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REVIEW ARTICLE

Traditional uses, chemical composition and pharmacological activities of *Alstonia* R. Br. (Apocynaceae): A review

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KEYWORDS

Alstonia R. Br. (Apocynaceae);
Chemical components;
Biological activities;
Traditional uses

Abstract *Alstonia* R. Br. (Apocynaceae) is widely used in the traditional therapeutic systems. Due to its rich natural active ingredients, it is used in China, India, Thailand, Malaysia, Philippines, Africa, Australia and other countries to treat malaria, dysentery, asthma, fever, epilepsy, skin diseases, snake bites, and so on. The aim of this review is to describe in detail the botanical properties, traditional uses, chemical compositions, pharmacological activities and toxicity of the genus *Alstonia* for analyzing the value of this plant in clinical applications. There was information on the genus *Alstonia* collected through the internet searches such as Baichain Library, Web of Science, China National Knowledge Infrastructure (CNKI), Baidu Scholar, PubMed, Wan Fang Database and ACS, etc. The keywords used include genus *Alstonia*, folk medicinal uses, botanical studies, chemical composition, pharmacological activities, bioactivities and other relevant terminology. The scientific names and geographic location of the genus *Alstonia* were provided in the Subject Database of the Flora of China, the Plant List (www.theplantlist.org), the WFO Plant List (www.worldfloraonline.org) and the World Checklist of Selected Plant Families (http://wcsp.science.kew.org/qsearch.do). Currently, at least 400 compounds were isolated from genus *Alstonia*, including alkaloids, triterpenes, flavonoids, volatile oils, phenolic acids, etc. Through extensive pharmacological experiments, it was demonstrated that genus *Alstonia* had good pharmacological effects *in vitro* and *in vivo*, including β_2AR, vasodilatory, antifungal, antineoplastic, antiplasmodial, anti-inflammatory, antibacterial, antioxidant, analgesic, and radioprotective activities, etc. Many studies also confirmed that the combination of the genus *Alstonia* with other traditional Chinese medicines could improve effectiveness. This review demonstrates that the genus *Alstonia* has high clinical application and medicinal value, which will bring the attention of pharmacologists and clinicians

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to the territory of natural products Additionally, bioactivity-related mechanisms and structure–activity relationships of chemical components are not clear. Only by bridging the gap between bioactivity-related mechanisms and structure–activity relationships of chemical components can the development of *Alstonia* plants be further promoted.

1. Introduction

Various natural products exist in nature. And natural products are rich in chemical components with different structure, such as flavonoids, triterpenes, steroids, alkaloids, etc., which are a critical treasure trove for the discovery of new drug lead compounds. In traditional applications, these plants can be used medicinally to treat disease and have great advantages over other chemical drugs, such as *Alstonia*. The genus *Alstonia* is a tropical plant with widespread distribution throughout the world, mainly in Africa, Indo-Malaya, Australia, Asia and other regions (Narine et al., 2009; Ku et al., 2011).

Approximately 46 species of the genus *Alstonia* are known worldwide and can be found at https://wcsp.science.kew.org/qsearch.do, https://www.worldfloraonline.org and https://www.theplantlist.org. Eight of them are located in the regions of Guangdong, Guangxi and Yunnan in China. In traditional medicine, these species are used not only to treat a number of diseases, such as malaria, but also to provide fever-reducing, cough-suppressing and hemostatic effects (Channa et al., 2005; Gandhi and Vinayak, 1990; Wright et al., 1993; Leaman et al., 1995; Kam et al., 1997). Total alkaloids (TA) obtained from *Alstonia scholaris* (L.) R. Br. as a new investigational phytopharmaceutical (No. 2011L01436) are registered in advance of clinical application (Pan et al., 2016). TA are also approved by the Chinese Food and Drug Administration for Phase I/II clinical trials (Shang et al., 2010a, 2010b). Additionally, the genus *Alstonia* could be used in association with other traditional Chinese medicines to maximize effectiveness, such as the combination of *Khaya ivorensis* A. Chev. and *Alstonia boonei* De Wild. as antimalarial prophylaxis (Tepongning et al., 2011).

Phytochemical studies have shown that the genus *Alstonia* represents a treasure trove as a source of phytoconstituents. In excess of 400 compounds have been isolated from this genus (Wang et al., 2009). Chemical investigation of the alkaloidal constituents was undertaken by Sharp (1938) and Elderfield (1942) (Keogh and Shaw, 1943). So far, the most abundant compounds isolated from this genus are monoterpenoid indole alkaloids (MIAs), and the non-alkaloid components include flavonoids, terpenes, phenolic acids, volatile oils, and so on. MIAs are the products from the condensation of tryptophan with secologanin. It is the second most abundant metabolite of the genus (De, 2011). After comprehensive analysis of phytochemistry and pharmacology, most of the genus's crude extracts and purified compounds are pharmacologically potent. Beyond that, the genus *Alstonia* also has different pharmacological activities in different parts. *A. scholaris* is the majority researched and representative species in the genus *Alstonia*. Despite extensive work and studies on *A. scholaris*, the number of precursor molecules and herbal preparations available have been extremely small (Pandey et al., 2020).

There was information on the genus *Alstonia* collected through the internet searches such as Science Network, PubMed, Baichain Library, China National Knowledge Infrastructure (CNKI), Baidu Scholar, Wan Fang Database, and ACS, etc. The keywords used include genus *Alstonia*, folk medicinal uses, botanical studies, chemical composition, bioactivity, secondary metabolites, and other relevant terminology. The scientific names and geographic location of the genus *Alstonia* were provided in the Subject Database of the Flora of China, the Plant List (https://www.theplantlist.org), and the World Checklist of Selected Plant Families (https://wcsp.science.kew.org/qsearch.do).

