

Phytochemistry, biological activities, and toxicological insights into the genus *Cyclea* (Menispermaceae): A comprehensive review

Al-Ashiqur Rahman Alif^{1, 2, *} , Imran Hossain³ , Fatema-Tuz-Zohora^{1, 3} 

¹Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Dhaka, Dhaka, Bangladesh

²School of Pharmacy, BRAC University, Dhaka 1212, Bangladesh

³Department of Pharmacy, University of Asia Pacific, Dhaka 1205, Bangladesh

*Corresponding author

Al-Ashiqur Rahman Alif
Department of Pharmaceutical
Chemistry, Faculty of Pharmacy,
University of Dhaka, Dhaka,
Bangladesh
E-mail: alashiqurrahmanalif@gmail.com

Academic editor

Md Jamal Uddin, PhD
ABEx Bio-Research Center,
Bangladesh

Article info

Received: 04 August 2026
Accepted: 16 September 2026
Published: 24 September 2026

Keywords

Antineoplastic agents, Anti-inflammatory, Benzylisoquinolines, *Cyclea*, Ethnopharmacology, Tetrandrine, Toxicity

ABSTRACT

The genus *Cyclea* (Menispermaceae) comprises about 31 species distributed across southern and south-eastern Asia, several of which are long established in traditional and folk medicine, yet no genus-level synthesis of their chemistry, pharmacology, and safety exists. This review highlights the phytochemistry, biological activities, and toxicology of *Cyclea* spp., separates within-genus evidence from mechanistic data borrowed from related genera, and identifies research priorities. PubMed, Scopus, and Web of Science were accessed for recent literature on phytochemistry, pharmacology, and toxicity. The genus is chemically unified by bisbenzylisoquinoline alkaloids of tetrandrine, curine, and cycleanine types; tetrandrine is the marker alkaloid of *C. peltata*; *C. barbata* additionally yields azafluoranthene alkaloids, a phytoecdysone, and a gel-forming low-methoxyl pectin, and *C. gracillima* is rich in phenolic acids and flavonoids. Extracts and isolated constituents show anticancer, anti-inflammatory, antioxidant, antiplasmodial, antidiabetic, diuretic, hepatoprotective, and antivenom activities consistent with traditional use. Toxicological data are sparse and partly conflicting: an alkaloid extract of *C. peltata* gave an acute oral LD₅₀ >2500 mg/kg in mice, whereas values for *C. barbata* leaf extracts span 617 to >30,000 mg/kg. Tetrandrine is a cytochrome P450-activated hepatic and pulmonary toxicant and a weak genotoxicant, and substitution by aristolochic acid-containing *Aristolochia* species remains unaddressed. With no clinical or pharmacokinetic study reported, safety margins cannot be calculated. *Cyclea* is a promising but underexplored source of bisbenzylisoquinoline alkaloids. Authenticated standardized material, bioassay-guided fractionation, rigorous *in vitro* and *in vivo* replication, and guideline-compliant toxicology and pharmacokinetics are prerequisites for clinical translation.

INTRODUCTION

Plant-derived natural products remain one of the most productive sources of new therapeutic agents, with roughly one-third of all approved small-molecule drugs being natural products or their direct derivatives over the past four decades [1]. Among plant families, the Menispermaceae (moonseed family) occupy a distinctive position as a rich source of isoquinoline alkaloids and of the dimeric bisbenzylisoquinoline alkaloids (BBAs) [2,3]. Several BBAs have crossed from ethnomedicine into clinical practice: tetrandrine, obtained mainly from *Stephania tetrandra*, is used in China for the treatment of silicosis and has attracted sustained interest as an anticancer, anti-inflammatory, antifibrotic and antiviral lead [4,5], and cepharanthine and related dimers from *Stephania* are being explored for a comparable range of indications [6]. The recognition that bisbenzylisoquinoline alkaloids converge on a conserved endolysosomal-autophagy axis [7,8] has renewed interest in the plant genus.



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Within the Menispermaceae, the genus *Cyclea* Arn. ex-Wight is placed in the tribe Cissampelideae, alongside *Cissampelos* and *Stephania*, based on combined molecular and morphological data [9], a position recently reinforced by analyses of endocarp evolution that integrate extant and fossil taxa [10]. This genus comprises approximately 31 species of slender, dioecious, twining lianas with frequently peltate leaves and the curved, horseshoe-shaped endocarp characteristic of the family [11,12]. Several species of the genus *Cyclea* are used as traditional medicine in different systems. The tuberous roots of *Cyclea peltata* (Lam.) Hook.f. & Thomson constitute one of the two botanical sources of the classical Ayurvedic drug Patha, prescribed for fever, jaundice, dyspepsia, urinary disorders and snakebite [13,14], and its leaves are used as a diuretic [15]. In maritime South-East Asia, the leaves of *Cyclea barbata* Miers are processed into the mucilaginous cincau hijau or green grass-jelly, consumed both as a cooling food and as a folk remedy for fever, hypertension and gastric complaints [16], whereas *C. gracillima* Diels is a folk medicine in Taiwan [17] and *Cyclea* species feature in the ethnomedicine of Yunnan, China [18]. The genus therefore represents an ethnobotanically important but scientifically under-explored branch of pharmacologically active plant families.

