

REVIEW

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Recently isolated lycodine-type *Lycopodium* alkaloids and their total synthesis: a review



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Abstract

Background: Since long back, several plants species belonging to family Lycopodiaceae or Huperziaceae are being traditionally used in treatment of diseases like Alzheimer's disease and myasthenia gravis. In 1986, huperzine A, structurally lycodine type of alkaloid was isolated and established as potent acetylcholine esterase inhibitor. Hence, further, in pursuit of similar compounds, several hundreds of different types of lycopodium alkaloids have been isolated from different Lycopodiaceae or Huperziaceae plants species.

Main body: For few of these recently isolated alkaloids, the possible mechanisms of their biosynthesis have been proposed while few of them were tried for their laboratory total asymmetric synthesis. This review summarized lycodine-type *Lycopodium* alkaloids, whose isolation, biosynthesis, and total synthesis have been reported after 2000. It also includes structure–activity relationship.

Short conclusion: More than 40 lycodine-type alkaloids have been isolated and structurally elucidated since 2000. Their biosynthetic pathway suggested that they got biosynthesized from lysine, while structure–activity relationship established the structural requirement of lycodine-type alkaloids to possess potent acetylcholine esterase inhibitory activity.

Background

Lycopodium alkaloids with unique heterocyclic frameworks of different types like $C_{11}N$, $C_{15}N$, $C_{16}N$, $C_{16}N_2$, $C_{22}N_2$, or $C_{27}N_3$ have gained enormous research interest with focus on their biogenesis [1–3] and biological activities [4]. As per Ayer et al. 1991, lycopodium alkaloids are of four types: lycodine-type, lycopodane-type, fawcettimine-type, and miscellaneous-type [5]. The lycodine group consists of two nitrogens in structure containing a pyridine, anpyridone, or a hydrogenated pyridine ring.

Investigations on lycopodium alkaloids was started in 1881, when Bodekar first lycopodium alkaloid, lycopodine from *Lycopodium complanatum* [6]. Then, in 1938, Achmatowicz and Uzieblo again isolated lycopodine with correct molecular formula, and also two new nitrogen-containing compounds [7]. In the middle of twentieth century, Canadian Scientist, W.A. Ayer made significant

contribution in isolation of various alkaloids from lycopodium species and publishing research articles and reviews to make his findings open in public domain. During the same time, in 1944, Rothmalar re-established the taxonomy of Huperzia plant by separating it from family lycopodiaceae and placing into Huperziaceae or Urostachyaceae, which comprised of around 150 species of two genera, Huperzia and Phlegmariurus [8]. This taxonomic system has been supported by chemotaxonomic analysis made time to time in upcoming future. During the early 1980s, Chinese researchers screened Lycopodium species for new entity that could be used for treatment of myasthenia gravis [9]. The lycopodium alkaloid research was at peak in 4 years period of 1986–1990, when few lycopodium alkaloids with potent acetylcholinesterase inhibition activity were isolated. In 1986, Chinese scientist Liu and his co-workers isolated huperzine A from the plant *Qian Ceng Ta* (included in Chinese folk medicine) *Huperzia serrata* (Thunb.ex Murray) Trev.) was found to be most potent acetylcholinesterase inhibitor [10, 11]. Reported learning and

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memory-enhancing properties and pharmacological application of huperzine A in Alzheimer's disease and myasthenia gravis actually initiated the new tide of lycopodium alkaloid research. Now, as per our literature survey, since 2000, only few (14 out of 500+) species of plants belonging to family either lycopodiaceae or huperziaceae have been processed for isolation of active lycodine type of lycopodium alkaloid.

