

Review Article

Lysicamine in medicinal plants: Biosynthesis and pharmacological activities

Syahira Wahab¹, Juriyati Jalil^{1*}, Halimatul Saadiah Mohammad Noor²

¹Center for Drug and Herbal Development, Faculty of Pharmacy, Universiti Kebangsaan Malaysia, Jalan Raja Muda Abdul Aziz, 50300 Kuala Lumpur, ²School of Pharmacy, Management and Science University, University Drive, Off Persiaran Olahraga, Section 13, 40100 Shah Alam, Selangor, Malaysia

*For correspondence: **Email:** juriyatijalil@ukm.edu.my

Sent for review: 15 February 2025

Revised accepted: 22 July 2025

Abstract

Numerous studies have highlighted the significant pharmacological activities of lysicamine in combating and ameliorating various diseases. Nevertheless, a comprehensive compilation of the pharmacological properties of lysicamine has not yet been undertaken. Therefore, this review aimed to provide an extensive overview of the pharmacological applications of lysicamine derived from medicinal plants. Data were collected using several databases, including PubMed, Scopus, and Google Scholar. The findings indicated that lysicamine exhibited diverse pharmacological activities, including anti-inflammatory, antimicrobial, antiprotozoal, anticancer, antihypertensive, and other notable effects. This study underscored the potential of lysicamine as a promising lead compound for drug discovery and development, emphasizing its therapeutic significance and the need for further exploration.

Keywords: Lysicamine, Oxoaporphine alkaloids, Medicinal plants, Pharmacological activities, Biosynthesis

This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited.

Tropical Journal of Pharmaceutical Research is indexed by Scopus, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Lysicamine, a natural oxoaporphinoid alkaloid (Figure 1), is a heterocyclic compound containing nitrogen that is known for its numerous pharmacological benefits [1]. Lysicamine is one of the primary alkaloids isolated from plants of the Annonaceae family [2]. Lysicamine exists as a yellow amorphous solid with a molecular formula of $C_{18}H_{13}NO_3$ and a molecular weight of 292.09 g/mol [3]. In the mass spectrum of lysicamine, fragmentations were observed at m/z 277, attributed to the loss of a CH_3 group, $(M-15)^+$. The absorption peaks in its ultraviolet spectrum were observed at 236, 267, 360, and 396 nm, indicating a highly unsaturated oxoaporphine chromophore. In addition, the

carbon-13 nuclear magnetic resonance (^{13}C -NMR) spectra analysis of lysicamine revealed nine distinct quaternary carbons, aligning with the published data on its 1H - and ^{13}C -NMR [3].

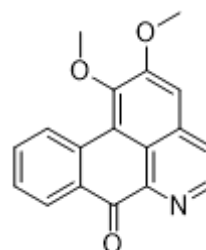


Figure 1: Chemical structure of lysicamine

Published data have documented the antimicrobial [2–6], antiprotozoal or leishmanicidal [7–10], antioxidant [11–13], anticancer [3,6,8,11,12,14–16], hypotensive [10], and sedative [17] activities of lysicamine. Lysicamine was first isolated from a Chinese medicinal plant [16] and has been identified in a total of 26 medicinal plant species. The oxoaporphinoid alkaloids have been studied for over four decades [18]. Nonetheless, data on the pharmacological activities of lysicamine remain limited. This systematic review aimed to provide a comprehensive compilation of scientific data on the pharmacological properties of lysicamine isolated from medicinal plants, offering valuable insights for various research fields.

METHODS

Search strategy

Data were primarily collected from online databases, such as PubMed, Scopus, and Google Scholar. The keywords used specifically for this search included “lysicamine”, “pharmacological activities”, “medicinal plants”, and “importance of lysicamine”. The papers included in this study were original research articles in English that focused on the pharmacological activities of lysicamine in medicinal plants, bioactivity studies conducted *in vitro* and/or *in vivo* and/or *ex vivo*, and with information on the toxicology and biosynthesis of lysicamine.

RESULTS

Lysicamine isolated from medicinal plants

The Annonaceae family is a large and diverse group comprising over 135 genera and more than 2,500 plant species, predominantly found in tropical and subtropical regions [19]. This family is chemically characterized by the presence of isoquinoline alkaloids, primarily aporphines [19]. To date, lysicamine has been isolated as a bioactive compound from 26 different plant species, as summarized in Table 1. Based on the data presented in Table 1, lysicamine is most commonly found in the Annonaceae family, particularly in 18 plant species. Other families where lysicamine has also been identified include Lauraceae [3, 20], Caricaceae [18], Nelumbonaceae [7], Rhamnaceae [17], Magnoliaceae [12,21], and Menispermaceae [22,23].

Notably, several species of the genus *Guatteria* are recognized for their edible fruits and therapeutic properties [2]. Lysicamine has been purified from two species of Lauraceae, three species of Menispermaceae, two species of Magnoliaceae, one species each from Caricaceae, Nelumbonaceae, and Rhamnaceae. Among these families, Nelumbonaceae was reported as a family known for its use in traditional medicine [7]. For instance, lysicamine from *Nelumbo nucifera* Gaertner cultivar *Rosa-plena* yielded a promising result in the evaluation of antihelminthic activity against *Anisakis simplex* and *Hymenolepis nana*. Lysicamine from *Alphonsea cylindrica* King also demonstrated antibacterial activity, effectively inhibiting *Staphylococcus aureus* and *Pseudomonas aeruginosa* [4]. Within the genus *Guatteria*, lysicamine has been isolated from various species collected in Brazil's national parks, such as *Guatteria ferruginea*, *Guatteria latifolia*, and *Guatteria sellowiana* [27]. Additionally, *Guatteria hispida* also yielded lysicamine, further supporting the prominence of this genus in lysicamine studies [2].