Research over the past 15 years has begun to substantiate these traditional applications. Phytochemically, *Cyclea* is characterized by BBAs of the tetrandrine, curine, and cycleanine types [3]. Tetrandrine is the dominant marker alkaloid of *C. peltata* [4], and bioassay-guided fractionation has identified it as the principal anti-inflammatory and antioxidant constituent of the root [19]. Phaeanthine, a diastereomeric congener, has been isolated from the same species [20]. *C. wattii* Diels has been reported to produce curine-type dimers [21], whereas *C. barbata* contains azafluoranthene alkaloids, a phytoecdysone, flavonoids, and a gel-forming low-methoxyl pectin [16,22,23]. *C. gracillima*, by contrast, is distinguished by a phenolic-acid- and flavonoid-rich profile [17]. Different plant extracts and isolated compounds from the genus *Cyclea* have shown anticancer activity mediated by reactive-oxygen-species- and caspase-dependent apoptosis [24], mitochondria-mediated apoptosis [20], and p53-independent cell-cycle arrest [25]. Additionally, anti-inflammatory and antioxidant effects [17,19], lipoxygenase inhibition [22], diuretic [15], hepatoprotective [23], and venom-neutralizing [26] activities have also been reported. At the compound level, the signature alkaloids display antiplasmodial [3], antifibrotic [27,28], neuroprotective [29], and broad-spectrum antiviral [7,8] actions. Beyond medicine, *C. peltata* leaf material has been developed into fermented herbal shampoo bases and related cosmetic formulations [30,31].

Despite these advances, the evidence base has several limitations. First, fewer than a quarter of the recognized species have been examined, and most reports concern *C. peltata* and *C. barbata* and originate from a small number of laboratories in India, China, Taiwan, and Indonesia. Second, the studies are methodologically heterogeneous, with inconsistent use of botanically authenticated and chemically standardized extracts, positive controls, and dose-response designs, which limits comparison across reports. Third, the most detailed mechanistic pharmacology of tetrandrine, fangchinoline and curine has been generated with compounds sourced from *Stephania* or from commercial suppliers rather than from *Cyclea* itself [27–29], so its relevance to the genus must be inferred rather than assumed. Fourth, limited studies have investigated the toxicological and pharmacokinetic aspects of *Cyclea* extracts [4], and no controlled clinical study of any *Cyclea* preparation has been reported. Finally, the taxonomy of the genus remains partly unresolved [10,32], and chemotypic variability within species [33] means that the botanical identity and chemical profile of the material studied are not always secure.

These gaps are compounded by the absence of a genus-level synthesis. Existing reviews are either species-specific, addressing *C. peltata* within the Ayurvedic Patha complex [14];

compound-specific, focusing on tetrandrine irrespective of its botanical source [4]; or devoted to related genera such as *Cissampelos* and *Stephania* [6,13]. Consequently, studies on the chemistry, bioactivity and toxicological findings of the genus *Cyclea* have not been critically assessed. A structured overview is therefore needed to consolidate what is known, distinguish direct evidence from the genus *Cyclea* from mechanistic evidence borrowed from related taxa, and identify the species, compounds and experimental questions that merit priority.

This review addresses such limitations by reviewing peer-reviewed primary literature retrieved from PubMed, Scopus and Web of Science. This study aims to i) compile the phytochemical constituents reported from *Cyclea* species, with emphasis on the BBAs that define the genus; ii) summarize the biological activities documented for extracts and isolated compounds in vitro and in vivo, together with the compound-level pharmacology of the characteristic alkaloids; iii) appraise the available toxicological and safety information; and iv) critically evaluate the quality of the evidence and highlight the principal knowledge gaps that should guide future research. The scope encompasses all species of the genus for which chemical or biological data could be located, namely *C. peltata*, *C. barbata*, *C. gracillima*, *C. wattii* and *C. atjehensis*, and the review is intended as a critical resource for researchers in pharmacognosy, natural-product chemistry and translational pharmacology.

OVERVIEW OF THE GENUS AND AVAILABLE EVIDENCE

The literature retrieved focused mainly on *C. peltata* and *C. barbata*, and much less is reported for *C. gracillima*, *C. wattii*, and *C. atjehensis*. Some of the plants of the genus *Cyclea* are shown in Figure 1. The research output originated mainly from India, China, and Taiwan and involved primarily phytochemical isolation, in vitro bioactivity assays, and rodent models.

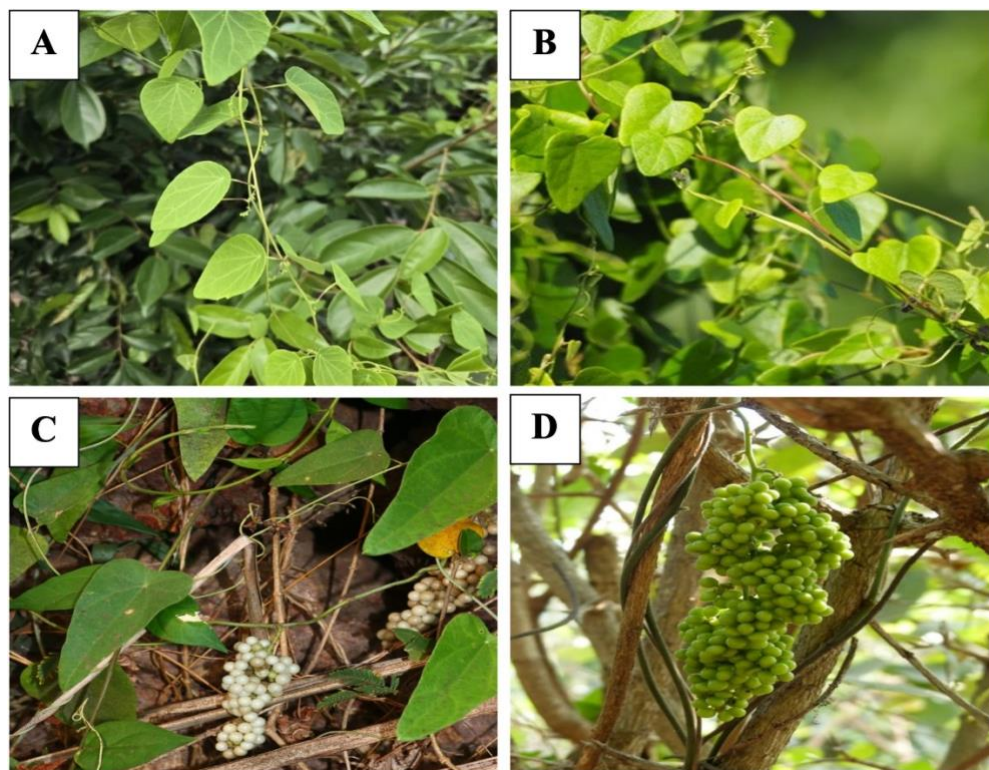


Figure 1. Morphological characteristics of some *Cyclea* species. (A) Leaves of *C. barbata* Miers [34], (B) Vining stems of *C. gracillima*, (C) Foliage of *C. peltata* [35], (D) Fruits of *C. peltata* [36].

