IC_{50}$ value of stigmastane-3-oxo-21-oic acid was not mentioned. An in vitro study showed that six alkaloids (8β-hydroxylycodoline, 11β-hydroxy-12-epilycodoline, lycopodine, deacetylfawcettiine, acetyllycofawcine, α-lofoline) isolated from *L. japonicum* displayed moderate activities against LPS-induced pro-inflammatory factors in BV2 macrophages with $IC_{50}$ in the range of 4.23–49.03 μM. Among them, α-lofoline showed the strongest activity with an $IC_{50}$ value of 4.23 μM. Untreated culture cells were used as a negative control and curcumin was used as the positive control ($IC_{50}$=3.12 μM) (Wang et al. 2009). Reportedly, obscurumine O (1.25, 2.5, 5, 10, 20, 40 μM), a lycopodine-type *Lycopodium* alkaloid from *L. obscurum*, exhibited inhibition of the secretion of IL-2 in phytohemagglutinin (PHA) and phorbol myristate acetate (PMA) stimulated Jurkat cells with dexamethasone as positive control, and the $IC_{50}$ value of obscurumine O was 17.2 μM (Jiang et al. 2016). But the dose of positive control was not presented. As above data show, a series of hydrophobic alkaloids from plants of genus *Lycopodium* exhibited potential anti-inflammatory effect in vitro. However, there is a lack of in vivo investigation and mechanism report of these secondary metabolites, and thus related study on anti-inflammation in vivo is expected to offer new evidence for the clinical use of *Lycopodium* species.

## Other activities

The in vitro antimicrobial properties of the petroleum ether, chloroform, ethyl acetate, methanol extracts and alkaloid fraction of *L. clavatum* (0.25–512 μg/mL) were evaluated against two Gram-positive, five Gram-negative bacteria, as well as two yeast-like fungi using micro-well dilution method. Results revealed that *Staphylococcus aureus* (ATCC 25,923) is the most susceptible bacteria with a minimum inhibitory concentration (MIC) of 4 μg/ml and all the extracts possess noteworthy activity against it.

Ampicilline (MIC<0.12 μg/ml) and ofloxacine (MIC =0.5 μg/ml) were served as positive controls for the antibacterial tests. As for the antifungal tests using ketoconazole (MIC=1 μg/ml) and fluconazole (MIC =4 μg/ml) as positive controls, ethyl acetate, methanol extracts and alkaloid fraction inhibited *Candida albicans* (ATCC 10,231) and *C. parapsilosis* (ATCC 22,019) (MIC=16 μg/ml) moderately but better than petroleum ether and chloroform extracts (MIC=32 μg/ml) (Orhan et al. 2007b). The SAP of *Candida albicans* have been shown to be a major virulence factor in Candida infections (Hoegl et al. 1999). Several secondary metabolites isolated from *L. cernuum* were tested in a *Candida*- SAP inhibition assay at three concentrations (50, 10, 2 μg/ml). Only a serratene triterpene (3β, 14α, 15α, 21β, -29-pentahydroxyserratane-24-oic acid) and a flavone glycoside (apigenin-4′-O-(2″, 6″-di-O-*p*-coumaroyl)-β-D-glucopyranoside) were active, with $IC_{50}$ value of 20 and 8.5 μg/mL, respectively. The aspartic protease inhibitor pepstatin A was used as a positive control ($IC_{50}$=0.0015 μg/mL) (Zhang et al. 2002a). In addition, the chloroform extract of *L. clavatum* exerted good antiviral effect towards the DNA virus HSV (8–16 μg/ml). The maximum nontoxic concentration (MNTC) is 16 μg/ml, which is similar to that of acyclovir (<0.25 to 16 μg/ml), except for its therapeutic range was narrower. In particular, the alkaloid fraction showed quite similar anti-PI-3 effect and MNTC value to that of oseltamivir (<0.25 to 32 μg/ml) (Orhan et al. 2007b). Encouraged by the records on traditional use of several *Lycopodium* species as anti-infective in Turkey, Orhan et al. assessed in vitro growth-inhibitory activity of different extracts (0.123–90 μg/mL) of *L. clavatum* and *L. complanatum* subsp. *Chamaecyparissus* against clinically relevant stages of *Trypanosoma brucei rhodesiense* (bloodstream forms), *Trypanosoma cruzi* (intracellular amastigotes in L6 rat skeletal myoblasts), *Leishmania donovani* (axenic amastigotes) and *Plasmodium falciparum* (blood stage forms of K1 strain resistant to chloroquine and pyrimethamine). Both fern species showed anti-protozoan activity, indicating that their extracts may have the potential to provide novel antiprotozoal agents and deserve further phytochemical investigations (Orhan et al. 2013). This discovery confirmed the traditional uses of the treatment of some infectious diseases, like dysentery, rubella, intestinal infection and viral hepatitis caused by bacteria or viruses. It has also been reported that *Lycopodium* alkaloids have cardiovascular and auditory function protective activities (Jiang et al. 2015; Ishiuchi et al. 2016; Kong et al. 2013). The ethanol or aqueous extracts of *L. clavatum* and *L. serratum* showed some anti-diabetes and wound healing activities (Tam et al. 2011; Manjunatha et al. 2007) (see Table 7). However, these studies reported in the literature are too preliminary and seriously suffer from important experimental shortcomings, such as single dose-testing and absence of appropriate positive and negative controls.