Lysicamine has been detected in various plant parts, including bark, fruits, stems, leaves, and aerial parts. In some cases, lysicamine could be found in multiple parts within a single species (Table 1). For instance, lysicamine has been isolated from the bark of *Alphonsea cylindrica* King [4], *Artabotrys crassifolius* [4], *Fissistigma latifolium* (Dunal) Merr. [25], *Guatteria hispida* (R.E.Fr.) Erkens & Maas [2], *Guatteria blepharophylla* Mart. [11], and *Michelia alba* leaves [1]. Other than the bark, lysicamine has also been identified in the fruit of *Zizyphus jujuba* Miller var. *inermis* [17]. Lysicamine has also been isolated from the leaves of *Guatteria amplifolia* Triana & Planch., and *Guatteria dumetorum* R.E.Fr. [9], *Phoebe grandis* Nees Merr. [3], and *Liriodendron tulipifera* L. [12]. Some species, namely, *Annickia kummerae* (Engl. & Diels) Setten & Maas [8], *Annona pickelii* (Diels) H. Rainer [6], and *Fissistigma cupreonitens* Merr. & Chun [14] have been reported to contain lysicamine in multiple parts. While lysicamine has been studied in various plant species, its isolation from *Annickia kummerae* species was first reported in 2013 [8]. More recently, lysicamine was discovered in the tubers of *Tinospora dentata* [22].

Biosynthesis of lysicamine

For many years, research groups have dedicated substantial efforts to developing efficient synthetic pathways for isoquinoline alkaloids.

Table 1: Lysicamine isolated from plant species

Family	Plant species	Plant part	Reference
Annonaceae	<i>Annickia kummerae</i> (Engl. & Diels) Setten & Maas	Leaf, root bark and stem bark	[8]
Annonaceae	<i>Alphonsea cylindrica</i> King	Bark	[4]
Annonaceae	<i>Annona pickelii</i> (Diels) H. Rainer	Stem bark	[24]
Annonaceae	<i>Annona cherimola</i> Mill. x <i>Annona squamosa</i> L.	Leaf	[19]
Annonaceae	<i>Artabotrys crassifolius</i> Hook.f. & Thomson	Bark and leaf	[6]
Annonaceae	<i>Duguetia pycnastera</i> Sandwith	Leaf	[25]
Annonaceae	<i>Fissistigma cupreonitens</i> Merr. & Chun	All parts	[14]
Annonaceae	<i>Fissistigma latifolium</i> (Dunal) Merr.	Bark	[26]
Annonaceae	<i>Guatteria amplifolia</i> Triana & Planch.	Leaf	[9]
Annonaceae	<i>Guatteria blepharophylla</i> Mart.	Bark	[11]
Annonaceae	<i>Guatteria dumetorum</i> R.E.Fr.	Leaf	[9]
Annonaceae	<i>Guatteria ferruginea</i> A. St. -Hil.	Aerial parts	[27]
Annonaceae	<i>Guatteria hispida</i> (R.E.Fr.) Erkens & Maas	Bark	[2]
Annonaceae	<i>Guatteria latifolia</i> (Mart.) R.E.Fr.	Aerial parts	[27]
Annonaceae	<i>Guatteria multivenia</i> Diels	Root	[28]
Annonaceae	<i>Guatteria sellowiana</i> Schlttdl.	Aerial parts	[27]
Annonaceae	<i>Polyalthia longifolia</i> var. <i>pendula</i> Benthall	Root bark	[10]
Annonaceae	<i>Rollinia papilionella</i> Diels	Root	[29]
Caricaceae	<i>Asimina triloba</i> (L.) Dunal	Twig	[18]
Lauraceae	<i>Cassytha filiformis</i> L.	All parts	[20]
Lauraceae	<i>Phoebe grandis</i> (Nees) Merr.	Leaf	[3]
Magnoliaceae	<i>Liriodendron tulipifera</i> L.	Leaf	[12]
Magnoliaceae	<i>Michelia x alba</i> DC.	Bark	[1]
Menispermaceae	<i>Abuta rufescens</i> Aubl.	Stem	[15]
Menispermaceae	<i>Chasmanthera dependens</i> Hoschst.	Stem	[23]
Menispermaceae	<i>Tinospora dentata</i> Diels	Tuber	[22]
Nelumbonaceae	<i>Nelumbo nucifera</i> Gaertn. cv. Rosa-plena	All parts	[7,13]
Rhamnaceae	<i>Zizyphus jujuba</i> Miller var. <i>Inermis</i>	Fruit	[17]

These endeavors have led to the creation of novel compounds with reconfigured molecular structures, originating from the basic isoquinoline alkaloid skeleton. These advancements have spurred interest due to the potential pharmacological properties of these compounds [30]. Among the bioactive compounds in medicinal plants, benzyloisoquinoline alkaloids (BIAs), particularly those belonging to the aporphine and bisbenzyloisoquinoline structural classes, are considered highly significant [31]. Aporphine alkaloids, derived biologically from isoquinoline alkaloids, are commonly found in a diverse range of medicinal plants. Oxoaporphine alkaloids, a subset of aporphine compounds, typically appear as yellow, orange, or reddish-orange substances [32]. Structurally, the aporphine skeleton comprises four rings (A–D), with a nitrogen atom located in the B ring (Figure 2).

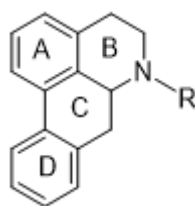


Figure 2: Aporphine core structure

As shown in Figure 2, the core structure of aporphine alkaloid is produced through direct intramolecular oxidative coupling (ortho-ortho or ortho-para) of (S)-reticuline as the bis-dienone radical in plants. Benzyloisoquinoline serves as a precursor for aporphine alkaloids. Specific O-substitution positions, such as C-3 or C-7, can lead to the oxidation of the aporphinoid nucleus. Alternatively, aporphine alkaloids may arise from proaporphine through the ortho-para cyclization of a tetrahydroisoquinoline diradical, followed by protonation and a dienone-phenol rearrangement [32]. Lysicamine, classified as an oxoaporphine alkaloid, follows a proposed biosynthetic pathway as illustrated in Figure 3. This process begins with the production of benzyloisoquinoline alkaloids, which originate from two molecules of L-tyrosine. One molecule undergoes decarboxylation to produce tyramine, which is then oxidized by an enzyme named phenol oxidase to form L-dopamine. Concurrently, the second molecule of L-tyrosine undergoes transamination, yielding 4-hydroxyphenylpyruvic acid, which is subsequently decarboxylated to produce 4-hydroxyphenylacetaldehyde. A Mannich reaction between dopamine and 4-hydroxyphenylacetaldehyde, catalyzed by

norcoclaurine synthase, resulted in the formation of (S)-norcoclaurine [32]. The conversion of (S)-norcoclaurine to (S)-reticuline involves several enzymes, including the norcoclaurine 6-O-methyltransferase (6OMT), coclaurine N-methyltransferase (CNMT), (S)-N-methylcoclaurine-3-hydroxylase (NMCH), and 3-hydroxy-N-methylcoclaurine-4'-O-methyltransferase (4'OMT). These enzymatic processes are critical precursors for the synthesis of aporphine alkaloids. Aporphine compounds undergo a systematic *in vivo* transformation, culminating in the formation of oxoaporphines via dehydro- and didehydroaporphine intermediates (Figure 3) [32].