In this review, a comprehensive compilation of botanical information, traditional uses, phytochemistry, bioactivities and toxicity involved in the genus *Alstonia* is presented. The purpose of this review is to discover lead compounds from the genus *Alstonia* that provide potential development value and clinical application value. In addition, a clearer structured review of the structure–activity relationships of chemical compositions is expected to afford a more reliable basis for the pharmacological mechanisms and new drug development of *Alstonia*.

2. Distribution and botanical studies

Genus *Alstonia* plants are generally shrubs or trees. All the species of the genus *Alstonia* are known worldwide, eight of which are located in the Guangdong, Guangxi, and Yunnan regions of China. The names and geographical distribution of the identified 46 species are listed in Table S1.

In accordance with *Flora of China*, *Alstonia* is a member of the Apocynaceae family. They are mostly trees and shrubs with milk, and their branches grow on wheels. The leaves are usually in whorls of 3–4(-8), rarely opposite. Lateral veins are numerous, crowded and parallel. Flowers are white, yellow, or red, consisting of multiple flowers forming an umbellike polyglobulus inflorescence, terminal or nearly terminal. Calyx short, sepals are double-covered imbricate arrangement. There are no interior glands, and the corolla is salver-shaped. Crown tube is cylindrical, expanding above the middle, without corona at the throat. Corolla lobes are covered to the left at the time of the buds (Chinese species). Stamens are separated from the stigma and the anthers are oblong. Ovary is composed of two detached carpels, with multiple ovules per carpel. Flowering style is filiform, whereas stigmas are clubbed. Flower disk consists of 2 ligulate scales, which are alternate with the carpels. Seeds are flat and covered at both ends by long marginal hairs.

A. scholaris is a representative species of the genus *Alstonia*, which has a typical milky white latex that cuts the bark and flows freely. The genus is distributed primarily in tropical Africa, Asia, and Australia. In the evergreen rainforest of tropical West Africa, *Alstonia* becomes a tremendous tree, thriving on damp river banks (Adotey et al.,2012).

3. Traditional uses

A number of plants in the genus *Alstonia* have been used in folk medicine from ancient times. For example, in the tribes of the Indian Gulf Islands, the leaves of *Alstonia macrophylla* Wall. ex G. Don are commonly decocted to treat stomach pains (Dagar and Dagar, 1991). In West and Central Africa, *A. boonei* is regarded as a medicinal plant by local people. *A. boonei* is widely used in the treatment of malaria, intestinal helminths, rheumatism, hypertension, and so on (Terashima, 2003; Betti, 2004; Abel and Busia, 2005). The flowers of *A.*

scholaris can be used as a CNS depressant (Sood and Thakur, 2015) and also to treat respiratory problems and asthma (Anonymous, 1985). When ear pain, boils and injuries occur, the latex of *A. scholaris* is combined with oil as a treatment for the disease (Bhardwaj and Gakhar, 2005). *Alstonia mairei* H. Lév. is used in folklore as an essential medicinal plant for stopping bleeding and dissolving poison (Li et al., 1995; Wang, 2014).

The genus *Alstonia* bark is most generally used in traditional medicine, but the most commonly used part is the thick bark of mature trees (Adotey et al., 2012). *Alstonia*'s bark has a natural analgesic effect and serves as one of the analgesic herbs (Abbiw, 1990). In daily treatment, the bark not only treats rheumatism, inflammation, pain, malaria, diabetes (mild hypoglycemia), but also exerts anthelmintic, antimicrobial and antibiotic effects (Hadi and Bremner, 2001; Fakae et al., 2000; Kam et al., 1997). The decoction of *Alstonia* also provides mild antibacterial action and may relieve the soreness involved with malarial fevers (Adotey et al., 2012). The fresh bark of *Alstonia* is used to make an herbal tincture for snake, rat or scorpion poisoning (Adotey, et al., 2012). The cold infusion is used orally to expel roundworms and nematodes (Abbiw, 1990). Extracts of the leaves have been developed commercially as typical herbal medicines and are also hospital prescription drug, available in pharmacies (Cai et al., 2008). In Table 1, the traditional uses (edible and medicinal) of the genus *Alstonia* are provided.

4. Chemical components

In addition to volatile oils, a total of 392 chemical constituents are obtained from genus *Alstonia*. The chemical composition of *Alstonia* plants (as shown in Table S2.) involves alkaloids (**1**–**319**), triterpenes (**320**–**362**), flavonoids (**363**–**379**), fatty acid (**380**), phenolic acids (**381**–**388**), lignans (**389**–**391**), and ester (**392**).

The earliest study of the phytochemical composition of *Alstonia* plants could be dated in the 19th century. In 1875, a new crystalline alkaloid belonging to the aluammiline alkaloids was isolated from the bark of the genus *Alstonia*, which was named Echitamine (Goodson, 1932). After that, with the development of two-dimensional nuclear magnetic resonance

Table 1 The traditional uses of genus *Alstonia*.