## Clinical trials

Clinical trials with *Lycopodium* alkaloids have been carried out since the 1990s after the anti-AChE activity of Hup A was detected. In 1996, Hup A was approved as a second-generation AChE inhibitor for the treatment of AD in China according to the second class of new drugs (Wang et al. 2006a). It was approved for listing by the FDA of the United States as a dietary supplement in 1997. In recent years, many clinical trials have been published, which confirm that Hup A has a good therapeutic effect on patients with early and middle AD, and also has a certain therapeutic effect on cognitive dysfunction associated with vascular dementia (VaD), schizophrenia, Parkinson's disease, diabets and other diseases.

### Treatment of AD

Most of clinical trials of Hup A in the treatment of AD have been performed in China, where an estimated more than 100,000 people have been treated by Hup A. Results of these studies indicate that Hup A is a safe and effective drug that improves cognitive function. In 2002, Zhang et al. conducted a placebo controlled, randomized, and multicenter study with 202 AD patients. One group of 100 patients was administered 400 μg/day Hup A for 12 weeks and 102 patients received placebo. The treatment group displayed improvements in cognition measured on the Alzheimer's disease Assessment Scale (ADAS-Cog) as well as an increase in behavior and mood (ADAS non-Cog) and improvement in the ability to do activities of daily living (ADL). Hup A had good safety, with mild and transient adverse

events (insomnia and edema of bilateral ankles) occurring in 3% of Hup A treated patients (Zhang et al. 2002b). Later, Qiu et al. and Li et al. got similar results in their researches (Qiu et al. 2009; Li et al. 2011). A study of the safety and efficacy of Hup A in the United States observed dose-related improvements with higher Mini-Mental State Examination (MMSE) scores at higher dosage, and no serious side effects. 26 patients met the Diagnostic and Statistical Manual of Mental Disorders—Fourth Revision (DSM IV-R) and the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS-ADRDA) criteria for uncomplicated AD and probable AD. An oral dose of 50 μg Hup A was given to 22 patients twice a day, and the 4 other patients received a dose of 100 μg twice daily. This study lasted 3 months. A mean dementia baseline score of 22.6 was measured with the MMSE. The changes in this score, for the 50 μg group and for the 100 μg group, respectively, were 0.5 and 1.5 points at 1 month; 1.2 and 1.8 points at 2 months, and 1.1 and 1.0 points at 3 months (Mazurek et al. 2000). In addition, a multicenter randomized controlled study was conducted in the Department of Neurology, University of California School of Medicine. 210 patients with mild to moderate AD were randomly divided into three groups. 70 patients in each group were given placebo, Hup A 200 or 400 μg twice a day, respectively, for a period of not less than 16 weeks. The results showed that the cognitive score of AD rating scale (ADAS-Cog) in Hup A 200 μg group was not improved, but the ADAS-Cog score in 400 μg group was increased by 2.27 points, and that in the corresponding placebo group was decreased by 0.29 points (Rafii et al. 2011).

In view of the fact that AD is a neurodegenerative disease with multiple etiologies and complicated pathogenesis, it has become a new therapeutic strategy to explore multi-target drugs or combination drugs for the treatment of AD. The multi-target effect and the good efficacy of Hup A in combination with other drugs indicating a broad prospect in clinical application. In the future, it still needs to be further expanded and further studied in clinical practice in terms of indications, therapeutic dose, combination method and treatment course. The clinical study of stricter design, larger sample size, longer treatment cycle and adjusting dose within the range of dosage will have more guiding significance for the rational application of Hup A in the treatment of AD.