TAXONOMIC DETAILS

Cyclea Arn. ex-Wight belongs to the family Menispermaceae (Ranunculales) and, according to recent classifications, is placed in the tribe Cissampelideae of the subfamily Menispermoidae [10]. In the dioecious genus *Cyclea* (family Menispermaceae), floral morphology is highly dimorphic depending on the sex of the flower [9]. Male flowers typically feature four to five sepals that are characteristically connate (fused) into a campanulate or subglobose calyx, alongside four to five petals that often unite to form a cup-shaped corolla [37]. Conversely, female flowers are extremely reduced and asymmetrical; they generally possess only one to three free sepals and a corresponding number of small petals (though petals are occasionally absent), while completely lacking stamens or staminodes [9,37]. The presence of a peltate leaf insertion in the type species accounts for the epithet *peltata*, whereas the mucilaginous leaves of *C. barbata* are responsible for its vernacular name 'green jelly' [16]. The species of interest for their medical use, *C. peltata*, *C. barbata*, *C. gracillima*, *C. wattii* and *C. atjehensis*, are mainly distinguished by floral, endocarp and foliar characters, but the genus is still taxonomically complex, and some names have not yet been revised [9].

GEOGRAPHICAL DISTRIBUTION

The genus is distributed from the Indian subcontinent (India, Sri Lanka, Bangladesh and the Andaman and Nicobar Islands) eastward through Myanmar, Thailand and Indochina to southern China, Taiwan and the Ryukyu Islands of Japan, and southward through western and central Malesia (Peninsular Malaysia, Sumatra, Java, Borneo, the Philippines, Sulawesi and the Lesser Sunda Islands) [11,12]. The taxa of medicinal interest broadly follow this distribution: *C. peltata* extends from peninsular India and Sri Lanka, where it is well represented in the Western Ghats, through Bangladesh and north-eastern India to Myanmar and Indochina; *C. barbata* is widespread on the mainland, from north-eastern India and Bangladesh through Myanmar, Thailand and Indochina to south-eastern China and Hainan, and extends into Sumatra, Java and the Lesser Sunda Islands; *C. gracillima* occurs in Taiwan, Hainan and Vietnam; *C. wattii* is restricted to north-eastern India and south-western to central China (Yunnan, Guizhou, Sichuan, Chongqing and Hunan); and *C. atjehensis* is known only from Sumatra and Thailand [11,12,17,32,38]. This distribution broadly parallels the use of the genus within local traditional medicine systems [17,18,22].

TRADITIONAL ETHNOMEDICINAL IMPORTANCE

There are several species of *Cyclea* that are well established in the traditional South and South-East Asian pharmacopoeias. The tuberous roots of *C. peltata* are a recognized source of the classical drug Patha (Rajapatha), used in Ayurveda and allied Indian systems of medicine to treat fever, jaundice and other hepatic disorders, dyspepsia, diarrhea, urinary disorders, urolithiasis and asthma. Root preparations are applied externally to wounds, skin diseases and pruritus, and leaf preparations are used for snakebite [15,26,39]. In South-East Asia, the leaves of *C. barbata* are used to prepare a cooling product known as 'cincau hijau' (green grass-jelly), which is consumed as a refreshing food and used in folk medicine against fever, hypertension, gastric complaints and inflammation [16]. The ethnomedical uses of these plants—hepatoprotective, antipyretic, diuretic, anti-inflammatory and antivenom—closely resemble the pharmacological activities subsequently reported for the genus and justify continued phytochemical investigation.

In addition to medicine, several species of the genus *Cyclea* are used in food, cosmetics and biotechnology applications. The leaves of *C. barbata* are an important source of a gel-forming polysaccharide known as 'green grass-jelly' or 'cincau', which is widely used in maritime South-East Asia as a natural gelling agent and functional food ingredient [16]. In line with its traditional use in hair and scalp care, exopolysaccharide-rich fermented herbal shampoo bases and related cosmetic formulations have been developed from the leaf material of *C. peltata*, which has also served as a reducing and capping agent in the green synthesis of silver nanoparticles [30,31]. These applications illustrate the broader economic and technological potential of the genus alongside its pharmacological value.

PHYTOCHEMISTRY

The genus is characterized by bisbenzylisoquinoline alkaloids [3,20,21]. Their structural assignment has been reinforced by the total synthesis of tetrandrine and its diastereomer isotetrandrine, which also rationalized the stereochemical basis of their diversity [40]. In *C. peltata*, tetrandrine is the dominant marker alkaloid; it has been quantified and isolated from alkaloid-enriched fractions by high-performance thin-layer chromatography and reverse-phase chromatography with LC-ESI-MS validation [19,41], while the related alkaloid phaeanthine has been obtained from rhizomes [20]. Preliminary screening of leaf extracts revealed the presence of phytosterols, flavonoids, tannins, saponins, and diterpenes [15].