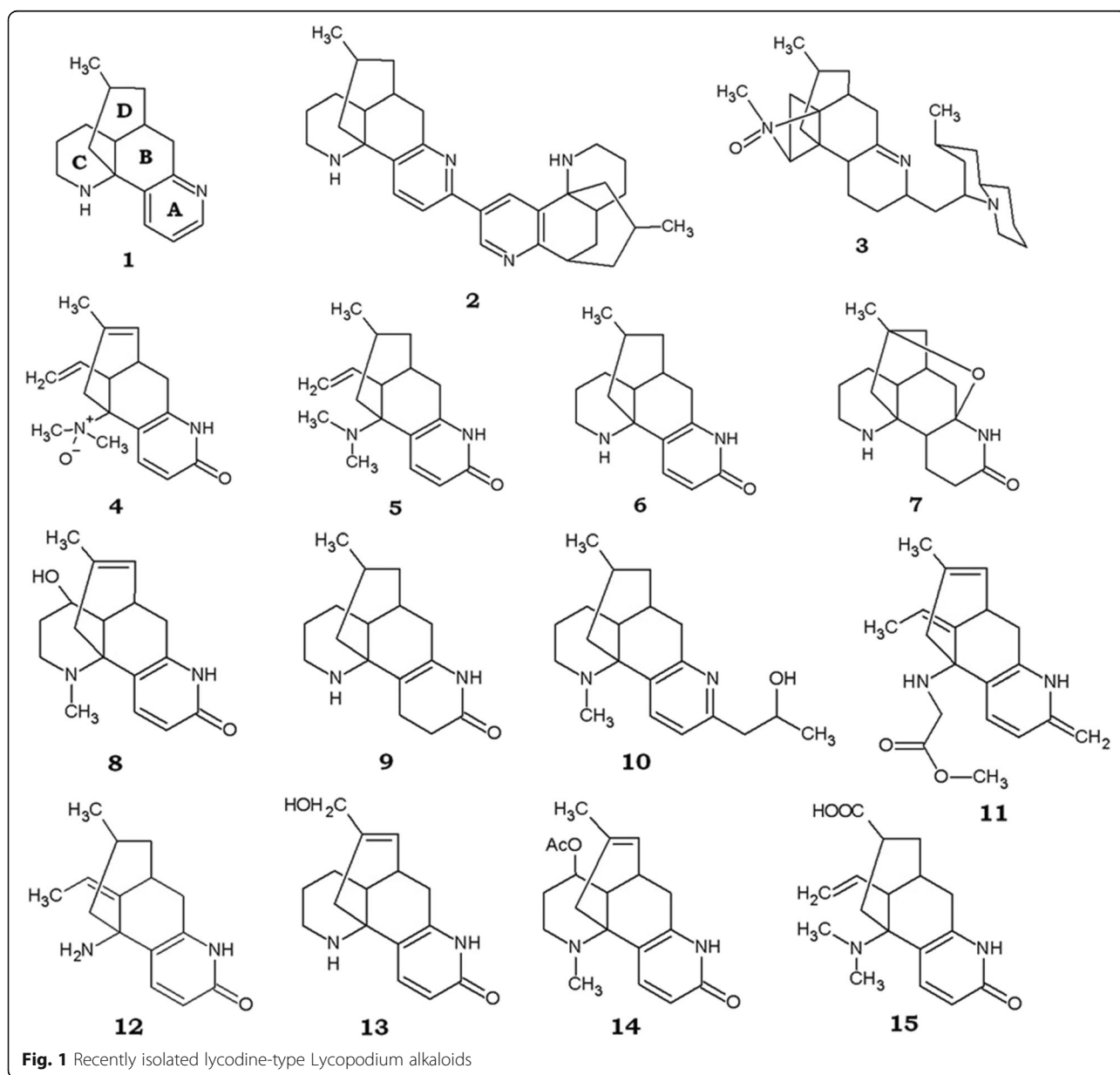
Main text

Biological significance and need of isolation of new *Lycopodium* alkaloids

Since long back, several traditional Chinese medicinal plants of family Lycopodiaceae and Huperziaceae are being

used in treatment of sprains, strains and myasthenia [12]. Advanced phytochemical analysis and pharmacological screening revealed that lycopodium alkaloids present in these plants have potential acetylcholinesterase (AChE) inhibitory activity and thereby therapeutic application in treating Alzheimer's disease [4, 13].

In order to meet increasing global demands for promising remedy on acetylcholine-dependent autonomic nervous system diseases, several attempts have been made for total synthesis of potent and biologically safe lycopodium alkaloids. But it was observed that a polycyclic carbon skeleton with different levels of oxidation is the common feature in all *Lycopodium* alkaloids, posing the challenging target for total synthesis [33–35].



Hence, in pursuit of potent acetylcholinesterase (AChE) inhibitory lycopodium alkaloids, researcher so far continued their efforts in isolation and structural elucidation of novel lycopodium alkaloids. This review consists of comprehensive data of newly isolated and pharmacologically screened Lycodine-type of lycopodium alkaloids, reported since 2000 (Figs. 1, 2, and 3; Table 1).

Extraction and isolation of lycodine type *Lycopodium* alkaloids

Isolation of lycodine-type *Lycopodium* alkaloids involves alcoholic extraction of plant material and column

chromatographic separation using suitable combination of stationary and mobile phase. For this, fresh or air-dried powdered material of aerial part or whole plant of any selected club moss species is firstly, extracted, mostly with methanol (occasionally with ethanol). This alcoholic extract is then concentrated in vacuum and 3% tartaric acid is added to it. Then, in order to remove non-alkaloid components, it is partitioned with ethyl acetate and polar fraction is made alkaline with sodium carbonate or sodium bicarbonate or sodium hydroxide, potassium carbonate or ammonia water. Due to alkaline nature and presence of lone of electrons on nitrogen, alkaloidal contents remain unionized. Further,