Pharmacological activities

Natural phytochemicals derived from plants have garnered significant global interest due to their pharmacological effects. These phytochemical compounds typically exhibit low toxicity levels while demonstrating potent biological activity, which contributes to the therapeutic properties of medicinal plants [14]. Oxidative stress, caused by hydrogen peroxide or superoxide anions, plays a vital role in the formation of free radicals and reactive oxygen species (ROS). The imbalance between ROS production and antioxidant defenses of the body can lead to various illnesses, including cancer and other health conditions [7]. Various studies have investigated the pharmacological properties of lysicamine from the Annonaceous family. For instance, the *in vitro* study of *Artabotrys suaveolens* (Blume) demonstrated cytotoxic effects of lysicamine, highlighting its anticancer activity [6]. Similarly, lysicamine from *Nelumbo nucifera* Gaertn. cv. *Rosa-plena* against parasites, specifically *Anisakis simplex* and *Hymenolepis nana*, underscoring its antihelminthic potential [7]. The pharmacological activities of lysicamine from medicinal plants are summarized in Table 2 -4.

Anticarcinogenic activity

Recent statistics reported that approximately 60 % of the anticancer medicines were derived from natural sources, and about 1,000 of the 250,000 known plant species possessed the potential to inhibit or eradicate cancer [3]. One of the critical mechanisms in cancer therapy involves the activation of caspase enzymes, specifically the cysteine proteases, which function as the inactive zymogens within cells and mediate apoptosis (programmed cell death).

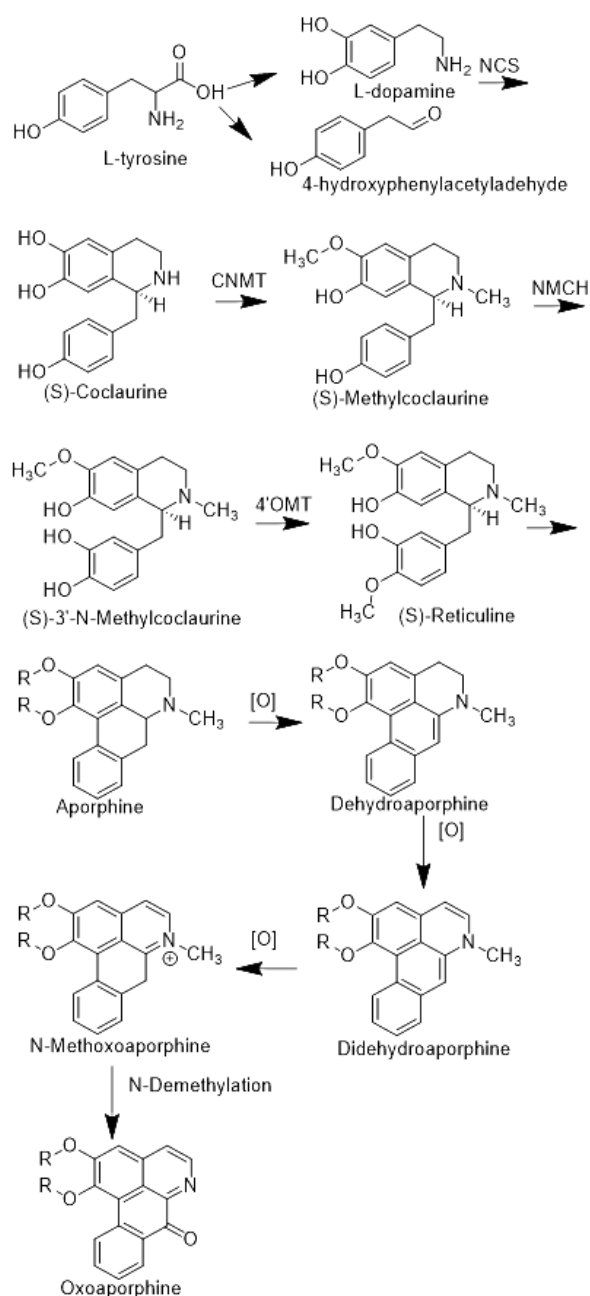


Figure 3: Proposed biosynthesis of oxoaporphine alkaloids

Among these enzymes, the caspase-3 has emerged as a pivotal target for cancer therapy due to its essential role in the execution phase of apoptosis [16].

Lysicamine demonstrated anticarcinogenic activity against multiple cancer cell lines, including HepG2 and NCI-H460. Notably, lysicamine complexed with metals, such as rhodium (Rh) and manganese (Mn), further enhanced the anticarcinogenic activity. These metal complexes activated the caspase-3, -9, and -8 by proportions of 21.1, 8.1 and 10.3 % for

Rh complexes, and 18.8, 17.0, and 12.2 % for Mn complexes, respectively. These findings highlighted the efficacy of lysicamine metal complexes in inducing apoptosis via a caspase-dependent mitochondrial pathway [16].

Free radicals in the body were reported to contribute to cellular instability, leading to cancer development [12]. The imbalance between ROS and natural antioxidants in the body could promote cancer cell proliferation [12]. Lysicamine, derived from *Liriodendron tulipifera*, exhibited both antioxidative and chemopreventive effects against A375 human skin melanoma cells. In the A375 cells, lysicamine demonstrated significant antioxidative and chemopreventive effects, as evaluated by the MTT cell sensitivity assay, with 0.5% dimethyl sulfoxide (DMSO) serving as a positive control [12]. At this concentration, DMSO did not affect the growth of melanoma cells. In contrast, lysicamine at a concentration of 100 mM exhibited a significant cytotoxicity against A375 cells, with an IC_{50} of 58.12 mM [12]. The mechanism of action for lysicamine was validated to be aligned with that of batracycline, a marketed drug for malignant melanoma that could help to inhibit the A375 cell growth and suppress the proliferation of HCT-116 colorectal carcinoma cells [6]. Additionally, lysicamine isolated from *Fissistigma cupreonitens* demonstrated significant efficacy against several cancer cell lines, including human non-small cell lung carcinoma (NCI-H226), nasopharyngeal carcinoma (NPC-TW01), and T-cell leukaemia (Jurkat E6-1). Findings reported that lysicamine showed significant cytotoxicity against NCI-H226 cells, with an IC_{50} value of 12.83 mM, comparable to the positive control reference drug, cisplatin (IC_{50} = 13.37 mM) [14]. These findings supported that lysicamine could be a potential lead compound in developing new therapies targeting the cisplatin-resistant cancers.