### Treatment of VaD

The pathological conditions of ischemia and hypoxia in the brain of the patient can also cause damage to the central cholinergic system, and the clinical application proves that the Hup A can also relieve the dementia symptoms of the patients. After 6 to 48 weeks of twice-daily oral Hup A (0.1–0.2 mg) treatment, hundreds of patients with VaD showed significant improvement in MMSE, Clinical Dementia Rating (CDR) and ADL compared to conventional treatment (Zhao et al. 2007; Zhang et al. 2011). The patients taking both the Hup A and the medicine that improve cerebral circulation and dilate blood vessels, such as *Ginkgo biloba* preparations and Nimodipine Tablets, had better therapeutic effect (Ma et al. 2007a; Fan et al. 2009; Zhang et al. 2007).

### Treatment of other cognitive disorders

In patients with schizophrenia, taking antipsychotic drugs (such as cloproterol, clozapine, etc.) at the same time, twice-daily treatment with Hup A (0.1–0.2 mg) for 4 to 12 weeks could help to improve the cognitive function of patients (Chen et al. 2007; Liang et al. 2009). Yao et al. used Hup A (0.1 mg) combined with cognitive function rehabilitation training to treat patients with Parkinson's disease. After 6 weeks of treatment three times a day, the results of WMS score showed that the cognitive function of the patients was improved (Yao et al. 2006). Besides, Wang et al. injected 0.3 mg Hup A intravenously 30 min before anesthesia in 15 patients under general anaesthesia. It was found that the level of ACh in the brain of the patients during recovery was increased, which was helpful to the recovery of cholinergic nerve function in the brain (Wang et al. 2006b). After taking Hup A (0.1 mg) three times a day for 8 weeks, the MMSE score, latency and amplitude of diabetic patients were improved before treatment (Zhang et al. 2008). The deficiency was that most of the trial treatment courses were short, the number of samples was small, and the positive controls were lacking.

## Toxicity and side effects

There are few data about the toxicity or side effect of species of the genus *Lycopodium*. But the plants such as *L. serratum*, *L. japonicum* and *L. clavatum* still have a certain level of toxicity.

The Great Dictionary of Chinese Medicine (《中药大辞典》) points out that the use of *L. serratum* to take care of the overdose, which could lead to poisoning, dizziness, nausea, vomiting and other symptoms (Wang et al. 2012a, b). Especially for pregnant women, it could cause fetal stunting, deformities and miscarriages in severe cases. This indicated that the *L. serratum* has certain toxicity. Meanwhile, Hup A isolated from *L. serratum* is important in AD treatment. The $LD_{50}$ of Hup A mice was given intravenously at 10.2 μmol/kg and intraperitoneally at 7.4 μmol/kg, respectively. The experimental results showed that the acute toxicity of Hup A to mice and rats was significantly lower than that of physostigmine (Phys), neostigmine (Neos) and Gal. The therapeutic indexes of Hup A in mice and rats were 23.1 and 72.9 respectively, which were 7–10 times larger than Phys and most of the *Lycopodium* alkaloids have certain toxicity, among which the toxicity of lycopodine is relatively high. The $LD_{50}$ of lycopodine injected into mice by intraperitoneal and intravenous injection is 78 mg/kg and 28 mg/kg, respectively. The main symptoms of poisoning in mice, frogs and rabbits are hyperexcitability, rigidity and paroxysmal convulsion, asphyxia, paralysis and death. However, the toxicity of clavatine and clavatoxine is slightly less than that of lycopodine. The $LD_{50}$ of clavatine is 50 mg/kg for cats and 100–200 mg/kg for rabbits and rats, while clavatoxine has excitatory effects on the respiration of mammals and can paralyze the central and peripheral nervous system of frogs.