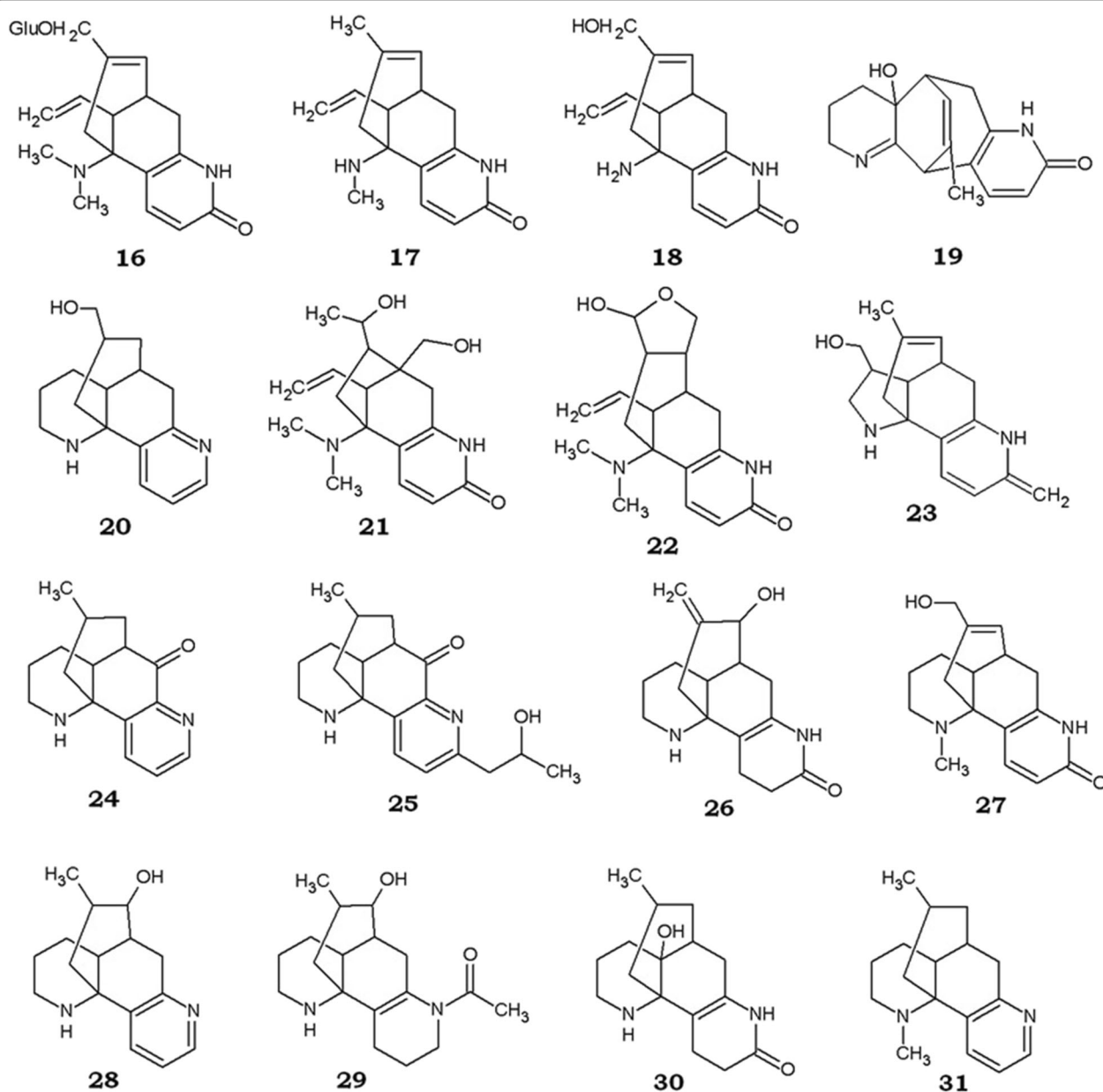


Fig. 2 Recently isolated lycodine-type *Lycopodium* alkaloids (cont..)

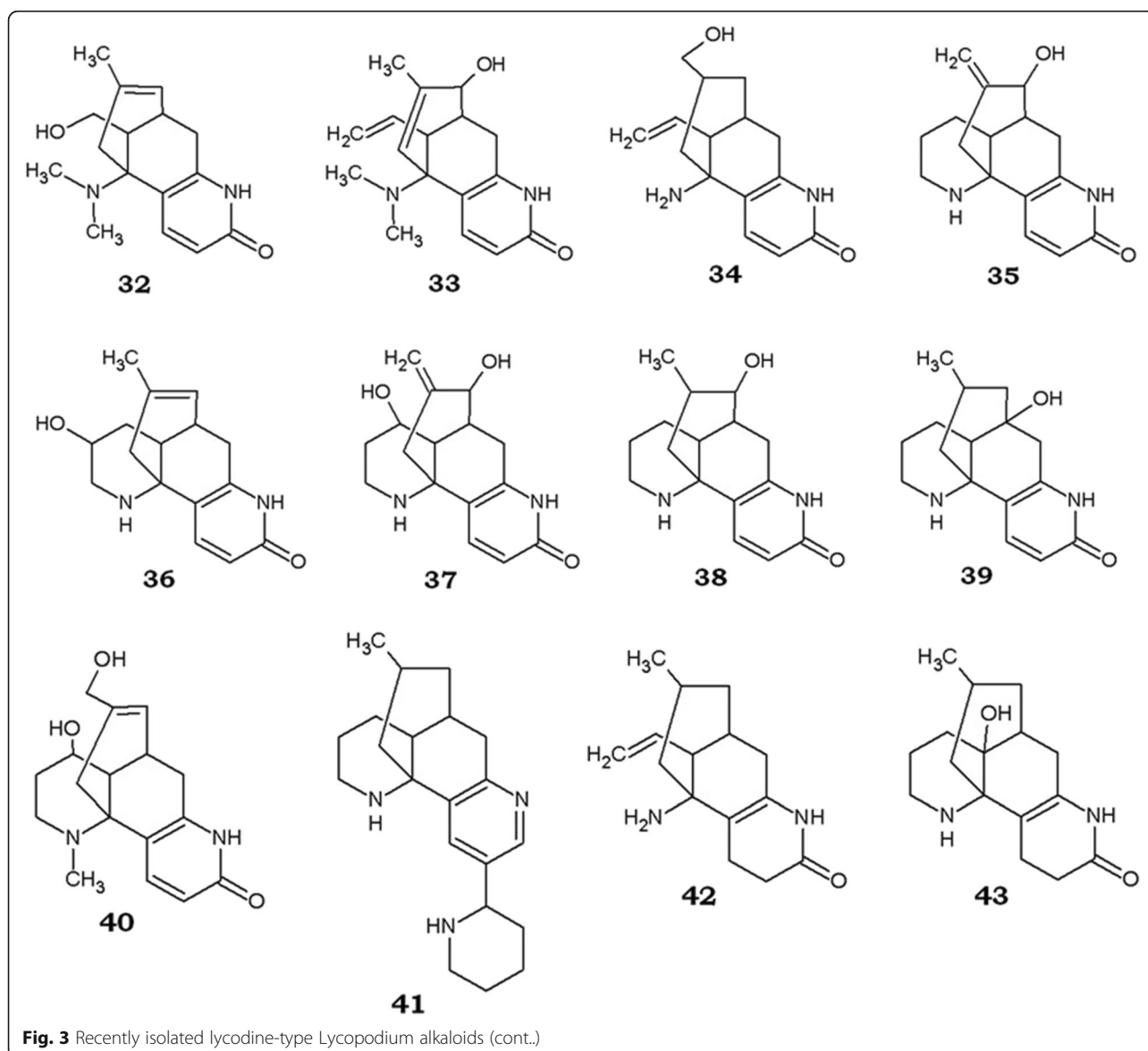


Fig. 3 Recently isolated lycodine-type *Lycopodium* alkaloids (cont..)

alkaloids are extracted from this alkaline system using dichloromethane or chloroform, which are further dried over anhydrous sodium sulfate. Concentrated dichloromethane or chloroform soluble semi dried, viscous portion is chromatographed over silica gel, Sephadex LH-20 or Mitsubishi Chemical Ion exchange resins eluted with a varying combination of solvents, based on either increase or decrease in polarity of mobile phase. In few cases, preparative HPLC is used for even fine separation. The compound isolated is further structurally elucidated using advance techniques and evaluated for (AChE) inhibitory activities.