Alstonia plants	Parts of the plant	Edible methods	Traditional and clinical uses	Reference
Alstonia scholaris (L.) R. Br.	Ripe fruits	–	Curing for syphilis, insanityand epilepsy	(Jahan et al., 2009)
	Milky juice	–	Curing for ulcers, wounds and rheumatic pain	(Varshney and Goyal, 1995)
	Bark	Decoction	Curing for falciparum malaria, asthma, hypertension, lung cancer and pneumonia	(Varshney and Goyal, 1995)
		Powdered bark	Curing for malaria, diarrhea, and dysentery	(Kirtikar and Basu, 1918; Akhtar et al., 1992)
	Leaves	–	Curing cough, chronic bronchitis, asthma, fever and other respiratory infections after infection	(Dey and De, 2011; Sharma et al., 2001)
	Flowers		Curing for respiratory problems and asthma	(Anonymous, 1985)
	Root	–	Curing for treat gum or dental problems	(Pan et al., 2014)
	Latex	Mixed with oil	Curing for earache, boils, and wounds healing	(Bhardwaj and Gakhar, 2005)
Alstonia yunnanensis Diels	Root	–	Curing for headache, fever and hypertension	(Chen et al., 1983)
Alstonia venenata R. Br.	The whole plant	–	Curing for insanity and epilepsy	(Ray and Dutta, 1973)
Alstonia angustifolia A. DC.	Leaves	–	Curing for relapsing fever of spleen area	(Ray and Dutta, 1973)
Alstonia macrophylla Wall. ex G. Don	Leaves and bark	Decoction	Curing for stomachache, skin diseases and urinary infection	(Dagar and Dagar, 1991; Bhargava, 1983)
	Leaves	Copra oil mixed with heated leaves	Curing for sprains, bruises, dislocated joints and muscle injuries	(Asolkar and Kakkar, 1992)
	Bark	Powdered form	Curing for antipyretic and dysentery Aid in the menstrual cycle	(Changwichit et al., 2011; Chattopadhyay et al., 2004)
	Bark	Powdered form mixed with water	Curing for astringent and skin diseases	(Das et al., 2008)
Alstonia boonei De Wild.	Stem bark	Decoction	Curing for astringent, alternative tonic, diarrhea and a febrifuge for relapsing fevers	(Abbiw, 1990)
	Leaves and latex	–	Curing for rheumatic and muscular pain and hypertension	(Abbiw, 1990)
Alstonia congensis Engl.	Leaves	Aqueous decoction	Curing for diarrhoea	(Lumpu et al., 2012)
Alstonia mairei H. Lév.	–	–	Curing for haemostasis, disintoxication	(Li et al., 1995; Wang, 2014)

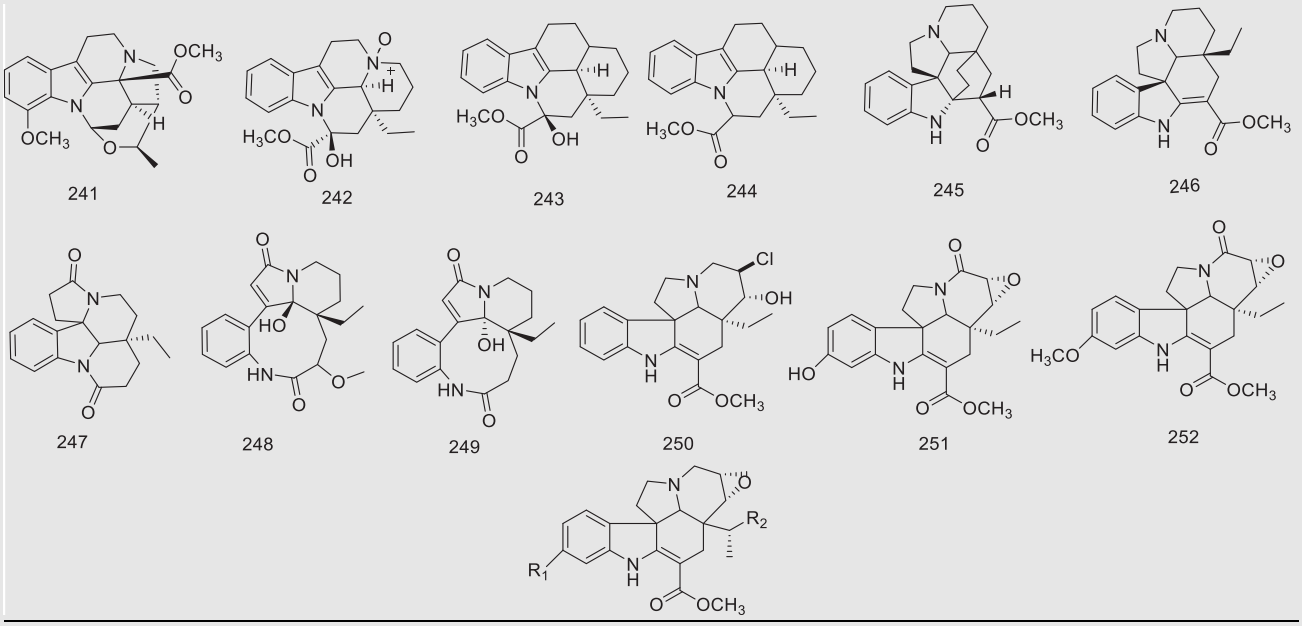
—: not mentioned.

(2D NMR) and quadrupole time of flight mass spectrometer (Q-TOF-MS), this technique for the chemical composition of genus *Alstonia* identification was provided a new method. Until 21st century, with the proposed bioactivity-oriented separation strategies, more bioactive components have been identified (El-Askary et al., 2012). In addition, bioactive-based liquid chromatography-coupled electrospray ionization tandem ion trap/time of flight mass spectrometry (HPLC-ESI-MS/MS) technology was also applied to detect bioactive components in *Alstonia* plants (Hou et al., 2012a).