In *C. barbata*, stem investigations revealed two azafluoranthene alkaloids and a phytoecdysone, the first report of both structural types in the genus, along with several known constituents [23]. The leaves are notable for their gel-forming, low-methoxyl pectic polysaccharide, rich in galacturonic acid, which underlies traditional green-jelly preparations [16]. *C. gracillima* is relatively rich in phenolics: ethanol and hot-water extracts contain ferulic, sinapic and syringic acids and flavonoids, including naringenin, myricetin, naringin and apigenin [17]. From the roots of *C. wattii*, the curine-type alkaloids wattisines A and B were isolated alongside (-)-curine [21], and comparative alkaloid screening of *C. barbata* and *C. atjehensis* characterized cycleanine, cycleatjehine and cycleatjehenine among a broader panel of BBAs [42]. Representative constituents are summarized in Table 1, and some of them are shown in Figure 2.

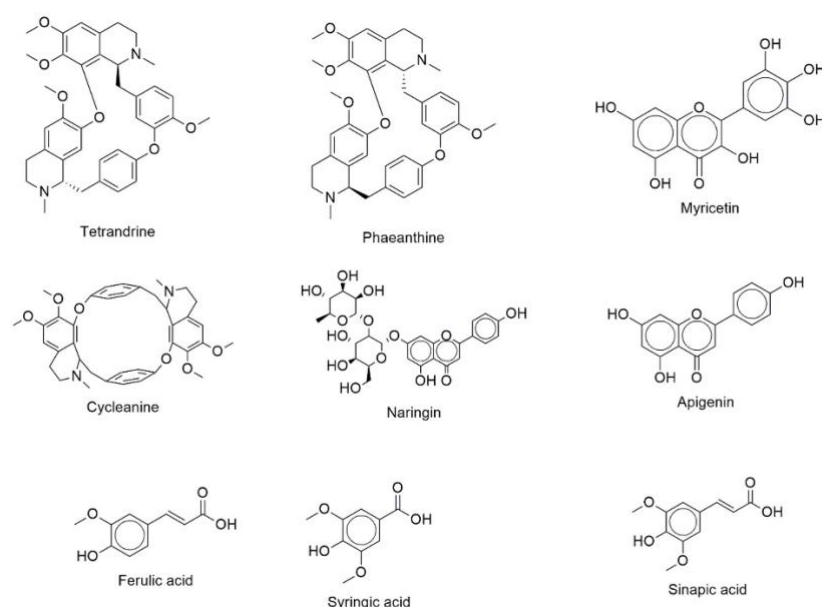


Figure 2. Chemical structures of some characteristic phytochemicals of *Cyclea* spp.

Table 1. Representative phytochemicals reported across *Cyclea* species.

Species	Plant part	Major constituents	Reference
<i>C. peltata</i>	Roots, rhizome, whole plant, leaf	Tetrandrine (marker), phaeanthine; phytosterols, flavonoids, tannins, saponins	[15,19,20,41]
<i>C. barbata</i>	Stems, leaves	Azafluoranthene alkaloids, phytoecdysone; flavonoids; low-methoxyl pectic polysaccharide	[16,22,23]
<i>C. gracillima</i>	Aerial/whole herb	Ferulic, sinapic, syringic acids; naringenin, myricetin, naringin, apigenin	[17]
<i>C. wattii</i>	Roots	Wattisines A and B (urine-type BBAs), (–)-urine	[21]
<i>C. atjehensis</i>	Roots/tuber	Cycleanine, cycleatjehine, cycleatjehinine and related BBAs	[42]

BIOLOGICAL ACTIVITIES

Antiplasmodial and cytotoxic activity

A screen of 53 natural BBAs, including alkaloids from *C. barbata* and *C. atjehensis*, identified several compounds with selective antiplasmodial activity against chloroquine-sensitive and chloroquine-resistant *Plasmodium falciparum*, with cycleanine among the more selective agents and structure–activity relationships governed by stereochemistry and substitution patterns [42].

Anticancer activity

Tetrandrine isolated from *C. peltata* induced dose- and time-dependent cytotoxicity in breast (MDA-MB-231) and pancreatic (PANC-1) carcinoma cells through reactive oxygen species generation and caspase-mediated apoptosis [24]. Phaeanthine from the same species was selectively cytotoxic to cervical cancer (HeLa) cells, triggering mitochondria-mediated apoptosis with downregulation of Akt, an effect corroborated by molecular docking [20]. At the extract level, a methanolic extract of *C. peltata* leaves and its fractions were cytotoxic to MCF-7 breast cancer cells in the MTT assay; the n-hexane fraction was the most active (IC₅₀ 42 µg/mL) and induced apoptosis with loss of mitochondrial membrane potential, as shown by acridine orange/ethidium bromide and JC-1 staining [43]. Among *C. wattii* constituents, wattisine A showed significant cytotoxicity against HCT-8 and Bel-7402 lines [21], and (–)-urine induced G1 arrest and cell death in hepatocellular carcinoma cells independent of p53 status [25].

Anti-inflammatory and antioxidant activity

In *C. peltata*, the alkaloid-enriched fraction and purified tetrandrine suppressed lipopolysaccharide-induced iNOS, COX-2, and TNF-α expression in RAW 264.7 macrophages and displayed antioxidant activity, with tetrandrine being the most potent constituent [19]. Polyphenol-rich extracts of *C. gracillima* exhibited strong radical-scavenging, reducing, and metal-chelating capacity and inhibited low-density lipoprotein oxidation and erythrocyte hemolysis [17].

Antidiabetic, diuretic and hepatoprotective activity

An aqueous root extract of *C. peltata* decreased fasting and postprandial glucose levels, increased insulin levels, reduced TNF-α levels, and increased skeletal muscle glycogen levels in type 2 diabetic rats [39]. Ethanol leaf extracts produced significant diuresis comparable to that of furosemide [15]. Constituents isolated from *C. barbata* stems

showed moderate hepatoprotective activity against acetaminophen-induced toxicity in HepG2 cells [23].