Screening of lycodine type *Lycopodium* alkaloids for acetylcholinesterase (AChE) inhibitory activity

For most of the newly isolated and structurally elucidated lycopodium alkaloids, acetylcholinesterase (AChE)

inhibitory potential was determined according to the method using human RBC membranes as described by Ellman et al. 1961 with few modifications [36].

Briefly, the isolated compounds were diluted with buffer. Then, to each well of 96-well microplate, test sample was added together with acetylthiocholine iodide (ATCI), 5,5-dithiobis(2-nitrobenzoic acid) (DTNB) and acetylcholinesterase (AChE) enzyme in distilled water or buffer pH 7.4 to 8.

These solutions isolated compounds were used to determine their IC₅₀. Huperzine A [31], physostigmine salicylate [37], tacrine [38], or galanthamine [39] was used as positive control. Determinations were carried out by tracking the formation of the 5-thio-2-nitrobenzoate anion at 405 nm, after 30 s cycle, for 3 min and then the reaction mixtures were incubated at

Table 1 Recently isolated lycodine type Lycopodium alkaloids and their acetylcholinesterase (AChE) inhibitory activity

Lycopodium alkaloid	Plant spp.	LC ₅₀	Reference
Complanadine A (2)	<i>Lycopodium complanatum</i>	–	[14]
Himeradine A (3)	<i>Lycopodium chinense</i>	–	[15]
Huperzine N-oxide (4)	<i>Lycopodium casuarinoides</i>	–	[16]
8,15-dihydrohuperzine (5)		–	
N-demethyl-obscure (6)	<i>Lycopodium serratum</i>	–	[17]
Lycodine (1)		–	
Casuarine A (7)	<i>Lycopodium casuarinoides</i>	–	[18]
Casuarine B (8)		46.4 μM	
N-demethyl-sauroxine (9)	<i>Huperziasaururus</i>	–	[19]
N-methylhydroxypropyllycodine (10)	<i>Lycopodium japonicum</i>	–	[20]
Huperserine E (11)	<i>Huperzia serrata</i>	6.71 μM	[21]
8,15-dihydrohuperzine A (12)	<i>Huperziacarinata</i>	2.6 μM	[22]
16-hydroxyhuperzine B (13)	<i>Lycopodiastrum casuarinoides</i>	87.3 μM	[23]
N-methyl-11-acetoxylhuperzine B (14)		–	
8,15-dihydrolycoparin A (15)		–	
(7S,12S, 13R)-huperzine D-16-O-β-D-glucopyranoside (16)		–	
N-demethylhuperzine (17)		1.9 μM	
Lycoparin C (18)		23.9 μM	
N-methylhydroxypropyllycodine (10)	<i>Lycopodium japonicum</i>	–	[24]
Phlegfargesine A (19)	<i>Phlegmariurus fargesii</i>	–	[25]
16-hydroxylycodine (20)	<i>Phlegmariurus henryi</i>	–	[26]
Lycocasuarine A (21)	<i>Lycopodiastrum casuarinoides</i>	> 100 μM	[27]
Lycocasuarine B (22)		> 100 μM	
Lycocasuarine C (23)		7.4 μM	
lycoannotine G (24)	<i>Lycopodium annotinum</i>	–	[28]
lycoannotine H (25)		–	
Lycofargesine A (26)	<i>Huperzia fargesii</i>	–	[29]
Lycofargesine B (27)		–	
Lycofargesine C (28)		8.63 μM	
Lycofargesine D (29)		–	
12α-hydroxy-N-demethyl-sauroxine (30)	<i>Phlegmariurus saururus</i>	33.8 μM	[30]
N-methyllycodine (31)		547.5 μM	
N-demethyl-sauroxine (9)		1.38 μM	
Lycocasuarine I (32)	<i>Lycopodiastrum casuarinoides</i>	> 200 μM	[31]
Lycocasuarine J (33)		> 200 μM	
Lycocasuarine K (34)		171.9 μM	
Lycocasuarine L (35)		> 200 μM	
Lycocasuarine M (36)		97.2 μM	
Lycocasuarine N (37)		112.1 μM	
Lycocasuarine O (38)		137.8 μM	
Lycocasuarine P (39)		127.8 μM	
Lycocasuarine Q (40)		> 200 μM	
Lycoplatyrine A (41)	<i>Lycopodium platyrhizoma</i>	> 30 μM	[32]
Lycoplatyrine B (42)		> 30 μM	
Lycoplanine D (43)		–	