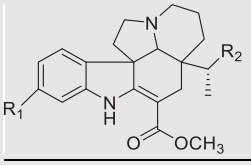
4.1. Alkaloids (1–319)

Alkaloids are a highly diverse set of compounds. They are mainly distributed in the Apocynaceae family, such as *Alstonia* R. Br. Alkaloids are only associated with the presence of nitrogen atoms in heterocyclic rings and are the main active and typical components of genus *Alstonia*. So far, 319 alkaloids have been obtained in the genus *Alstonia*, mainly divided into MIAs, bisindole alkaloids and other alkaloids. MIAs constituted a broad and various population of natural products characterized by the combination of indole units with extensively modified monoterpenoid molecules (Zhang et al., 2020). In the genus *Alstonia*, the MIAs are mainly corynantheine-strychnine alkaloids (**1**–**157**), sarpagine alkaloids (**158**–**174**), ajmaline alkaloids (**175**–**201**), macroline alkaloids (**202**–**240**), eburnamine and kopsifoline alkaloids (**241**–**261**). Because of their impressive structures and wide range of bioactivities, MIAs were often located on the list of popular molecules in natural product synthesis (Zhang et al., 2009; Xu et al., 2014; Adams et al., 2012; Pan et al., 2016). (Tables 2-5) show that the alkaloids identified from different species of the genus *Alstonia*. The proportions of the different types with alkaloids in the genus *Alstonia* are shown in the Fig. 1.

Table 2 The structure of eburnamine and kopsifoline alkaloids.



No.	compound	R_1	R_2
253	Alstomairine D	OCH_3	CH_3COO
254	Lochnericine	H	H



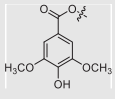
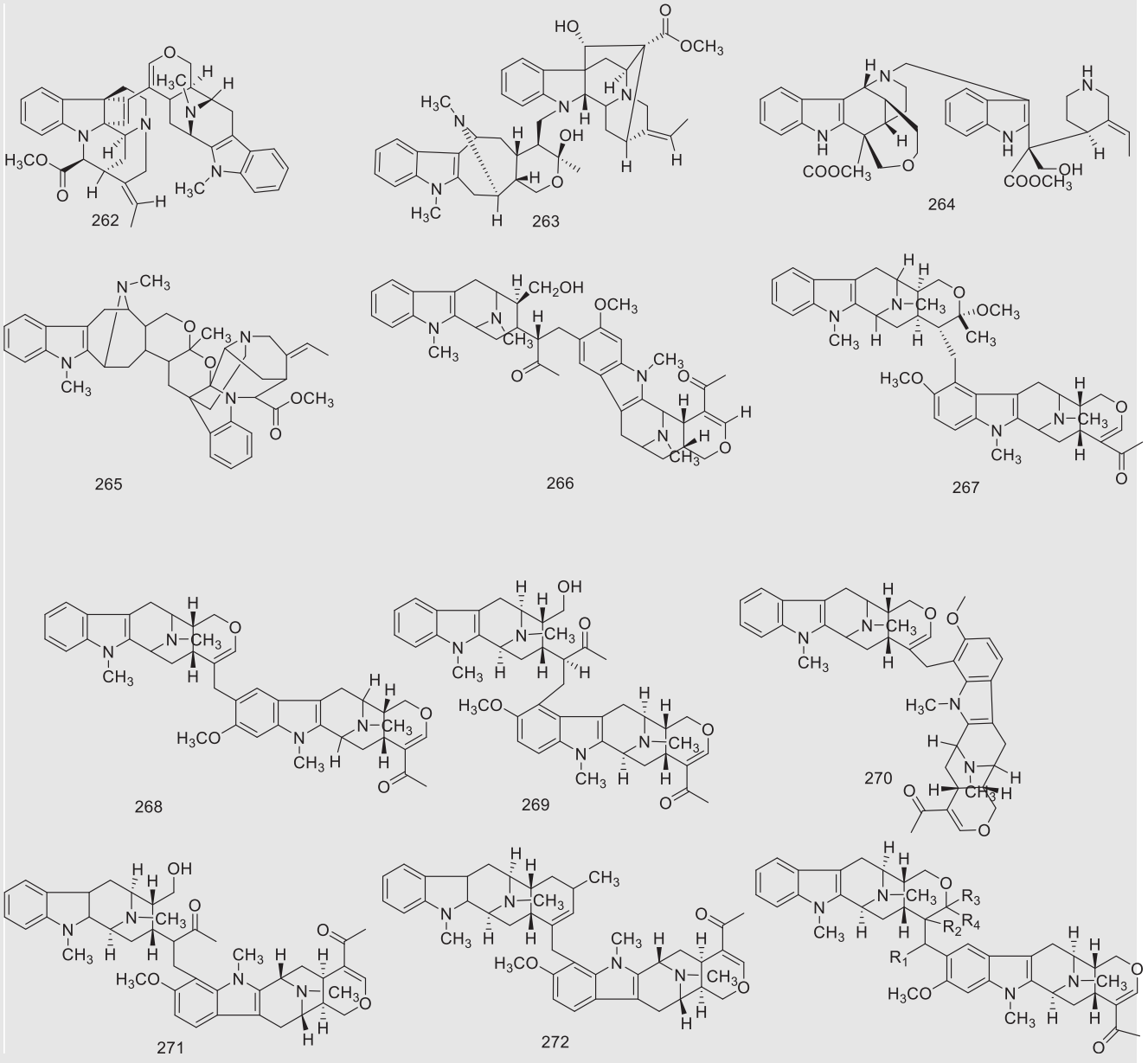
No.	compound	R_1	R_2
255	Echitoveniline	H	OH
256	Tabersonine	H	H
257	16-methoxytabersonine	OCH_3	H
258	19-hydroxytabersonine	H	OH
259	Vandrikidine	OCH_3	OH
260	19-acetoxy-11-methoxytabersonine	OCH_3	CH_3COO
261	Vincadifformine	H	