The chloroform, *n*-butanol, and water extracts of *L. japonicum* after acute toxicity test were intragastrically administrated to NIH mice at 0.4 mL/10 g body weight respectively. The results showed that the maximum tolerance dosage of the three extracts was more than 80 g crude drug/kg body weight, which indicated that the herb had low toxicity (Zeng et al. 1999). It is not safe to use *L. japonicum* externally. A case of contact dermatitis caused by *L. japonicum* was diagnosed and treated by Li Suping in 1995. External application after mashing the plant, the local skin felt burning pain after about two hours. Twelve hours later, the external skin appeared the phenomenon of red swelling, blisters and severe pain. It was diagnosed as contact dermatitis. After the use of *L. japonicum* was stopped, it was cured by anti-allergy treatment within a week (Li et al. 1995).

Sharma et al. conducted a toxicity assessment with *Denio rerio* (Zebrafish) model in vivo. This experiment using homeopathy, Zebrafish embryos were treated at different concentration (1, 5 and 10%) of *L. clavatum* mother tincture for 120 h and was examined these developmental defects at 24, 48 and 72 hpf (hour post fertilisation). These results indicate that 10% of *L. clavatum* mother tincture was found to be highly toxic as mortality rates of 80% at 24 hpf and 100% at 48 hpf. Whereas 5% of *L. clavatum* mother tincture showed 50% mortality rate of 24 hpf and remained constant at 48 and 72 hpf with moderate toxicity and side effects. However, 1% of *L. clavatum* mother tincture is considered completely safe and non-toxic to zebrafish embryos. Therefore, *L. clavatum* mother tincture affects the normal growth and development of zebrafish embryos in a dose-dependent manner (Sharma et al. 2019).

At present, the study on the toxicity of the genus *Lycopodium* is insufficient. Further studies are required to reveal the possible toxicity and side effect of *Lycopodium* species in order to better explain the safety of them and provide security for clinical medication.

## Quality control

The most common used medicinal herb of this genus is the whole plant of *L. japonicum*. In Chinese Pharmacopoeia 2015 edition, only microscopic and TLC identification was required for the quality standard of this herb. In order to make a comprehensive evaluation on the quality of *L. japonicum*, Zou et al. used HPLC method to determine the content of α-obscurine in 10 batches of *L. japonicum* at different altitudes. The chromatographic separation was conducted at 25 °C on Hypersil ODS and Spherigel $C_{18}$ Columns (200 × 4.6 mm, 5 μm), with methanol and water (65:35, V/V) as the mobile phase at a flow rate of 1.0 mL/min, and the wavelength for detection is at 248 nm. The content of α-obscurine was between 0.083 and 0.215%, which was related to the origin but

not to the altitude. α-Obscurine is an effective component with anti-inflammatory and anti-platelet aggregative activities, which can be used as a marker for the quality control of *L. japonicum* (Zou et al. 2010). You et al. successfully identified flavonoids, triterpenoids and alkaloids in *L. japonicum* by TLC with high specificity and sensitivity. Meanwhile, HPLC was used to determine the content of α-obscurine, with good reproducibility and high accuracy. However, the contents of flavonoids and triterpenoids were not determined (You et al. 2012). Furthermore, an HPLC fingerprint analysis was established by Yang for the analysis of *L. japonicum*. A total of 19 mutual peaks were indicated, and the similar degrees of the ten batches were between 0. 923–0. 985, which provided a basis for effective control and scientific evaluation of the quality of this herb. However, none of the indicated peaks was identified (Yang et al. 2013). Except for α-obscurine, there is no specific study implemented for the content of other alkaloids in *L. japonicum*, thus more research is needed to improve the quality standard of *L. japonicum*.