In another study, lysicamine derived from the leaves and barks of *Artabotrys crassifolius* through silica gel column chromatography had inhibitory effects on breast carcinoma MCF-7 (estrogen receptor-positive, ER+), breast carcinoma MDA-468 (estrogen receptor-positive, ER-), and colorectal carcinoma (HCT-116) cells [6]. The inhibitory effect of lysicamine on these carcinoma cells had GI_{50} values ranging from 3.3 to 3.9 mM. Quercetin served as a positive control at the equivalent concentration [6].

Table 2: Pharmacological activities of lysicamine from medicinal plants

Pharmacological activity	Plant species	Description	Reference
Anticancer	<i>Guatteria blepharophylla</i> Mart.	Lysicamine exhibited strong antiproliferative effects on non-small cell lung carcinoma (NCI-H460) with a Total Growth Inhibition (TGI) value of 49.52 mmol/L, outperforming doxorubicin (TGI 14.27 mmol/L).	[11]
	<i>Abuta rufescens</i> Aublet	The cytotoxicity of lysicamine was studied on human HCT-116 colon, ACHN renal, and A549 lung cancer cells. Lysicamine exhibited strong cytotoxic activity in cancer cell lines (reported as IC ₅₀ (mM) ± SD for each cell line). The values for HCT-116 (colon cancer), ACHN (renal cancer), and A549 (lung cancer) were 50.0 ± 6.7 mmol/L, 16.0 ± 15.3 mmol/L, and 20.0 ± 10.2 mmol/L, respectively. When anticancer drugs, such as doxorubicin, etoposide, camptothecin, and vinblastine, were employed as the positive controls, lysicamine also exhibited cytotoxic activity with the highest effectiveness.	[15]
	<i>Phoebe grandis</i> (Nees) Merr.	Lysicamine demonstrated significant inhibitory effects on the human oestrogen receptor-positive (ER+) breast cancer cell line (MCF7), with an IC ₅₀ value of 26 mg/mL. Doxorubicin served as the positive control in this study. The <i>in vitro</i> cytotoxicity test revealed that lysicamine inhibited the growth of the human liver cancer cell line (HepG2), with an IC ₅₀ value of 27 mg/mL. These results indicated that lysicamine had a moderate level of anticancer activity against the respective cell lines.	[3]
	<i>Liriodendron tulipifera</i> L.	In skin melanoma cells (A375), lysicamine demonstrated chemopreventive properties. Lysicamine exhibited significant cytotoxicity at 100 mM with an IC ₅₀ of 58.12 mM.	[12]
	<i>Artabotrys crassifolius</i> Hook.f. & Thomson	In this study, lysicamine exhibited a growth inhibition 50 (GI ₅₀) value of 3.9 mM, effectively inhibiting the growth of colon cancer (HCT-116) and human estrogen receptor-positive (ER+) breast cancer (MCF-7) cells. Quercetin was used as a positive control at the same concentration as lysicamine. Notably, lysicamine in this study demonstrated no cytotoxic effects on human embryonic kidney cells (HEK297) at concentrations up to 50 mg/mL.	[6]
	<i>Fissistigma cupreonitens</i> Merr. & Chun	Lysicamine exhibited significant cytotoxicity against the non-small cell lung carcinoma (NCI-H226) cell line, with an IC ₅₀ value of 12.83 mM. This data was comparable to the cisplatin, the reference drug which had an IC ₅₀ value of 13.37 mM as a positive control.	[14]

Table 3: Pharmacological activities of lysicamine from medicinal plants (*continued*)

Pharmacological activity	Plant species	Description	Reference
Antimicrobial	<i>Guatteria hispida</i> (R.E.Fr.) Erkens & Maas	Lysicamine isolated from <i>Guatteria hispida</i> was evaluated for its antimicrobial activity. Chloramphenicol was used as the positive control against <i>Staphylococcus epidermidis</i> , while ketoconazole served as a positive control against <i>Candida dubliniensis</i> (strain ATCC 777). Lysicamine demonstrated comparable efficacy to chloramphenicol in inhibiting the growth of <i>Staphylococcus epidermidis</i> (6ep), with a minimum inhibitory concentration (MIC) value of 50.0 µg/mL.	[2]
	<i>Phoebe grandis</i> (Nees) Merr.	Lysicamine demonstrated significant antibacterial activity, with inhibition zones of 15.50 ± 0.57 mm against <i>Bacillus subtilis</i> (B145), 13.33 ± 0.57 mm against <i>Staphylococcus aureus</i> (S1434), and 12.00 ± 0.00 mm against a clinically isolated strain of <i>Staphylococcus epidermidis</i> . These results were comparable to streptomycin sulfate, which was used as a positive control in the antibacterial activity assays.	[3]
	<i>Artabotrys crassifolius</i> Hook.f. & Thomson	Based on the <i>in vitro</i> antibacterial test, lysicamine isolated from the bark of <i>Artabotrys crassifolius</i> Hook.f. & Thomson exhibited both bacteriostatic and bactericidal activities against Gram-negative, extended-spectrum beta-lactamase-producing Klebsiella. The MIC of lysicamine was 10 µg/mL, while the minimum bactericidal concentration (MBC) was 20 µg/mL, comparable with streptomycin, which was used as a positive control.	[5]
	<i>Alphonsea cylindrica</i> King	In a disc diffusion assay, lysicamine exhibited inhibitory zones against <i>Staphylococcus aureus</i> , <i>Pseudomonas aeruginosa</i> , and <i>Bacillus cereus</i> at a concentration of 1 mg/mL. Among the tested alkaloids, lysicamine displayed the largest inhibition zone against <i>Pseudomonas aeruginosa</i> , with a diameter of 13.33 ± 1.53 mm. The MIC values of lysicamine were 125 mg/mL for both <i>Staphylococcus aureus</i> and <i>Pseudomonas aeruginosa</i> , and 250 mg/mL for <i>Bacillus cereus</i> .	[4]
Antioxidant	<i>Guatteria blepharophylla</i> Mart.	The Oxygen Radical Absorbance Capacity (ORAC) value of lysicamine was measured at 0.86 ± 0.95 µmol of Trolox Equivalents (TE/g), demonstrating a good antioxidant capacity comparable to the three positive controls, namely the quercetin (5.62 ± 0.90 µmol of TE/g), isoquercitrin (5.25 ± 1.80 µmol of TE/g), and caffeic acid (2.95 ± 2.05 µmol of TE/g). The results of the assay indicated that lysicamine exhibited significant antioxidant activity.	[11]
	<i>Liriodendron tulipifera</i> L.	In the ferric reducing antioxidant power (FRAP) assay, lysicamine exhibited a ferric reducing power of 0.1 ± 0 at the concentration of 100 µM and optical density (OD) of 700 nm. For comparison, the 100 mM ethylenediaminetetraacetic acid (EDTA) and 3-tert-butyl-4-hydroxyanisole (BHA) were used as positive controls in this assay. These results suggested that lysicamine was not a potent antioxidant, as it exhibited the lowest ferric reducing power in this study.	[12]