Table 3 The structure of bisindole monoterpenes indole alkaloids.

macroline-ajmaline and macroline-pleiocarpamine type

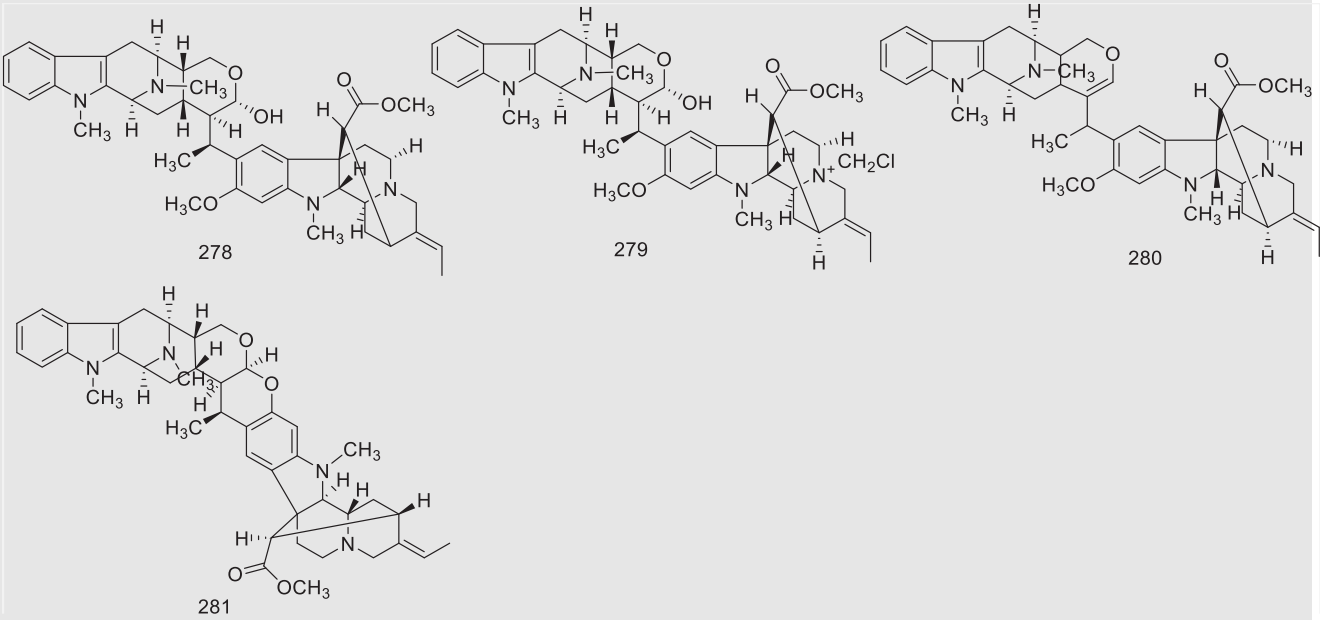


No.	compound	R_1	R_2	R_3	R_4
273	Macralstonine	H	β-H	α-OH	β-CH_3
274	*O*-methylmacralstonine	H	α-H	OCH	CH_3
275	Lumusidine B	α-CH_3	β-H	β-OH	H
276	Lumusidine C	H	α-H	β-CH_2CH_3	CH_3
277	*O*-acetylmacralstonine	H	α-H	$OCOCH_3$	CH_3

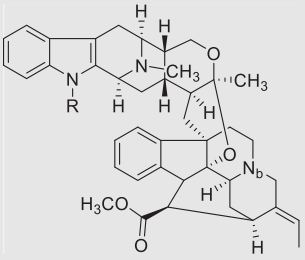
macroline-akuammiline type

(*continued on next page*)

Table 3 (*continued*)



macroline-corynantheine type



No.	compound	R	N_b
282	Villalstonidine F	H	
283	Villalstonine	CH_3	
284	Villastonine N_b-oxide	CH	N_b-oxide