Antivenom and other activities

In preclinical assays, an aqueous root extract of *C. peltata* neutralized the lethal, enzymatic and hemolytic effects of *Naja naja* venom, supporting its ethnomedical antivenom use [26]. Consistent with the traditional application of the plant to hair and scalp care, *C. peltata* leaf material has also been developed into fermented herbal shampoo bases and used to green-synthesize silver nanoparticles [30,31]. Reported activities are listed in Table 2.

Table 2. Summary of biological activities reported for *Cyclea* species and their constituents.

Activity	Species/agent	Model/key outcome	Reference
Antiplasmodial	<i>C. barbata</i> , <i>C. atjehensis</i> (BBAs)	Selective activity vs <i>P. falciparum</i> clones	[42]
Anticancer/ cytotoxic	<i>C. peltata</i> (tetrandrine, phaeanthine)	ROS/caspase apoptosis in MDA-MB-231, PANC-1; Akt-linked apoptosis in HeLa	[20,24]
	<i>C. peltata</i> (leaf)	Cytotoxicity and apoptosis in MCF-7	[43]
	<i>C. wattii</i> (wattisine A, curine)	Cytotoxicity in HCT-8, Bel-7402; G1 arrest in HCC	[21,25]
Anti- inflammatory, antioxidant	<i>C. peltata</i> ; <i>C. gracillima</i> ; <i>C. barbata</i>	↓iNOS/COX-2/TNF- α in RAW 264.7; radical scavenging, anti-LDL oxidation; ↓ Lipoxygenase	[17,19,22]
Antidiabetic	<i>C. peltata</i> (root)	↓ glucose, ↑ insulin, ↑ muscle glycogen in T2D rats	[39]
Diuretic	<i>C. peltata</i> (leaf)	Significant diuresis in rats	[15]
Hepatoprotective	<i>C. barbata</i> (isolates)	Protection vs APAP toxicity in HepG2	[23]
Antivenom	<i>C. peltata</i> (root)	Neutralization of <i>Naja naja</i> venom effects	[26]
Cosmetic/green synthesis	<i>C. peltata</i> (leaf)	Herbal shampoo base; AgNP synthesis	[30,31]

PHARMACOLOGY OF ALKALOIDS

Tetrandrine, curine and their congeners are the signature alkaloids of *Cyclea*; the closely related fangchinoline and isotetrandrine occur in other Cissampelideae [44–46]. Although these compounds are shared with other Menispermaceae such as *Stephania*, the substantial body of compound-level pharmacology available for them provides mechanistic context for the genus [47]. Tetrandrine attenuated experimental silicosis by inhibiting canonical and noncanonical NLRP3 inflammasome activation in lung macrophages [28] and alleviated pulmonary fibrosis by restoring PINK1/Parkin-mediated mitophagy in alveolar epithelial cells [27]. In the central nervous system, tetrandrine mitigated tau aggregation and cognitive deficits by restoring lysosomal calcium homeostasis and autophagic flux [29]. A shared endolysosomal mechanism also underlies broad antiviral effects: BBAs, including tetrandrine, fangchinoline, isotetrandrine, berbamine and cepharanthine, inhibited flavivirus entry and replication [7] and impaired African swine fever virus internalization and replication by alkalinizing late endosomes and lysosomes [8].

TOXICOLOGY AND SAFETY

Toxicity of *Cyclea* extracts

Formal toxicological evaluation of *Cyclea* preparations is remarkably scarce given their long history of use as shown in Table 3.

Chellappan et al. reported no toxicity of *C. peltata* up to 2000 mg/kg root extract given orally in Wistar rats [48]. No subacute, subchronic, chronic, reproductive, genotoxicity or carcinogenicity study of any *C. peltata* extract was found, and the in vitro anticancer studies of its extracts and alkaloids did not include non-malignant control cells, so selectivity indices cannot be derived [20,24,43]. For *C. barbata*, conflicting results are reported. Angelina et al. reported the LD₅₀ of *C. barbata* leaf extract in mice to exceed 30,000 mg/kg of body weight [49]. A recent evaluation of a leaf ethanol extract in Wistar rats found no mortality at 2000 mg/kg, 20% mortality among females at 5000 mg/kg and, in a 28-day study, a reduction in leukocyte counts from 400 mg/kg/day upward, yielding an acute NOAEL of 2000 mg/kg (GHS category 5) and a subacute NOAEL of 300 mg/kg/day [50]. In contrast, an earlier mouse study reported an LD₅₀ of approximately 617 mg/kg for a leaf extract and classified it as moderately toxic [51]. The discrepancy most probably reflects differences in extraction solvent, plant material and dosing design, and underlines the need for chemically characterized test materials. No median lethal concentration (LC₅₀) values have been reported for any *Cyclea* extract, and no toxicological data are available for *C. gracillima*, *C. wattii*, *C. atjehensis* or the remaining species of the genus.

Table 3. Toxicological data reported for *Cyclea* extracts and for tetrandrine, the characteristic alkaloid of the genus.