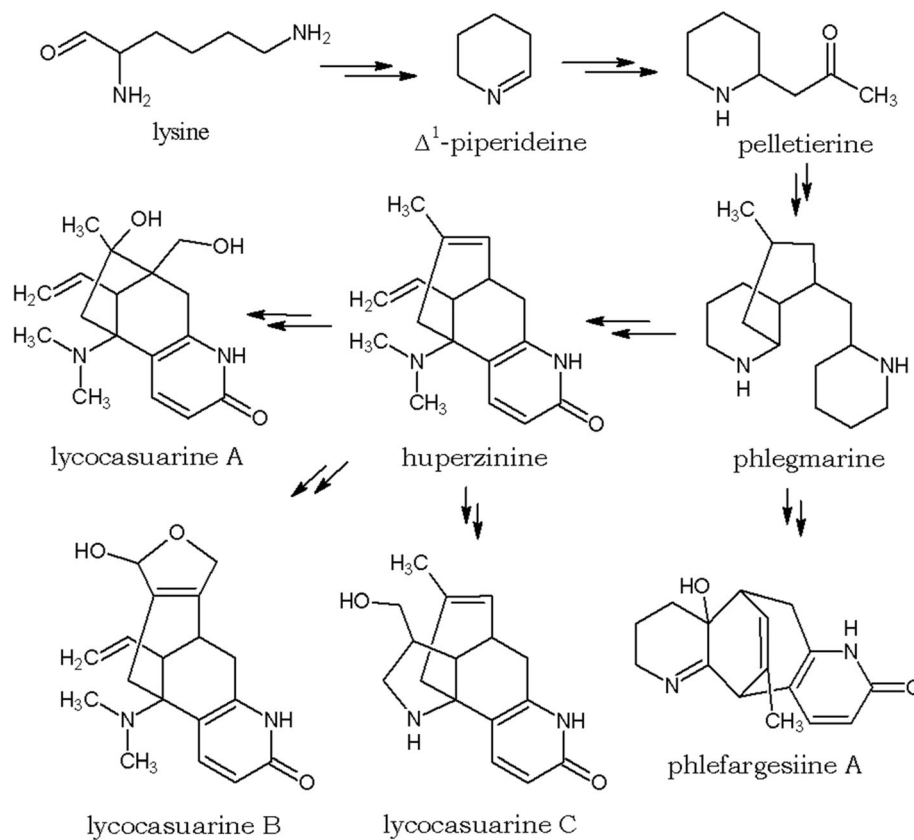


Fig. 4 Possible biosynthetic pathway for lycodine-type *Lycopodium* alkaloids

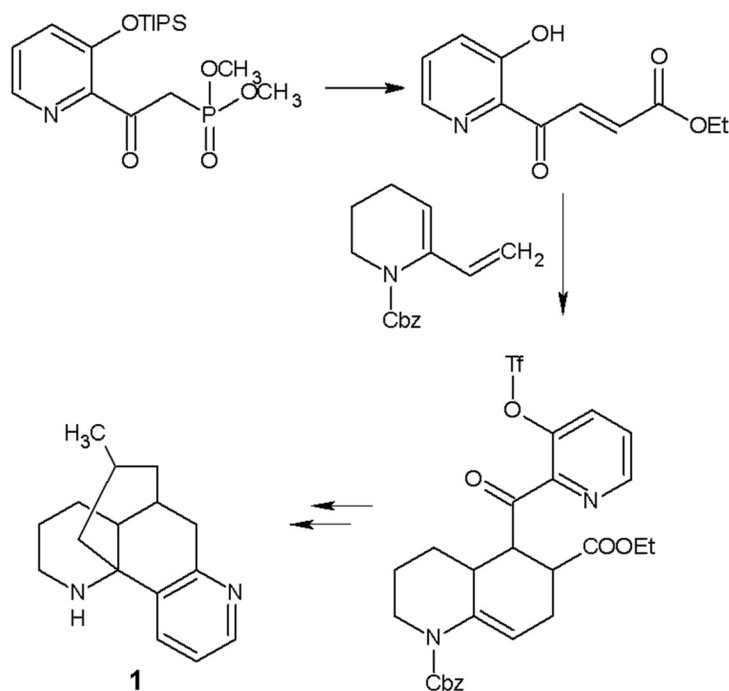


Fig. 5 Total synthesis of lycodine

room temperature for 20 to 30 min. After lapse, the absorbances were recorded again in identical way. The inhibitory percentage of each sample was calculated based on the absorbance (A) of the blank (A_0) and the test compound (A_1) using the following equation:

$$\text{Inhibition (\%)} = (1 - A_1/A_0) \times 100.$$

Results were analyzed by using software like GraphPad Prism 6 and thus, the IC_{50} obtained.

Structure of lycodine-type *Lycopodium* alkaloids and their AChE inhibitory activity relationship

In many cases, huperzine A was used as positive control; therefore, comparison of LC_{50} values of new alkaloids with that of huperzine A (0.17 μM , [31]) could be made, as a function of potency; thereby their structure-activity relationship could be explained. The higher the LC_{50} value, the lower is the potency and vice versa.

Compound 9 with no double bond between C-8 and C-16, ketone group at C-1, and double bond between C-4 and C-5 had less LC_{50} value. Cleavage of C-ring and ketone group at C-1, as found in compounds 11, 12, 17, and 18, exhibited potency close to that of huperzine A. Replacement of six-membered C-ring of lycodine structure by five-membered nitrogen ring, as in compound 23, have shown lesser LC_{50} value meaning higher potency. Compound 28 represented potency nearly equal to that of huperzine A, may be due to hydroxyl group at C-8. Compound 41 was lycodine structure substituted with a piperidine moiety at C-2 and exhibited moderate activity. N-methylation of lycodine decreased the activity.

Plausible biogenesis of lycodine-type *Lycopodium* alkaloids

For few of the newly isolated lycodine-type lycopodium alkaloids, a plausible biogenetic pathway has also been proposed. On detail literature survey, it was found that, in all cases, biogenesis starts with amino acid, lysine, proceeds through sequential formation of intermediates like pelletierine, Δ^1 -piperidine, phlegmarane skeleton, and lycodoline-type skeleton compounds, which by several reactions like oxidation, cyclization, Polonovski-type reaction, Michael type reaction, and Wagner–Meerwein rearrangement; finally, converted to final lycodine-type lycopodium alkaloids. Liu et al. 2013 quoted a plausible biogenetic pathway for casuarine A according to which des-N-methyl-a-obscurine underwent an oxidation to produce intermediate, followed then by an addition in the acidic conditions to afford another intermediate, which underwent tautomerism and a cyclization to yield casuarine A [18]. As per Meng et al. 2016, phlegfargesine A could be either derived from a lycodine-type precursor