akuammiline-ajmaline and yohimbine-kopsinine type

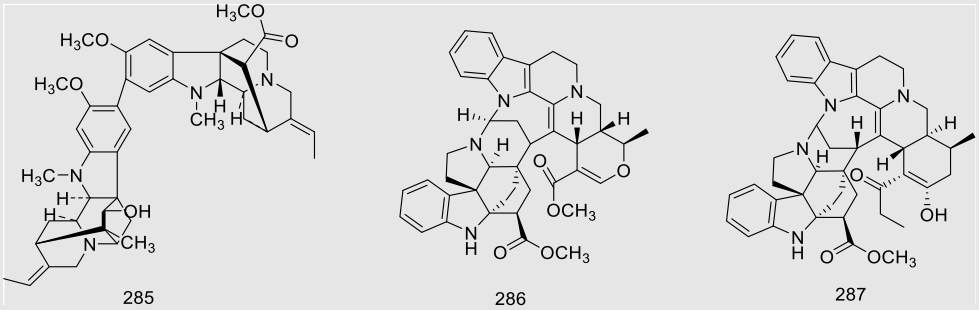
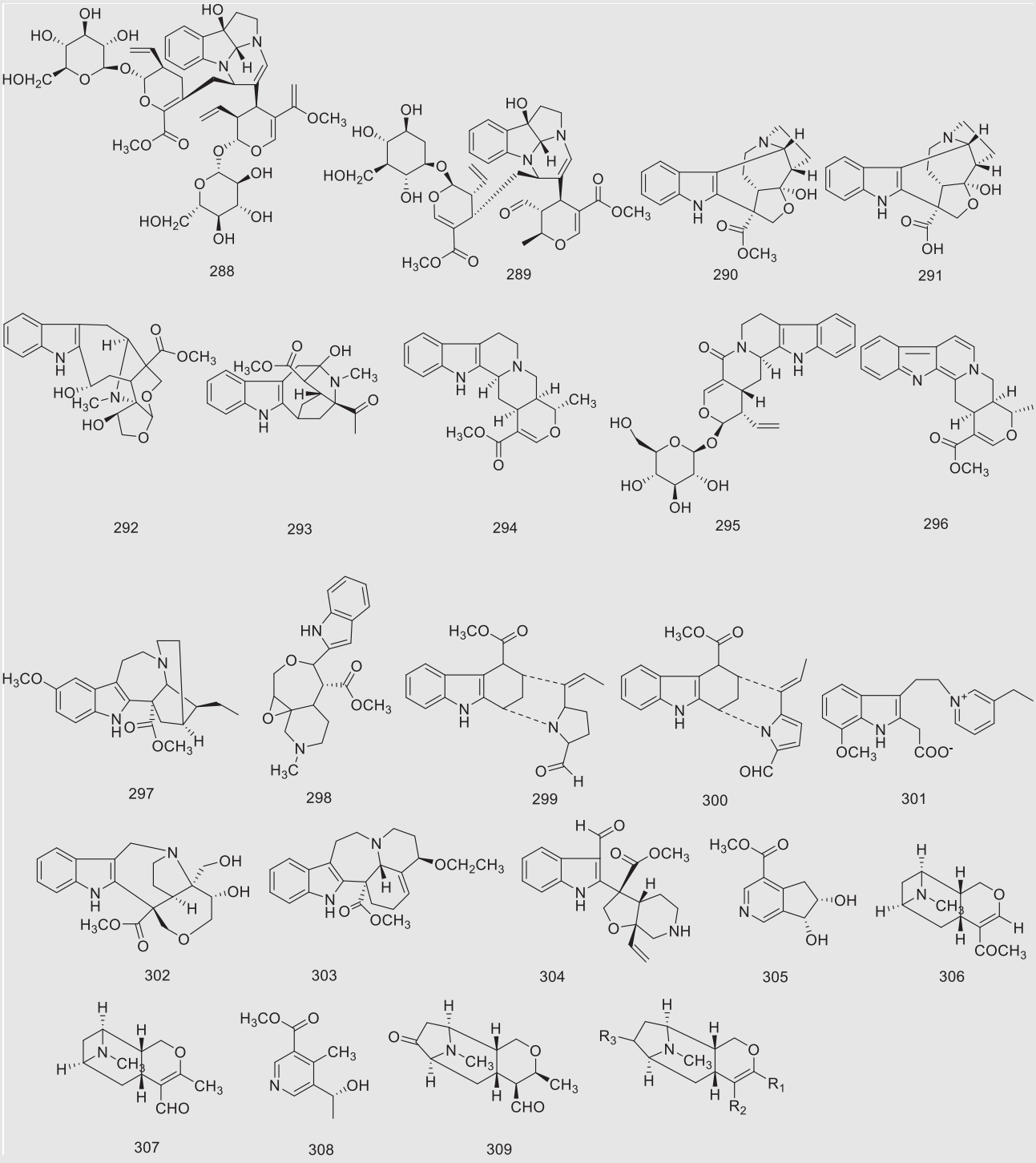


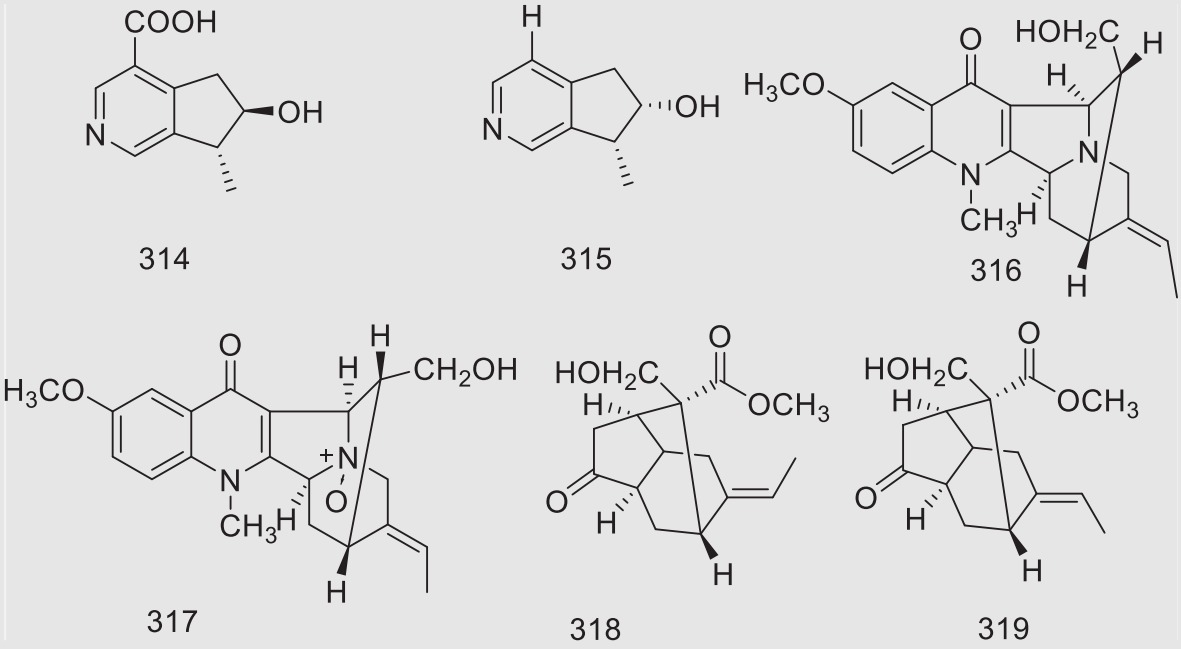
Table 4 The structure of other alkaloids.