Hup A isolated from *L. serratum* is a reversible AChE inhibitor, which has significant effects on Alzheimer's disease, simple memory impairment, myasthenia gravis, etc. (Liu et al. 1986; Zhang et al. 1991). Thus, it is a representative marker for quality standard of medicinal species of the genus *Lycopodium.* Determination of Hup A in different parts of *L. serratum* from 12 producing areas revealed that the highest content of Hup A was 0.0900%, the lowest content was 0.0014%, and the content in leaves was generally higher than that in stems and roots. The analytical conditions were carried out as follows: using an UItimate XB—$C_{18}$ column (4.6 mm × 250 mm, 5 μm), with the mobile phase of acetonitrile—methanol—water (10:55:240) containing 0. 32% phosphoric acid and 0. 5% triethylamine (Yuan et al. 2012). Wang et al. found that the average content of Hup A in the seedlings and young plants was significantly higher than that in mature plants, and there were significant differences in the average content in different areas. The content of Hup A ranged from 0.0447% to 0.066%, which was seriously affected by habitat factors. Among them, the annual rainfall was negatively correlated with the content of Hup A, whereas elevation and annual average temperature had no significant effect (Wang et al. 2014). Then Lai et al., found that the dynamic variation of Hup A in the plant was December>September>June>March, and the highest was 325.9 μg/g. But only two regions of plants were measured, and the rule was not fully representative (Lai et al. 2014). In addition to the commonly used HPLC method, Li et al. used the liquid chromatography tandem mass spectrometry (LC–MS) method to determine the content of Hup A in different parts of plants from four producing areas. The chromatographic separation was conducted at 28 °C on an ZORBAX SB—$C_{18}$ column (250 × 4.6 mm, 5 μm), and the mobile phase at a flow rate of 0.5 mL/min was composed of methanol and water (90:10, V/V). The results showed that the content in the leaves and stems was between 0.02% and 0.06%, and the content in leaves was greater than that in stems. However, the content of Hup A of the whole plant was not determined (Li et al. 2017).

The above results showed that the content of Hup A in *L. serratum* is relatively low, and the content of Hup A in the plant in different regions also varies greatly under the influence of environment.

To sum up, the quality evaluation research of plants of this genus is too few, and there is no ideal standard for qualitative identification and content determination of active components or indicator components. Therefore, it is necessary to apply various advanced quality control methods and establish scientific and comprehensive quality control methods on the basis of in-depth and systematic study on chemical components of those herbs.

## Conclusion and further scope

In the present review, we summarize knowledge on traditional uses, secondary metabolites, pharmacology, toxicity, clinical trials and quality control of the *Lycopodium* plants. In view of the wide distribution of club-mosses, extensive literature survey revealed that most of the species are used ethnopharmacologically in different Europe, America and Asia countries. Since 1840s, the studies have resulted in isolation of 508 secondary metabolites including alkaloids, triterpenoids, glycosides and others. Many pharmacological studies were carried out using various in vivo and in vitro biological techniques after the detection of anti-AChE activity of Hup A in

1990s. In terms of current research, *Lycopodium* alkaloids and serratene triterpenoids as the main active ingredients exhibit a variety of biological activities including anti-AD, neuroprotection, anti-tumor, anti-inflammation and so on, which supports most of traditional medicinal uses of *Lycopodium* plants. For example, *L. saururus* and *L. serratum* have been popularly used in Chinese and Europe traditional medicine for its memory-enhancing effect since centuries. It indicated that these plants may treat central nervous system-related diseases. And now available studies have showed neuroprotective activity and a certain therapeutic effect on AD of alkaloids dominated by Hup A and few triterpenoids isolated from plants of genus *Lycopodium*. Moreover, bioassay-guided fractionation of the alkaloid fraction of *Lycopodium* species revealed that the alkaloids are responsible for the anti-inflammatory activity of the extract, which supports the traditional uses of treating inflammation-related ailments such as dermatitis and rheumatic arthritis. On the other hand, pharmacological studies on *Lycopodium* species have also explored the effects such as antitumor and cardiovascular protection not found in ancient times. However, gaps exist in the scientific studies on *Lycopodium* plants. therefore, we provide a summary several topics that should have priority for detailed investigation.

Firstly, the use of an infusion of *Lycopodium* species is widely known in traditional medicine around the world, and the most common form in traditional medicine is water decoction. However, modern secondary metabolites and pharmacological researches focus on alkaloids, triterpenoids and some hydrophobic extracts (chloroform, ethanolic, ethyl acetate, petroleum ether). Further, a hydrophilic secondary metabolite [apigenin-4′-O-(2″,6″-di-O-*p*-coumaroyl)-β-D-glucopyranoside] has been found to exhibit remarkable antifungal activity. Thus, much more effort should be paid to investigate the bioactivity of water-soluble components.

Secondly, most of the investigations regarding anti-AD, anti-tumor, anti-microbial, antiviral and cardiovascular protection currently collected were limited to the in vitro studies without a detailed exploration of the exact molecular mechanism of action, which may be due to the complex pathogenesis, involving a variety of pathways such as Alzheimer's disease. Besides, the in vitro studies of the hydrophobic extracts of *Lycopodium* species showed anti-microbial and antiviral activity, but the extracts were not standardized and the results require confirmation in vivo. Therefore, mechanism-based in vitro and in vivo investigations should be performed to further understand the underlying mechanisms linked to ethnopharmacological uses.