Table 4: Pharmacological activities of lysicamine from medicinal plants (*continued*)

Pharmacological activity	Plant species	Description	Reference
Antioxidant	<i>Nelumbo nucifera</i> Gaertn. cv. <i>Rosa-plena</i>	The antioxidant capacity of lysicamine was evaluated using assays for radical scavenging, metal chelation, and ferric reducing power. At a concentration of 100 mM, lysicamine demonstrated antioxidant activity of 6.4% and 24.7% in the 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) and 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assays, respectively, along with 7.8% metal chelating activity. The ferric reducing power measured at OD 700 was 0.302. These results indicated that lysicamine exhibited only modest antioxidant activity, with limited ferric reducing capability.	[13]
Antihelminthic/ antiprotozoal	<i>Annickia kummerae</i> (Engl. & Diels) Setten & Maas	Lysicamine isolated from the leaves of <i>Annickia kummerae</i> collected in Tanzania demonstrated potent antiplasmodial activity against the multidrug-resistant <i>Plasmodium falciparum</i> K1 strain with an IC ₅₀ value of 0.12 ± 0.01 µg/mL, selectivity index (SI) of 250. Meanwhile, moderate activity was observed against <i>Trypanosoma brucei rhodesiense</i> STIB 900 strain (IC ₅₀ values = 2.50 ± 0.19 µg/mL; SI = 12). Mild activity was observed against <i>Leishmania donovani</i> axenic MHOM-ET-67/82 (IC ₅₀ values = 9.25 ± 0.54 µg/mL; SI = 3.2).	[8]
	<i>Nelumbo nucifera</i> Gaertn. cv. <i>Rosa-plena</i>	Exposure to 100 mM lysicamine for 72 hours resulted in the highest cestocidal effect against <i>Hymenolepis nana</i> in the assay, characterized by a complete absence of peristalsis activity. Treatment with lysicamine on <i>H. nana</i> at various incubation periods (24, 48, and 72 hours) demonstrated oscillation percentages ranging from 0 to 100%. These findings indicated that lysicamine had significant antihelminthic activity against <i>H. nana</i> .	[7]
Antihypertensive	<i>Polyalthia longifolia</i> var. <i>pendula</i> Benthall	<i>Polyalthia longifolia</i> var. <i>pendula</i> Benthall was evaluated for its antihypertensive effects in rats, demonstrating a significant reduction in blood pressure in both normotensive and egg yolk-induced hypertensive models. The median lethal dose (LD ₅₀) for the plant root bark (PRB) in mice was determined to be 100 mg/kg. Lysicamine treatment at a dose of 20 mg/kg resulted in a mean arterial blood pressure (MABP) change of 10.18 ± 1.56 mm Hg in rats. These findings suggested that lysicamine had lower potency as an antihypertensive agent.	[10]
Sedative effect	<i>Zizyphus jujuba</i> Miller var. <i>inermis</i>	Lysicamine administration at doses of 1 mg/kg and 3 mg/kg extended hexobarbital-induced sleeping time to 34.3 ± 18.5 minutes and 44.7 ± 17.8 minutes, respectively. Meanwhile, the control group exhibited a shorter sleeping time of 29.5 ± 11.1 minutes. These results indicated that lysicamine significantly enhanced hexobarbital-induced sedation, suggesting a notable sedative effect.	[17]

In this study, lysicamine at concentrations up to 50 mg/mL was reported to be non-toxic to human embryonic kidney cells (HEK297), further underscoring its safety profile [6].

Besides that, lysicamine, isolated from *Fissistigma cupreonitens*, was evaluated *in vitro* for its cytotoxic activities against tumor and non-tumor human cell lines [14]. Notably, lysicamine from this plant source exhibited significant cytotoxicity against human non-small cell lung carcinoma (NCI-H226) [14]. In the context of *in vitro* studies on human cancers, the platinum-based chemotherapy drug named cisplatin is one of the most widely used treatments for a range of malignancies. Nevertheless, acquired resistance to cisplatin often leads to clinical failures in cancer therapy. A previous study reported that lysicamine demonstrated notable cytotoxicity against the NCI-H226 cell line, with an IC_{50} value of 12.83 mM, comparable to cisplatin, which had an IC_{50} value of 13.37 mM [14]. These findings suggested that lysicamine could potentially be a lead compound in the development of novel therapeutic agents to address cisplatin-resistant cancers. In addition, lysicamine isolated from the *Abuta rufescens* was evaluated *in vitro* for cytotoxicity against human colon (HCT-116), renal (ACHN), and lung (A549) cancer cells, with IC_{50} values reported as 16.0 ± 15.3 mM, 50.0 ± 6.7 mM, and 20.0 ± 10.2 mM, respectively [15]. The potency of lysicamine was comparable to other established anticancer agents, such as doxorubicin, etoposide, camptothecin, and vinblastine [15].