Test material	Model and route	Key findings	Ref.
<i>C. peltata</i> root alkaloid extract	Mice, oral, acute	No mortality; LD ₅₀ > 2500 mg/kg	[45]
<i>C. peltata</i> root ethanol extract	Wistar rats, oral, acute	No mortality; LD ₅₀ > 2000 mg/kg	[48]
<i>C. barbata</i> leaf ethanol extract	Wistar rats, oral; acute (2000 and 5000 mg/kg) and 28-day subacute (100–500 mg/kg/day)	No mortality at 2000 mg/kg; 20% mortality in females at 5000 mg/kg; acute NOAEL 2000 mg/kg (GHS category 5); subacute NOAEL 300 mg/kg/day, LOAEL 400 mg/kg/day (reduced leukocyte count)	[50]
<i>C. barbata</i> leaf extract	Mice, oral, acute	No mortality; LD ₅₀ > 30000 mg/kg	[49]
<i>C. barbata</i> leaf extract	Mice, oral, acute (200–1600 mg/kg)	LD ₅₀ ≈ 617 mg/kg; classified as moderately toxic	[51]
Tetrandrine	Female BALB/c mice, intravenous; acute and 14-day	LD ₅₀ 444.7 ± 35.8 mg/kg; no adverse effect at ≤ 90 mg/kg/day for 14 days; transient hepatic, pulmonary and renal toxicity at 150 mg/kg/day	[54]
Tetrandrine	CD-1 mice in vivo; human lung cells expressing CYP3A5	Dose-dependent pulmonary injury; CYP-mediated bioactivation to a reactive quinone methide, glutathione depletion, ROS and apoptosis	[55,56]
Tetrandrine	Rat primary hepatocytes	Mitochondrial dysfunction and ATP depletion driven by CYP450 (especially CYP2E1)-generated ROS	[57]
Tetrandrine	Renal tubular cells in vitro; rats in vivo	Cytotoxic to renal tubular cells; renal injury less severe than that of aristolochic acid	[59]
Tetrandrine	V79 cells (± S9); mouse spleen cells in vivo	Increased sister-chromatid exchange only with metabolic activation (100–200 mg/kg in vivo); no micronucleus induction; weak indirect-acting genotoxicant	[60]
Tetrandrine tablets	Silicosis patients, oral 60 mg three times daily (retrospective cohort)	Mild adverse events: facial pigmentation (28%), pruritus (9%), mild liver-function abnormalities (9%), transient diarrhea (6%), appetite loss (2%)	[61]

Adverse effects in traditional use

Classical Ayurvedic sources and modern ethnobotanical surveys describe Patha and cincau as safe at customary doses, and no case report of poisoning attributable to *Cyclea* was retrieved. This absence of reports should not be equated with proof of safety, because adverse-event surveillance for traditional preparations in South and Southeast Asia is

minimal, and because *Cyclea* roots share their alkaloid profile with *Stephania* species that are used at comparable doses in Chinese medicine [52]. A related safety concern is botanical substitution: Menispermaceae drugs traded as 'Fang Ji' have repeatedly been adulterated with, or substituted by, *Aristolochia fangchi*, which contains nephrotoxic and carcinogenic aristolochic acids; in one survey, nine of ten commercial samples contained aristolochic acid I and lacked tetrandrine and fangchinoline [53]. Although that survey did not include *Cyclea*, the same risk applies to any tuberous-root Menispermaceae drug; therefore, authentication of *Cyclea* raw material should include screening for aristolochic acids.

Toxicology of the characteristic alkaloids

Most of what is known about the toxicity of *Cyclea* constituents comes from studies of tetrandrine, usually obtained from *Stephania tetrandra* or commercial sources. In female BALB/c mice, the intravenous LD₅₀ of tetrandrine was 444.7 ± 35.8 mg/kg; single doses up to 340 mg/kg produced no biochemical or histological changes, and 14-day dosing at 30 or 90 mg/kg/day was without adverse effect, whereas 150 mg/kg/day caused transient hepatic, pulmonary and renal toxicity that resolved after withdrawal [54]. The lung and liver are the principal target organs. In CD-1 mice, tetrandrine produced dose-dependent pulmonary injury that was linked to cytochrome P450-mediated metabolic activation [55], and CYP3A5 was subsequently shown to bioactivate tetrandrine to a reactive quinone methide intermediate that depletes glutathione, generates reactive oxygen species and triggers apoptosis in human lung cells [56]. In rat hepatocytes, cytochrome P450-derived reactive oxygen species, particularly those generated by CYP2E1, mediate tetrandrine-induced mitochondrial dysfunction and ATP depletion [57], and the C-12 methoxy group has been identified as a structural determinant of hepatotoxicity [58]. Tetrandrine is also cytotoxic to renal tubular epithelial cells, although in a direct comparison its nephrotoxicity was markedly less than that of aristolochic acid [59]. In genotoxicity assays, tetrandrine increased sister-chromatid exchange in V79 cells only in the presence of metabolic activation and in mouse spleen cells at 100–200 mg/kg, but did not induce micronuclei in vitro or in vivo, leading to its classification as a weak, indirect-acting genotoxicant [60]. Comparable toxicological characterization of fangchinoline, isotetrandrine, phaeanthine, curine, cycleanine and the watisines is lacking; their potent cytotoxicity toward cancer cell lines [20,21,24,25] implies that they should not be assumed to be innocuous.

Clinical safety data and safety margins

Clinical exposure data exist only for tetrandrine. In silicosis patients receiving tetrandrine tablets at 60 mg three times daily in cyclic courses, adverse events were mild and comprised facial pigmentation (28%), transient pruritus (9%), mild liver-function abnormalities (9%), transient diarrhea (6%) and loss of appetite (2%) [61]; earlier clinical experience likewise reported good tolerability, although the high tablet burden and reports of gastrointestinal, hepatic and renal effects remain concerns [58]. No clinical pharmacokinetic or safety study of a *Cyclea* extract has been published, and because the tetrandrine content of *C. peltata* roots varies with source and extraction method [24,45], the human exposure resulting from traditional doses of Patha cannot presently be estimated. A formal safety margin for any *Cyclea* preparation therefore cannot be calculated, which is the single most important toxicological gap identified by this review.

CRITICAL APPRAISAL OF THE EVIDENCE

The included studies were heterogeneous in design and generally preclinical. In vitro and phytochemical reports were typically well characterized analytically, whereas in vivo studies varied in their reporting of randomization, blinding, and dose-response [39,45,50,51], limiting formal quality grading. Positive controls were used inconsistently across bioassays [39,43], and several compound-level pharmacology reports did not source the test alkaloid from the *Cyclea* genus [8,28,54-60]; thus, their findings are best regarded as mechanistic support rather than direct evidence of genus activity. Research was concentrated in a small number of laboratories and countries, raising the possibility of publication and geographic bias.