Thirdly, anti-microbial and antiviral activity shown in pharmacological studies mainly come from various extracts (petroleum ether, chloroform, ethyl acetate, and methanol) and alkaloids fraction. From a limited number of studies, alkaloid fraction might be considered worthy of advance phytochemical investigation to find out the active ingredients, although lycopodine, the major alkaloid of *L. clavatum* and *L. complanatum*, seems to be possibly responsible, which needs to be confirmed. Plant extracts are known to have a quite complex mixture and therefore, high probability of competing or synergistic interactions within the same extract may exist for any biological activity. Thus, further study should be directed toward bio-assay-guided isolation of the bioactive metabolites, studying their mechanisms of action individually or in combination.

Fourthly, there has been quite a number of researches on the structure–activity relationship of the *Lycopodium* alkaloid against AChE, but the exploration of structure–activity relationship in terms of other pharmacological activities is still lacking. Stimulating cholinergic anti-inflammatory pathway (CAP), a neuroscience and immunology pathway discovered back in 2002, can suppress local and systematic inflammatory responses. But so far, it is not clear about the structure–activity relationship of alkaloids and how they activate the cholinergic anti-inflammatory pathway. Thus, more in-depth investigation of structure–activity relationships should be performed.

Fifthly, in traditional medicine, herbs from the genus *Lycopodium* was generally reputed to be nontoxic except for *L. selago* that was known to be toxic and has been used for centuries to induce abortion. In addition, from the Argentinian ethnomedical references, the infusion is indicated to be the safest method, while the decoction can cause severe adverse reactions such as vomiting, drunkenness, convulsions, diarrhea, abortion in pregnant women and even death, which was deduced that the way in which it is prepared has an important

significance for the achievement of the effects that are attributed to it. Today, some *Lycopodium* plants and extracts are not commonly employed as herbal remedies as the side effects often exceed the benefits. According to the existing toxicity studies, most of the *Lycopodium* alkaloids have certain toxicity, among which lycopodine is highly toxic, and it can be speculated that the toxicity may mainly come from lycopodine class and lycodine class alkaloids. Therefore, it is essential to comprehensively study the potential toxicity and toxicity target organs of genus *Lycopodium*, formulate the safe starting dose for human use and safety parameters for monitoring and better serve for clinical safe drug use.

Sixthly, as a kind of fern, the spores are the main breeding methods of genus *Lycopodium.* The application of club moss spores directly to wounds and rashes is well known from natives in North America and Europe. In TCM, these spores namely "Shi Song Zi" are used as powder to treat skin erosion. Unluckily, there have been almost no documented studies on it.

Finally, among the ferns, many species have been widely used in medicine since ancient times to treat various diseases for the people, and genus *Lycopodium* is no exception. With the acceleration of the world aging population, the demand of Hup A is increasing. The wild resources of the *Lycopodium* species, especially *L. serratum* are exhausting, but it is extremely difficult to reproduction. Although some experiments such as the success of stem tip culture of *L. selago* bring hope to overcome this problem (Wojciech et al. 2005), there is a long way to go for mass production economically. Therefore, the increasing biotechnological research aimed at rapid reproduction of *Lycopodium* species is an urgent need of society.

Overall, we reviewed the traditional uses and studies of secondary metabolites, pharmacology, toxicity, clinical trials and quality control in recent 80 years. The research characteristics of *Lycopodium* plants are clearly understood. There is a good correspondence between traditional uses and pharmacological activities. The activities not shown in traditional uses found in modern pharmacological studies suggest that further research on active ingredients is worthwhile. Large quantities of alkaloids have been isolated from *Lycopodium* species, which showed abundant bioactivities in pharmacological studies due to their unique structures. Hup A also has been clinically used for quite a period of time because of its proven potent, reversible, and selective anti-AChE activity. Future research should focus on the molecular mechanism and structure–activity relationship of *Lycopodium* alkaloids. Last but not the least, other active ingredients (water-soluble and liposoluble) have rarely been purified and identified due to past emphasis on alkaloids and some triterpenoids. Therefore, studies of other types of secondary metabolites and possible mechanisms of synergy cannot be overlooked.

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**Compliance with ethical standards**

**Conflict of interest** The authors declare that there is no conflict of interest regarding the publication of this paper.

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