Aporphine alkaloids, including lysicamine from the leaves of *Phoebe grandis*, exhibited anticancer activity against the MCF-7 and HepG2 cell lines, with IC_{50} values of 27 and 26 μ g/mL, respectively, following a 24-hour continuous exposure. Lysicamine displayed moderate anticancer efficacy compared to the control, doxorubicin, further reinforcing its potential in cancer treatments [3].

Antimicrobial and antibacterial activity

The modes of action for antimicrobial agents typically involve disrupting the bacterial cell wall synthesis, plasma membrane integrity, nucleic acid processes, ribosomal activity, or folate metabolism. Despite the availability of antibiotics in the market, bacterial infections remain a critical public health challenge due to the rise of antibiotic resistance, particularly in gram-negative, extended-spectrum beta-lactamase-producing *Klebsiella* (ESBL-KP) [5]. An *in vitro* antibacterial test revealed that lysicamine

isolated from the bark of *Artabotrys crassifolius* Hook.f. & Thomson exhibited both bacteriostatic and bactericidal activities against ESBL-KP. The MIC of lysicamine was 10 μ g/mL, whereas the MBC was 20 μ g/mL, comparable to streptomycin as a positive control [5]. Lysicamine also significantly inhibited *Staphylococcus aureus* with an inhibition zone of 13.33 ± 0.57 mm, similar to its positive control, streptomycin sulfate. Moderate antibacterial activity shown by lysicamine against *Staphylococcus epidermidis* and *Bacillus subtilis*, with inhibitor zone diameters of 12.00 ± 0.00 and 15.50 ± 0.57 mm, respectively. In contrast, lysicamine showed no activity against *Pasteurella multocida* and *Enterobacter cloacae*, indicating these gram-negative bacteria were not susceptible to the compound [3]. Further antimicrobial assays of lysicamine isolated from *G. hispida* reported a comparable efficacy to chloramphenicol against *Staphylococcus epidermidis*, with an MIC of 50.0 μ g/mL [2]. The ketoconazole was used as a positive control against *Candida dubliniensis* (strain ATCC 777).

In a disc diffusion test, lysicamine with a concentration of 1 mg/mL demonstrated strong inhibitory activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Bacillus cereus*. The largest inhibition zone was observed against *Pseudomonas aeruginosa* (13.33 ± 1.53 mm), comparable to other alkaloid compounds in the study [4]. The MIC value for lysicamine against both *Staphylococcus aureus* and *Pseudomonas aeruginosa* was 125 mg/mL, and for *Bacillus cereus* was 250 mg/mL. The results highlighted the potential of *Alphonsea cylindrica* King as a natural antibacterial agent, supporting the traditional usage of *Alphonsea* species for medical treatment [4].

Antioxidant activity

Hydrogen peroxide and superoxide anions contributed to the generation of free radicals and ROS in the body [12]. Increased ROS production leads to higher oxidative stress, which can potentially trigger DNA damage and cause detrimental effects on cells and tissues. Pathophysiologically, free radicals are the primary cause of oxidative damage in both animals and humans [13]. The imbalance between ROS production and antioxidant activity of the cells remains a critical factor underlying multiple health issues.

The antioxidant activity study of lysicamine from *Liriodendron tulipifera* was evaluated in several assays with varying results [12]. In a DPPH

radical scavenging assay using vitamin C as a positive control, lysicamine at 100 μM exhibited no activity. Similarly, in the FRAP assay, lysicamine at the concentration of 100 μM demonstrated minimal antioxidant activity, with a low ferric reducing power of 0.1 ± 0 at OD 700 [12]. In this assay, the EDTA with a concentration of 100 mM and BHA served as positive controls [12].

Besides that, lysicamine isolated from *G. hispida* was evaluated for antioxidant capacity using the oxygen radical absorbance capacity (ORAC_{FL}) assay, in which fluorescein served as the fluorescent probe in this assay to measure scavenging activity against peroxy radicals. The assay was performed using a Synergy HT multidetection microplate reader system with incubation at 37 °C. Results were expressed as micromoles of TE per gram of dried lysicamine (μmol of TE/g). Lysicamine exhibited an ORAC value of 0.86 ± 0.95 μmol TE/g, which was lower but comparable to the positive controls, namely the quercetin (5.62 ± 0.90 μmol TE/g), isoquercitrin (5.25 ± 1.80 μmol TE/g), and caffeic acid (2.95 ± 2.05 μmol TE/g). These findings indicated that lysicamine possessed a significant antioxidant capacity [2].

The antioxidant activity of lysicamine isolated from *Nelumbo nucifera Gaertn. cv. Rosa-plena* species was further investigated using antiradical scavenging, metal chelating, and ferric reducing power assays. In addition to the DPPH assay, the ABTS assay was employed to assess the antioxidant activity [13]. Lysicamine exhibited a radical scavenging activity of 6.4% in the ABTS assay, which was lower than vitamin C (97%), the positive control. Based on the results from DPPH, ABTS, metal chelating, and ferric reducing power assays, lysicamine was concluded to possess moderate antioxidant activity [13].

Anthelmintic or antiprotozoal activity

The general mechanism of action for antiparasitic medication is bactericidal, primarily targeting parasites by killing them [8]. Additionally, antiparasitic treatments may disrupt the reproductive cycle of helminths by interfering with the normal growth of ova. Consequently, this mechanism paralyzed the eggs, preventing their progression through life cycle stages into larvae, and ultimately, adults. This mechanism hinders their ability to attach to the hosts. Malaria, trypanosomiasis, and leishmaniasis are among the most common parasitic infections in the poorest nations around the world. These diseases are especially concerning in tropical

areas due to their prevalence, severity, and increasing resistance to available medications [8]. Lysicamine, isolated from *Annickia kummeriae*, demonstrated potent antiplasmodial activity against the multidrug-resistant *Plasmodium falciparum* K1 strain, with an IC₅₀ of 0.87 ± 0.1 $\mu\text{g/mL}$ and a SI of 250. Comparatively, chloroquine, artemisinin, and podophyllotoxin were used as the positive controls [8]. As an antiprozoal agent, lysicamine showed moderate activity against *Leishmania donovani* MHOM-ET-67/L82 axenic amastigotes *in vitro*, with an IC₅₀ of 2.7 ± 0.0001 $\mu\text{g/mL}$ and no selectivity (SI = 1.5) [8]. The prominent antiplasmodial activity of lysicamine from *Annickia kummeriae* positioned it as a promising lead compound in the anthelmintic drug discovery.