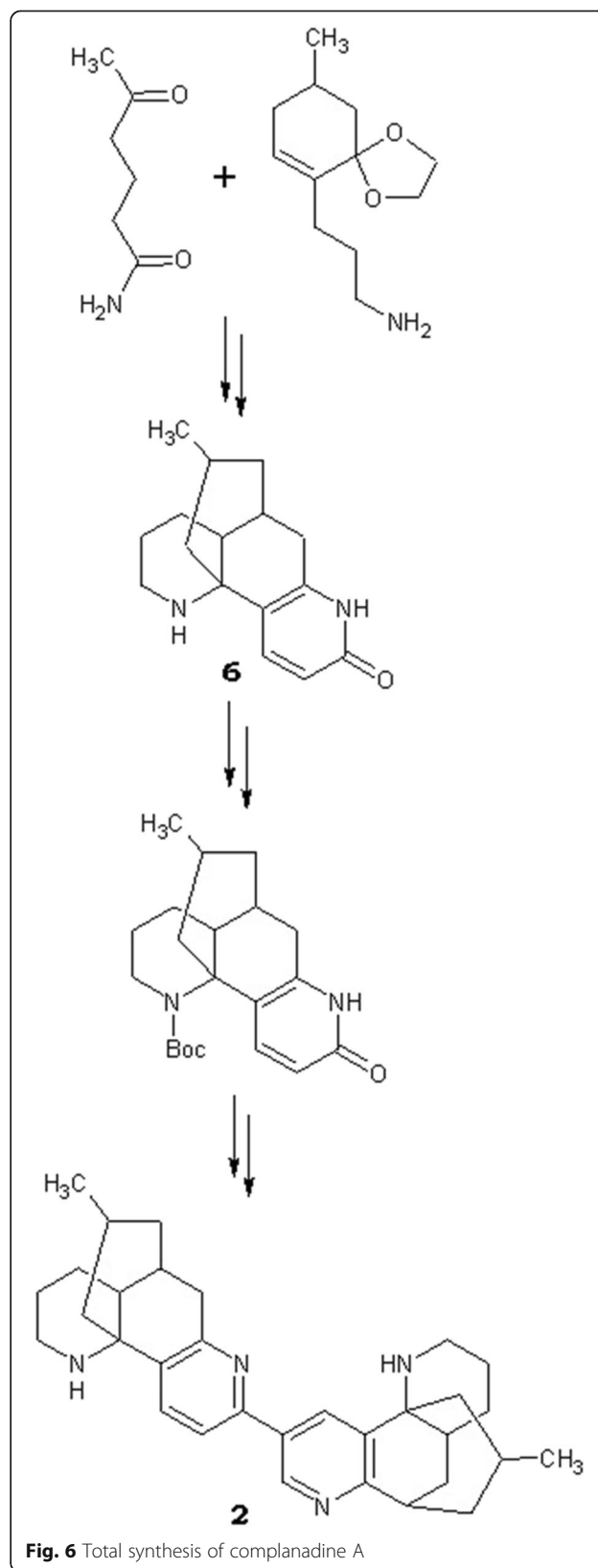


Fig. 6 Total synthesis of complanadine A

via the Wagner–Meerwein rearrangement (1,2-alkyl shift) followed by a series of dehydration and oxidation; or could be directly generated from a phlegmarine-type precursor by forming a new linkage between C-4 and C-14 forming the novel [6/7/6/6]-tetracyclic skeleton [25]. Lycocasuarines A, B, and Chave have also been described to be biosynthesized from huperzine. Huperzine, undergoes C-8/C-15 oxidative cleavage to form the intermediate which can spontaneously convert to its enol form. This enol intermediate cyclizes via an aldol reaction with the C-15 carbonyl group to afford a C-8 aldehyde intermediate, which finally reduces to Lycocasuarine A [27] (Fig. 4). Lycocasuarine I was reported to be biosynthesized from huperzine by subsequent oxidative cleavage and C₁₁ reduction [31]. Recently, considering the therapeutic effects of Lycopodiaceae and Huperziaceae plants and alkaloids isolated from them, Chen et al. 2020 discovered the

lycopodium alkaloids biosynthesis-related genes and genetic markers in *L. casuarinoides* stem and pin-like leaves transcriptome. They assembled 124,524 unigenes using 16.43 Gb clean data represented by 109 million RNA sequencing reads, out of which 47,538 open reading frames (ORFs) were detected. Several enzyme genes including those for lysine decarboxylase (LDC), primary amine oxidase (PAO), malonyl-CoA decarboxylase, etc. were also identified using bioinformatics tools. About 64 putative cytochrome p450 (CYP) genes and 827 putative transcription factors were located as biosynthesis modifiers. In 13352 simple sequence repeats (SSRs), dinucleotide motifs AG/CT were the most abundant (50.1%) [40].

Marketed preparations of Lycopodium species

Mostly, club mosses, mainly, *Lycopodium clavatum* is administered by oral route. Club moss powder is being