No.	compound	R_1	R_2	R_3
310	Angustimaline	H	$COCH_3$	α-OH
311	Angustimaline A	CH_3	CHO	α-OH
312	Angustimaline B	CH_3	CHO	β-OH
313	Angustimaline C	H	$COCH_3$	β-OH

(*continued on next page*)

Table 4 (*continued*)



4.1.1. Corynantheine-strychnine alkaloids (1–157)

Corynantheine-strychnine alkaloids mainly include akuammiline type (**1**–**94**), corynantheine type (**95**–**112**), strychnine (**113**–**146**) and yohimbine types alkaloids (**147**–**157**). Corynantheine-strychnine alkaloids are primarily detected in different parts of *A. scholaris* and *A. macrophylla*.

Among them, akuammiline type alkaloids are the most abundant. The name akuammiline alkaloids was derived from the local name for the Picralima klaineana tree growing in Ghana (formerly called as the Gold Coast) - Akuamma (Henry et al., 1952). These compounds were characterized by a bridging ring framework having a rigid structure (Duan, 2018). Then, most corynantheine alkaloids possess characteristic 6/5/6/6 ring systems. In addition to *A. scholaris* and *A. macrophylla*, corynantheine alkaloids were also available from *Alstonia angustifolia* A. DC. and *A. mairei*. The core structure

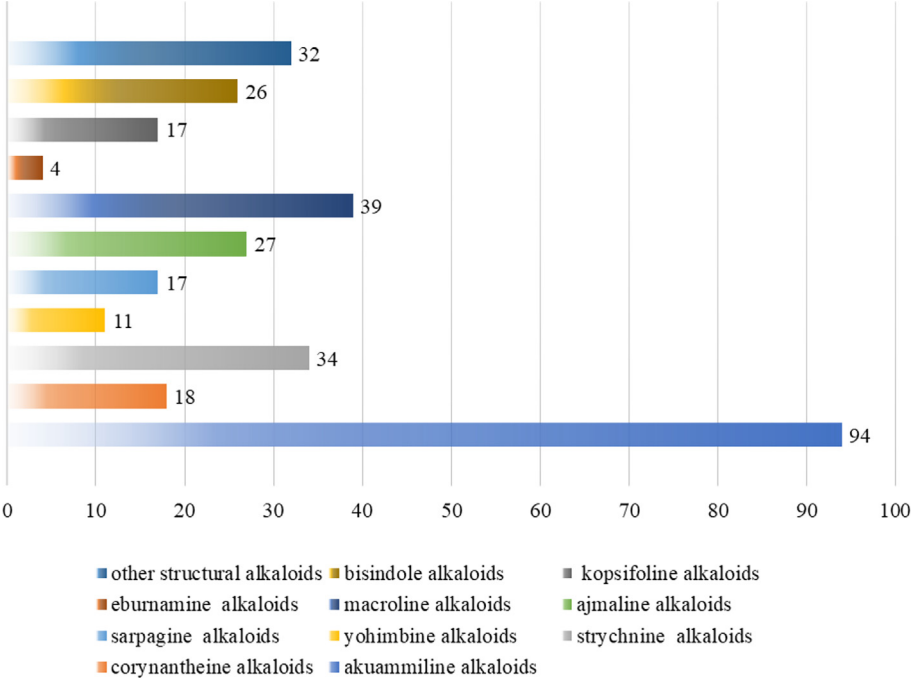


Fig. 1 The proportions of the different types with alkaloids in the genus *Alstonia*.

of strychnine alkaloids was extraordinarily compact with its twenty-four skeletal elements (21 radical, 2 nitrogens, 1 oxygen) forming seven fused and/or bridged rings (**127**) (Zlotos et al., 2022), in addition to contain 6 chiral centers. Yohimbine alkaloids have a less complex structure, possessing characteristic 6/5/6/6/6 ring systems (**147**–**157**) containing 5 chiral centers; the C-3 and C-16 sites are mostly *cis*-type structures in the genus *Alstonia* (**147**–**149 and 156**). In Table 2, the structure of corynantheine-strychnine alkaloids. are listed.