Antihypertensive activity

The pathophysiology of hypertension involves impaired renal pressure natriuresis, which is a feedback mechanism wherein the elevated blood pressure stimulates increased renal excretion of salt and water, subsequently lowering the blood pressure. Dysfunctional renal pressure natriuresis may result from impaired renal function, improper hormonal regulation, such as the renin-angiotensin-aldosterone system, or excessive activity of the sympathetic nervous system. Hypertension, often termed a “silent killer”, can lead to severe diseases without prior symptoms, such as cerebrovascular disorders, renal failure, and congestive heart failure [10]. Despite the availability of antihypertensive drugs, many individuals succumb to these complications [10].

Lysicamine isolated from the root bark of *Polyalthia longifolia* var. *pendula* was evaluated for its antihypertensive potential in normotensive and egg-yolk-induced hypertensive rats [10]. Intravenous administration of lysicamine (20 mg/kg) caused a transient increase in blood pressure, with 10.18 ± 1.56 % change in the mean arterial blood pressure (MABP). These findings indicated the limited potency of lysicamine as an antihypertensive agent [10].

Sedative activity

Sedative medications function by altering specific neural pathways in the central nervous system (CNS). The sedative activity of lysicamine isolated from *Zizyphi fructus* was assessed by the potentiation of a hexobarbital-induced hypnosis test. Lysicamine, suspended in 1% carboxymethylcellulose (CMC), was administered intraperitoneally for 30 minutes before a 50 mg/kg intraperitoneal injection of

hexobarbital sodium. The lysicamine administration at doses of 1 mg/kg and 3 mg/kg prolonged hexobarbital-induced sleeping time to 34.3 ± 18.5 minutes and 44.7 ± 17.8 minutes, respectively. In comparison, the hexobarbital-induced sleeping time of the control group was 29.5 ± 11.1 minutes, indicating the significant sedative activity of lysicamine [17].

Toxicology

Alkaloids are widely recognized for their significant anticancer properties [14]. In an *in vitro* study, lysicamine derived from *Artabotrys crassifolius* demonstrated high specificity and potent cytotoxicity against colorectal and breast cancer cell lines [6]. Notably, at concentrations up to 50 mg/mL, lysicamine exhibited no toxic effects on the human embryonic kidney cells (HEK297) [6]. Similarly, a cytotoxicity study of alkaloids from *Guatteria friesiana* on normal cell lines revealed that lysicamine was not toxic to the normal cells [33]. These compelling findings underscored the potential of lysicamine as a promising anticancer agent.

Conclusion and future perspectives

Lysicamine is a natural oxoaporphine alkaloid found in various medicinal plants. Methodical investigations have demonstrated that lysicamine is present across numerous genera and families of medicinal plants. Notably, lysicamine has been identified in 18 species of the *Annonaceae* family, followed by other families, such as *Guatteria*, *Lauraceae*, *Magnoliaceae*, *Menispermaceae*, *Nelumbonaceae*, and *Rhamnaceae*.

Furthermore, lysicamine is a compound with significant interest due to its presence in diverse plant species and the credible evidence supporting its wide range of pharmacological activities. This review compiled and summarized the pharmacological data on lysicamine accumulated over the years. Given the promising findings from preliminary studies, further clinical studies are warranted to explore the potential of lysicamine as a novel therapeutic agent. With advanced clinical studies, the future role of medicinal plants as fundamental sources in drug development could be reinforced.

DECLARATIONS

Acknowledgement/Funding

The authors would like to thank Universiti Kebangsaan Malaysia (UKM) for the financial support (GUP-2021-005). This research was

funded by the Universiti Kebangsaan Malaysia (UKM), under grant number of GUP-2021-005.

Ethical approval

None.

Availability of data and materials

Not applicable.

Conflict of interest

No conflict of interest is associated with this study.

Contribution of authors

We declare that this work was done by the author(s) named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

Open Access

This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited.

REFERENCES

1. Wang Z, Cheng Y, Zeng M, Wang Z, Qin F, Wang Y, Chen J, He Z. *Lotus (Nelumbo nucifera Gaertn.) leaf: a narrative review of its phytoconstituents, health benefits and food industry applications. Trends Food Sci Technol* 2021; 112: 631-650.
2. Costa Pinheiro MLB, Barison A, Campos FR, Salvador M J, Maia BHLNS, Cabral EC, Eberlin MN. Alkaloids from the bark of *Guatteria hispida* and their evaluation as antioxidant and antimicrobial agents. *J Nat Prod* 2010; 73(6): 1180–1183.
3. Omar H, Hashim NM, Zajmi A, Nordin N, Abdelwahab SI, Azizan AHS, Hadi AHA, Ali HM. Aporphine alkaloids from the leaves of *Phoebe grandis* (Nees) Mer. (*Lauraceae*) and their cytotoxic and antibacterial activities. *Molecules* 2013; 18(8): 8994-9009.
4. Talip MA, Azziz SSSA, Wong CF, Awang K, Naz H, Bakri YM, Ahmad MS, Litaudon M. New azafluorenone derivative and antibacterial activities of *Alphonsea cylindrica* barks. *Nat Prod Sci* 2017; 23(3): 151-156.