PROSPECTS AND FUTURE DIRECTIONS

This review provides the first genus-level synthesis of the phytochemistry, biological activities, and toxicology of *Cyclea*, and three principal findings emerge. First, the genus is chemically coherent: bisbenzylisoquinoline alkaloids (BBAs) of the tetrandrine, curine and cycleanine types recur in every species examined, consistent with its placement in the tribe Cissampelideae alongside *Stephania* and *Cissampelos* [9,21]. Second, the pharmacological activities documented for extracts and isolated constituents map closely onto the indications for which *C. peltata* and *C. barbata* are used in Ayurveda and in South-East Asian folk medicine, lending preliminary experimental support to their traditional applications [15,19,39]. Third, and in marked contrast, toxicological, pharmacokinetic and clinical evidence is disproportionately thin relative to the long history of human use, such that a safety margin cannot presently be calculated for any *Cyclea* preparation.

The dominance of tetrandrine in *C. peltata* [19,24], the co-occurrence of its diastereomer phaeanthine [20], the curine-type wattisines A and B and (–)-curine in *C. wattii* [21], and cycleanine, cycleatjehine and cycleatjehenine in *C. barbata* and *C. atjehensis* [42] together indicate that BBA biosynthesis is a conserved feature of the genus, and that the diversity within it arises chiefly from differences in the stereochemistry of the two benzylisoquinoline halves and the pattern of ether bridging and O-methylation. This is pharmacologically important, because stereochemistry and substitution govern both antiparasitic selectivity [42] and, as discussed below, hepatotoxicity [58]; the total synthesis of tetrandrine and isotetrandrine has clarified the structural basis of this diversity [40]. At the same time, the genus is not chemically monotonous. The azafluoranthene alkaloids and phytoecdysone of *C. barbata* stems were the first of their structural class reported from *Cyclea* [23], the leaves of the same species yield a gel-forming low-methoxyl pectin [16], and *C. gracillima* is distinguished by a phenolic acid- and flavonoid-rich profile rather than by alkaloids [17]. Given that fewer than a quarter of the recognized species have been chemically examined, and that even within *C. peltata* the tetrandrine content varies substantially between accessions grown under common-garden conditions [33], the unexamined species and chemotypes represent a considerable and largely untouched reservoir of structural novelty.

The anticancer data are the most extensively replicated in the genus and converge on a consistent picture. For instance, tetrandrine from *C. peltata* induced reactive oxygen species-dependent, caspase-mediated apoptosis in breast and pancreatic carcinoma cells [24], phaeanthine triggered mitochondria-mediated apoptosis with Akt downregulation in cervical cancer cells [20], wattisine A was cytotoxic to colorectal and hepatocellular lines [21], and (–)-curine arrested hepatocellular carcinoma cells in G1 independently of p53 status [25]. The demonstration of a p53-independent route to cell death is notable, since loss of p53 function is common in human tumors. Nevertheless, the translational

value of these observations is constrained by the absence of non-malignant comparator cells in every study conducted with material of *Cyclea* origin, so that selectivity indices cannot be derived, and by the lack of any in vivo antitumor study using genus-derived compounds. The anti-inflammatory findings are better anchored: bioassay-guided fractionation identified tetrandrine as the principal constituent suppressing iNOS, COX-2 and TNF- α in macrophages [19], an activity that is mechanistically consistent with the inhibition of canonical and non-canonical NLRP3 inflammasome activation demonstrated for tetrandrine in models of silicosis [28]. This provides a rare instance in which genus-level bioassay data and compound-level mechanism align. By contrast, the antidiabetic [39], diuretic [15], antivenom [26], and hepatoprotective activities [23] each rest on a single study, and none has been independently replicated or attributed to a defined constituent.

A recurring theme of the compound-level literature is the convergence of BBAs on the endolysosomal–autophagy axis. Tetrandrine restores PINK1/Parkin-mediated mitophagy in fibrotic lung epithelium [27], normalizes lysosomal calcium homeostasis and autophagic flux in tauopathy models [29], and, together with fangchinoline, isotetrandrine and cepharanthine, blocks flavivirus and African swine fever virus entry by compromising late endosomal and lysosomal function [7,8]. A single lysosomotropic mechanism could plausibly account for much of the pleiotropy of these alkaloids. However, this work was generated using tetrandrine sourced from *Stephania* or commercial suppliers, not from *Cyclea*. The mechanistic hypothesis it offers for the genus is therefore attractive but untested, and whether traditional *Cyclea* preparations deliver a tetrandrine exposure sufficient to engage these targets in humans is unknown.

The toxicological picture is internally consistent for tetrandrine and fragmentary for the plant. For *C. peltata*, an oral LD₅₀ above 2500 mg/kg for an alkaloid-enriched root extract [45] and LD₅₀ above 2000 mg/kg for root ethanol extract [48] are concordant evidence of low acute oral toxicity. Angelina et al. reported LD₅₀ above 30000 mg/kg for *C. barbata* leaf extract in mice [49]. For *C. barbata*, the divergence between an acute NOAEL of 2000 mg/kg with a subacute NOAEL of 300 mg/kg/day in rats [50] and an LD₅₀ of approximately 617 mg/kg in mice [51] most probably reflects differences in solvent, plant material and dosing design rather than a true species difference. These findings indicate why toxicological conclusions cannot be drawn from chemically uncharacterized extracts. The compound-level data indicate that tetrandrine is a bioactivation-dependent toxicant: CYP3A5 converts it to a reactive quinone methide that depletes glutathione and injures lung cells [55,56], CYP2E1-derived reactive oxygen species mediate hepatocyte mitochondrial dysfunction [57], and the C-12 methoxy group is a structural determinant of hepatotoxicity [58]. Its genotoxicity is weak and indirect [60], its nephrotoxicity is markedly lower than that of aristolochic acid [59], and in silicosis patients receiving 180 mg/day, the adverse events were mild [61]. Two implications follow. First, because the target organs are the lung and liver and the mechanism is metabolic, inter-individual variation in CYP3A5 and CYP2E1 expression, and co-administration of enzyme inducers, may modify the risk of *Cyclea* preparations in ways that acute rodent studies would not reveal. Second, the comparative toxicology of phaeanthine, curine, cycleanine, fangchinoline and the watisines is entirely lacking, and their potent cytotoxicity toward cancer cells argues against assuming that they are innocuous.