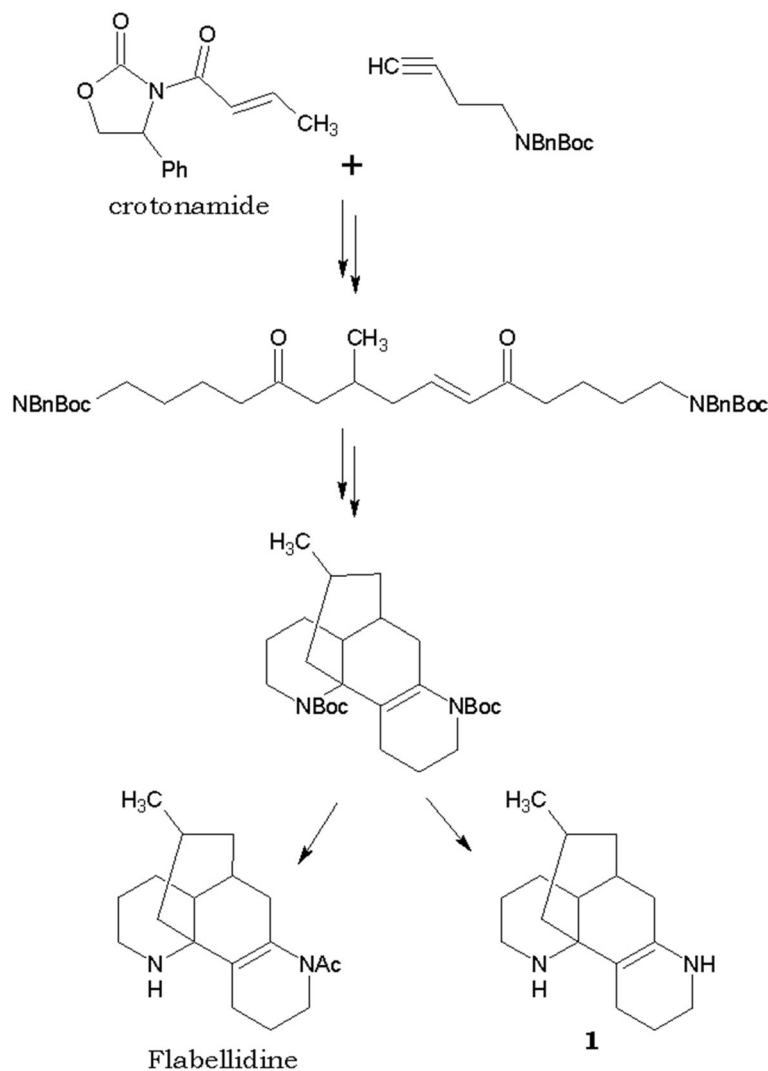


Fig. 7 Total synthesis of flabellidine and lycodine

sold in the form of tea bags by Terravita Tincture of club moss, sold by HerbalTerra, USA, and Hawaii Pharm Llc, Honolulu, USA, are the alcoholic preparations. Terravita sells *L. clavatum* in form of powder as well as capsules (each 450 mg of *L. clavatum* powder). Club moss glycerite liquid extract of *L. clavatum* has been made available by Terravita in various flavors like vanilla, chocolate, mint, or strawberry. New Zealand made Lycopodium liquid and is sold by NaturoPharm. Homeopathic formulation, liquid dilutions with *L. clavatum*, has been made available by SBL Pvt. Ltd. ADEL *L. clavatum* dilution 200 CH have been launched by Adel Pekana, Germany. Apart from all these oral formulations, *L. clavatum* material is available for topical application through the formulation cream, with brand name, Bianca rosa.

Total synthesis of newly isolated lycodine-type *Lycopodium* alkaloids

Since 2000, several lycodine type lycopodium alkaloids have been isolated. But only few of them have been reported to be got totally synthesized in laboratory. Lycodine as a basic skeleton was synthesized earlier but in 2010, Tsukano et al. explained its concise synthetic attempt [41]. Here, triisopropylsilyl protected methyl 3-hydroxypicolinate was first converted to intermediate α,β -unsaturated ester which was dienophile reacted with diene, to form Diels–Alder product. It is on triflation, formed tetracyclic intermediate which on several reactions, converted to lycodine (Fig. 5).

Fischer and Sarpong, 2010 described the synthesis of (+)-Complanadine A [42]. Initially, enamide underwent hydrolysis to form enol tautomer of ketoamide, which in turn reacts with oxygen-sensitive α,β -unsaturated imine to yield N-desmethyl α -obscurine, via series of cyclizations. Its Boc protection (en route) gave Boc-protected lycodine, which got converted to boronic ester. It was then by reaction with triflate, formed (+)-Complanadine A (Fig. 6).

Although biosynthesis of lycodine alkaloids is a bit complex to determine, Azuma et al. 2014 got inspired from biogenetic pathways to make flabellidine and lycodine successful total synthesis attempt [43]. They started with Hosomi–Sakurai allylation of crotonamide and then other reactions to get linear precursor. Further, it formed tetracyclic lycodine skeleton which on debenzoylation and simultaneous Boc protection to give easily separable di-Boc compounds. The removal of Boc groups of its amines and the chemoselective acetylation gave (+)-flabellidine exclusively, which after the selective oxidation of the A-ring furnished (–)-lycodine (Fig. 7).

Fu et al. 2015 initiated the synthesis of α -obscurine, N-desmethyl- α -obscurine, β -obscurine, and N-desmethyl- β -obscurine using pulegone, which undergoes Buchwald–Hartwig coupling, the Heck cyclization reactions, diastereoselective hydrogenation to form characteristic A/B/C-ring system prior to the construction of the D-ring (Fig. 8) [44].

Recently, Burtea et al. 2019 started synthesis of (–)-Himeradine A by Sonogashira coupling on starting compound 2-bromo-4-methyl pyridine [45]. After 5 steps of additional several carbons, formed alkene derivative of N-Boc [N-(tert-Butoxycarbonyl)] piperidine, which in presence of Hoveyda–Grubbs 2nd generation catalyst, formed its hydroxyl derivative. Then, by catalyst-controlled Overman rearrangement,