5. Tan KK, Khoo TJ, Rajagopal M, Wiert C. Antibacterial alkaloids from *Artabotrys crassifolius* Hook.f. & Thomson. *Nat Prod Res* 2015; 29(24): 2346-2349.
6. Tan KK, Shipton F, Azman NSN, Hossan S, Jin KT, Wiert C. Cytotoxic aporphines from *Artabotrys crassifolius*. *Nat Prod Commun* 2016; 11(3): 382-392.
7. Lin RJ, Wu MH, Ma YH, Chung LY, Yen CM. Anthelmintic activities of aporphine from *Nelumbo nucifera* Gaertn. Cv. *Rosa-plena* against *Hymenolepis nana*. *Int J Mol Sci* 2014; 15(3): 3624-3639.
8. Malebo HM, Wenzler T, Cal M, Swaleh SM, Omolo MO, Hassanali A, Séquin U, Häussinger D, Dalsgaard P, Hamburger M, Brun, R., Ndiege IO. Anti-protozoal activity of aporphine and protoberberine alkaloids from *Annickia kummeriae* (Engl. Diels) Setten & Maas (Annonaceae). *BMC Altern Med* 2013; 13(48): 1-10.
9. Montenegro H, Gutiérrez M, Romero LI, Ortega-Barría E, Capson TL, Rios LC. Aporphine alkaloids from *Guatteria* spp. with leishmanicidal activity. *Planta Med* 2003; 69(7): 677-679.
10. Saleem R, Ahmed M, Ahmed SI, Azeem M, Khan RA, Rasool N, Saleem H, Noor F, Faizi S. Hypotensive activity and toxicology of constituents from root bark of *Polyalthia longifolia* var. *pendula*. *Phytother Res* 2005; 19(10): 881-884.
11. Costa EV, De F, Marques A, Lúcia M, Pinheiro B, Braga RM, Delarmelina C, Cristina M, Duarte T, Lúcia A, Ruiz TG, Ernesto De Carvalho J, Maia BHLNS. Chemical constituents isolated from the bark of *Guatteria blepharophylla* (Annonaceae) and their antiproliferative and antimicrobial activities. *J Braz Chem Soc* 2011; 22(6): 1111-1117.
12. Kang YF, Liu CM, Kao CL, Chen CY. Antioxidant and anticancer constituents from the leaves of *Liriodendron tulipifera*. *Molecules* 2014; 19(4): 4235-4245.
13. Liu CM, Kao CL, Wu HM, Li WJ, Huang CT, Li HT, Chen CY. Antioxidant and anticancer aporphine alkaloids from the leaves of *Nelumbo nucifera* Gaertn. cv. *Rosa-plena*. *Molecules* 2014; 19(11): 17829-17838.
14. Chen IH, Yang MY, Juang SH, Lee CL, Thang TD, El-Shazly M, Lan YH. Bioactive components of *Fissistigma cupreonitens*. *Nat Prod Commun* 2018; 13(6): 679-682.
15. Swaffar DS, Holley CJ, Fitch RW, Elkin KR, Sturgill JP, Menachery MD. Phytochemical investigation and in vitro cytotoxic evaluation of alkaloids from *Abuta rufescens*. *Planta Med* 2012; 78(3): 230-232.
16. Yadav P, Yadav R, Jain S, Vaidya A. Caspase-3: A primary target for natural and synthetic compounds for cancer therapy. *Chem Biol Drug Des* 2021; 98(1): 144-165.
17. Hoon HB, Hwan PM. Sedative activity and its active components of *Zizyphi fructus*. *Arch Pharm Res* 1987; 10(4): 208-211.
18. Majrashi TA, Zulfiqar F, Chittiboyina AG, Ali Z, Khan IA. Isoquinoline alkaloids from *Asimina triloba*. *Nat Prod Res* 2019; 33(19): 2823-2829.
19. Rabêlo SV, Costa EV, Barison A, Dutra LM, Nunes XP, Tomaz JC, Oliveira GG, Lopes NP, Santos M de FC, Almeida JRG da S. Alkaloids isolated from the leaves of *Atemoya* (*Annona Cherimola* × *Annona Squamosa*). *Rev Bras Farmacogn* 2015; 25(4): 419-421.
20. Wu YC, Chao YC, Chang FR, Chen YY. Alkaloids from *Cassytha filiformis*. *Phytochem* 1997; 46(1): 181-184.
21. Wang HM, Lo WL, Huang LY, Wang YD, Chen CY. Chemical constituents from the leaves of *Michelia alba*. *Nat Prod Res* 2010; 24(5): 398-406.
22. Lam SH, Jian SD, Hwang TL, Chen PJ, Hung HY, Kuo PC, Wu TS. A new dimeric protoberberine alkaloid and other compounds from the tubers of *Tinospora dentata*. *Nat Prod Res* 2021; 35(1): 17-24.
23. Ohiri FC, Verpoorte R, Svendsen AB. Alkaloids from *Chasmanthera dependens*. *Planta Med* 1982; 46(4): 228-230.
24. Costa EV, Sampaio MFC, Salvador MJ, Nepel A, Barison A. Chemical constituents from the stem bark of *Annona pickelii* (Annonaceae). *Quim Nova* 2015; 38(6): 769-776.
25. Nardelli VB, Silva de Souza CA, da Silva CJ, Ferreira KHH, Araújo da Silva FM, Costa EV. Isoquinoline-derived alkaloids and one terpene lactone from the leaves of *Duguetia pycnastera* (Annonaceae). *Biochem Syst Ecol* 2021; 94: 104206.
26. Alias A, Hazni H, Jaafar FM, Awang K, Ismail NH. Alkaloids from *Fissistigma latifolium* (Dunal) Merr. *Molecules* 2010; 15(7): 4583-4588.
27. Dos Santos AR, Pires C, Marques FA, Lobão AQ, Maia BHNS. Isoquinoline alkaloids isolated from three *Guatteria* Species. *Biochem Sys Eco* 2017; 24(8): 167-193.
28. Zhang Z, ElSohly HN, Jacob MR, Pasco DS, Walker LA, Clark AM. New sesquiterpenoids from the root of *Guatteria multivenia*. *J Nat Prod* 2002; 65(6): 856-859.
29. Dabrah TT, Sneden AT. Oxoaporphine alkaloids from *Rollinia papilionella*. *J Nat Prod* 1983; 46(3): 463-463.
30. Atanes N, Castedo L, Guitian E, Saá C, Saá J M, Suau R. Intermolecular benzyne cycloaddition (IBC) approach to aporphinoids. Total syntheses of norcepharadione B, cepharadione B, dehydroanonaine, duguenaine, dehydronornuciferine, pontevedrine, O-methylatheroline, lysicamine, and alkaloid PO-3. *J Org Chem* 1991; 56(9): 2984-2988.
31. Menéndez-Perdomo IM, Facchini PJ. Benzyloisoquinoline alkaloids biosynthesis in sacred lotus. *Molecules* 2018; 23(11): 2899-2916.
32. Ramawat KG. Biodiversity and chemotaxonomy. Switzerland: Springer Cham; 2019. 318.
33. Costa EV, da Cruz PEO, Pinheiro MLB, Marques FA, Ruiz ALTG, Marchetti GM, de Carvalho JE, Barison A, Maia BHLNS. Aporphine and tetrahydroprotoberberine alkaloids from the leaves of *Guatteria friesiana* (Annonaceae) and their cytotoxic activities. *J Braz Chem Soc* 2013; 24(5): 788-796.