A distinct safety issue is botanical identity. Tuberous-root Menispermaceae drugs traded as 'Fang Ji' have repeatedly been adulterated with *Aristolochia fangchi*, and in one survey nine of ten commercial samples contained aristolochic acid I while lacking tetrandrine and fangchinoline [53]. Although *Cyclea* was not included in that survey, *Patha* shares the same morphology and market channels, and the unresolved taxonomy of the genus

[10] compounds the risk of misidentification. The absence of poisoning reports in ethnobotanical literature should not be read as evidence of safety, since adverse-event surveillance for traditional preparations in the region is minimal.

Several limitations temper these conclusions. The primary literature is concentrated in a small number of laboratories in India, China, Taiwan, and Indonesia, raising the possibility of geographic and publication bias, and a proportion of it appears in regional journals. Study designs are heterogeneous; positive controls and dose–response designs are used inconsistently [16,27,39,43], and the reporting of randomization and blinding in animal studies is often incomplete [39,45,50,51], which precluded formal quality grading. Much of the most detailed mechanistic pharmacology and toxicology concerns tetrandrine obtained from *Stephania* or commercial sources and is applicable to *Cyclea* only by inference [8,28,29,54–60].

The gaps identified here translate into a clear research agenda. The great majority of species, and the divergent chemotypes of *C. peltata*, should be profiled phytochemically using mass spectrometry-based dereplication so that new dimeric alkaloids and non-alkaloidal constituents can be discovered without repeated re-isolation of tetrandrine. Botanically, every pharmacological or toxicological study should begin with authenticated material, ideally combining DNA-based identification with chromatographic fingerprinting of the marker alkaloids and mandatory screening for aristolochic acids; chemotype-aware standardization of tetrandrine content would make results comparable across laboratories. Pharmacologically, priority should be given to reproducing the single-study activities with characterized extracts, positive controls and full dose–response designs; to including non-malignant cells in every cytotoxicity study so that selectivity can be quantified; to testing whether *Cyclea*-derived tetrandrine and phaeanthine engage the NLRP3, mitophagy and endolysosomal targets identified with commercial material; and to following up neglected leads such as the antiplasmodial selectivity of cycleanine and the broad antiviral activity of the BBA class. Toxicologically, the most pressing needs are guideline-compliant subacute and subchronic studies, genotoxicity and reproductive toxicity assessment, characterization of lung and liver as target organs, evaluation of cytochrome P450-mediated bioactivation and drug–interaction potential, and comparative toxicity data for the alkaloids other than tetrandrine. Pharmacokinetic studies quantifying the tetrandrine exposure produced by traditional doses of Patha and cincau are the essential bridge between the preclinical data and any estimate of a human safety margin. Beyond medicine, the gel-forming pectin of *C. barbata*, the cosmetic applications of *C. peltata* and its use in nanoparticle synthesis deserve development in parallel, and cultivation of the medicinally important species would both secure a consistent supply and support the resolution of the genus' taxonomy.

CONCLUSIONS

The genus *Cyclea* is an ethnobotanically important but scientifically under-explored member of the Menispermaceae whose species are chemically unified by bisbenzylisoquinoline alkaloids of the tetrandrine, curine and cycleanine types and further diversified by azafluoranthene alkaloids, phytoecdysones, phenolic acids, flavonoids and a gel-forming pectin. Extracts and isolated constituents of *C. peltata*, *C. barbata*, *C. gracillima*, *C. wattii* and *C. atjehensis* display anticancer, anti-inflammatory, antioxidant, antiplasmodial, antidiabetic, diuretic, hepatoprotective and antivenom activities that broadly corroborate the traditional uses of Patha and cincau hijau, and compound-level studies of tetrandrine point to a shared endolysosomal–autophagy mechanism that may underlie the pleiotropy of the genus' signature alkaloids. Yet the

evidence remains preclinical, methodologically heterogeneous and concentrated on two species, and much of the mechanistic detail has been borrowed from alkaloids sourced outside the genus. Most importantly, formal toxicological evaluation is confined to a handful of acute studies with partly conflicting results; tetrandrine is a cytochrome P450-activated hepatic and pulmonary toxicant, no clinical or pharmacokinetic study of any *Cyclea* preparation has been reported, and the risk of substitution by aristolochic acid-containing *Aristolochia* species has not been addressed for this genus. A safety margin for any *Cyclea* preparation therefore cannot currently be calculated. Realizing the therapeutic promise of the genus will depend on authenticated and chemically standardized plant material, exploration of its unexamined species, replication of single-study activities under rigorous designs, guideline-compliant toxicology and pharmacokinetic data that link traditional doses to human exposure. Until these foundations are laid, *Cyclea* should be regarded as a promising source of lead compounds rather than as a validated medicine.

ACKNOWLEDGEMENTS

None

AUTHOR CONTRIBUTIONS

ARA: Conceptualization, methodology, software, validation, formal analysis, investigation, data curation, visualization, supervision, project administration, writing-original draft, and writing-review and editing. FTZ: Investigation, data curation, writing-review and editing. IH: Investigation, data curation, writing-review and editing. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

There is no conflict of interest among the authors.

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