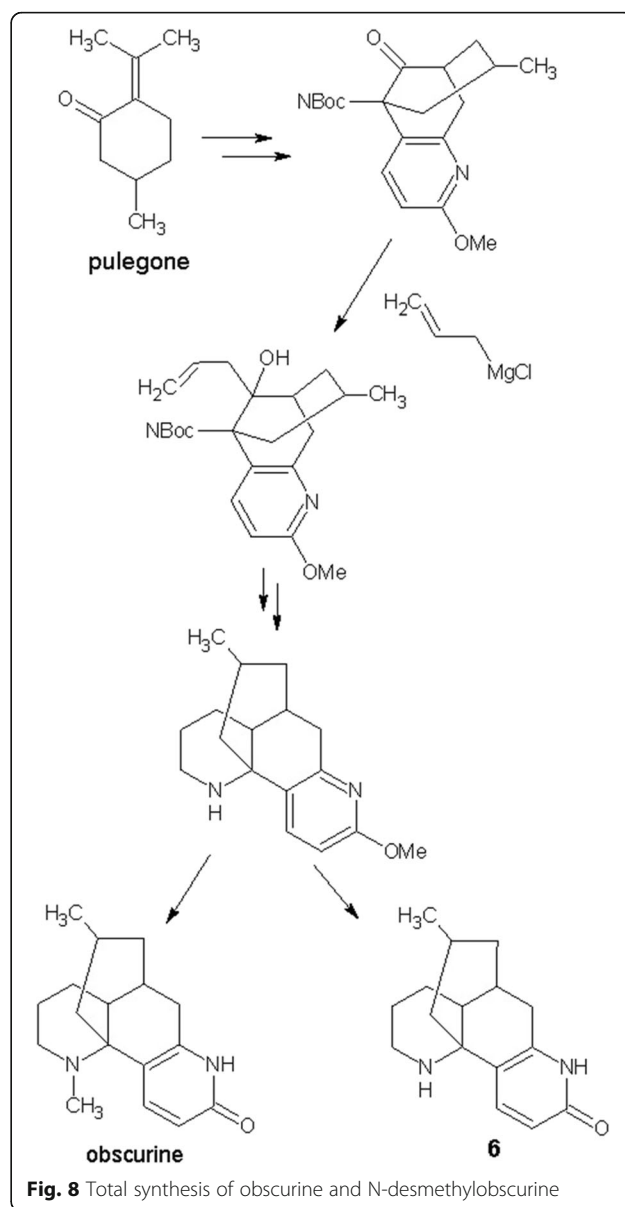
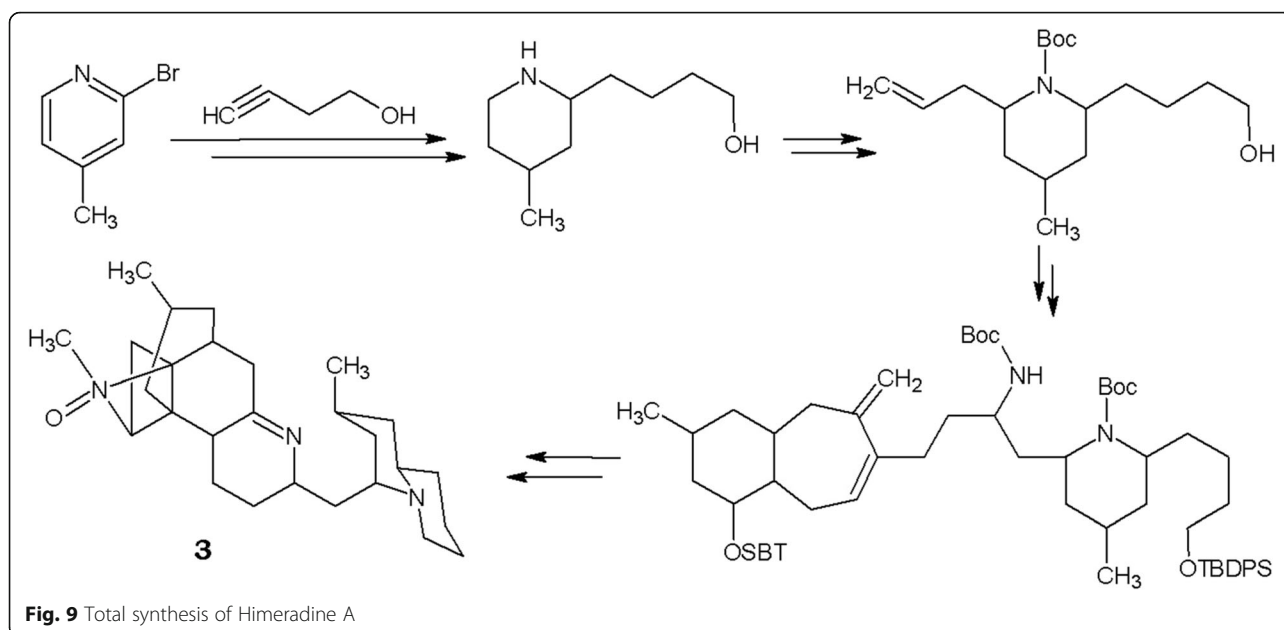


Fig. 8 Total synthesis of obscurene and N-desmethylobscurine



trichloroacetamide derivative is formed, which in presence of iridium photocatalyst, generated α -amino radical that underwent a stereoselective 1,4-addition to form enone derivative. Further by transannular Mannich cascade and cyclization; (-)-Himeradine A with 4 rings got synthesized in one reaction flask (Fig. 9).

Conclusion

Most of the lycodine-type alkaloids have AChE inhibitory activity with varying potency and thereby used in treatment of various diseases. Since 2000, more than 40 lycodine-type alkaloids have been reported to be isolated from different Lycopodiaceae or Huperziaceae plants. Researchers have also elucidated the plausible biogenetic pathways. Their structure–activity relationship revealed the potency with respect to structural variations. Few of these newly isolated alkaloids have been tried for total asymmetric laboratory synthesis. In the future, structures of these newly isolated compounds could be used to determine enzyme inhibition or protein binding through molecular docking approach, thereby necessary changes in existing structures could be made and accordingly, the new derivatives of lycodine structures could be synthesized. This will be helpful in increasing potency and reducing side effects, if any.

Abbreviations

AChE: Acetylcholinesterase; ATCI: Acetylthio choline iodide; DTNB: 5,5-dithiobis (2-nitrobenzoic acid); RBC: Red blood cells

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Author's contributions

SPP selected the topic to be made review upon; collected necessary data/research articles already published on the topic; drawn the structures; wrote manuscript with respect to recently isolated *Lycodine* alkaloids, their structure–activity relationship, biosynthetic pathways, and total synthesis; and also involved in critical thinking about entire write-up. The author read and approved the manuscript.

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