4.1.2. Sarpagine, macroline, and ajmaline alkaloids (158–240)

Sarpagine (**158**–**174**), ajmaline (**175**–**201**) and macroline alkaloids (**202**–**240**) are three structurally related indole alkaloids. Sarpagine alkaloids were mostly produced in the stem bark and leaves of *Alstonia penangiana* Sidiy. (Yeap et al., 2020). Most of the ajmaline alkaloids were in the leaves of *A. macrophylla* and the whole plant of *Alstonia yunnanensis* Diels (Arai et al., 2010; Cao et al., 2012). The macroline alkaloids were also detected in *A. yunnanensis*, *A. macrophylla*, *A. penangiana* and *A. angustifolia* (Kam and Choo, 2004a; Yeap et al., 2018; Kam et al., 2004; Kam and Choo, 2004a). Most of them had four stereocenters, which are C-3, C-5, C-15, and C-16 (**158**–**166 and 203**–**240**) (Lewis, 2006). In Table 3, the relevant structures of the compounds in the sarpagine macroline, and ajmaline alkaloids are shown.

4.1.3. Eburnamine and kopsifoline alkaloids (241–261)

These alkaloids include primarily eburnamine and kopsifoline types, possessing characteristic 6/5/6/5/6 ring systems in the genus *Alstonia*. Eburnamine alkaloids were mainly obtained from the trunk of *Alstonia rostrata* C.E.C. Fisch. and the leaves of *Alstonia pneumatophora* Backer ex Den Berger (**241**–**244**) (Koyama et al., 2010a, 2010b; Zhong et al., 2017). Kopsifoline type alkaloids (**245**–**261**) were mainly present in different parts of *A. angustifolia*, *A. mairei* and *A. yunnanensis* (Goh et al., 1989; Cao et al., 2012; Li et al., 2022a, 2022b; Tan et al., 2010). A summary of the structures relevant to the compounds in the eburnamine and kopsifoline types alkaloids is given in Table 2.

4.1.4. Bisindole alkaloids (262–287)

Bisindole alkaloids are polymerized from the same or different two monoterpene indole alkaloids, which are complicated in structure. The main bisindole alkaloids contained in the genus *Alstonia* were the macroline-ajmaline type (**262**–**264**), macroline-pleiocarpamine type (**265**) (Lim et al., 2013), macroline-macroline type (**266**–**277**) (Lim, et al., 2012), macroline-akuammiline type (**278**–**281**) (Yeap et al., 2018), macroline-corynantheine type (**282**–**284**) and akuammiline-ajmaline type (**281**), etc. A recently conducted study (Wang et al., 2021) showed that rupestrisines A and B (**285**–**287**) were an unprecedented yohimbine-kopsinine type dimeric indole alkaloid. In Table 3, the structures of relevant compounds in bisindole alkaloids are shown.

4.1.5. Other structural alkaloids (288–319)

In addition, there are several other types of indole alkaloids (**288**–**304**). For example, alstrostines A and B derived from the leaves of *A. rostrata* with a 6/5/5/6 tetracyclic system (**288**–**289**) (Cai et al., 2011). Recently two vobasinyl-type alkaloids, alstolarine A (**292**), alstolarine B (**293**), were yielded from the *A. scholaris* leaves (Zhang et al., 2020).

In addition to indole alkaloids, there are some non-indole alkaloids (**305**–**325**). For example, Yeap et al. discovered the first quinolone alkaloids isolated from *Alstonia* (**316**–**317**) (Yeap et al., 2020). The relevant structures of the compounds in other types of alkaloids are shown in Table 4.

4.2. Terpenoids (320–366)

Terpenoids refer to different saturated derivatives that satisfy the $(C_5H_8)_n$-pass formula and its oxygen content. It can be considered as a class of natural compounds consisting of isoprene or isopentane linked in different ways. The skeletons of the terpenoids in the genus *Alstonia* are predominantly iridoids (**320**–**330**) and triterpenes (331–362). Iridoids are mainly distributed in the stem bark of *A. macrophylla* and *A. scholaris*. Iridoids usually form iridoid glycosides with sugars (**320**–**321 and 330**), most of which are glucose, with a variety of physiological activities, such as stimulating gallbladder, strengthening abdomen, and anti-inflammatory. Apart from that, some triterpenoids were isolated in the genus *Alstonia*. These compounds may exist in nature with free form or with glycosides or esters. C-3 position combined with glucose to form triterpene saponins or glucopyranoside esters (Sultana et al., 2020). Such as, lanosta 5ene, 24-ethyl-3-*O*-D-glucopyranoside (**358**) was triterpene saponin; lanosta 5ene 24-ethyl-3-*O*-*β*-D-glucopyranosideester (**359**) was glucopyranoside ester. Triterpenoidesters and glycosides had anti-inflammatory activities (Sultana et al., 2020).

4.3. Flavonoids (363–379)

Flavonoids are widely distributed in nature with common C6-C3-C6 parent nucleus. The C-2, C-3 or C-4′ of flavonoids could be combined with sugars to form flavonoid glycosides (**363**–**366** and **368**–**369**) (Parveen et al., 2010; Nilubon et al., 2007; El-Askary et al., 2013). At present, 16 flavonoids have been collected from the genus *Alstonia*.

4.4. Other compounds (380–392)

In addition to the aforementioned compounds, the genus has also obtained fatty acids (**380**), phenolic acids (**381**–**389**), lignans (**390**–**391**), and esters (**392**). The C-3 position of lignan was linked to glucose to form a glycoside with strong α-glucosidase inhibitory activity (Nilubon et al., 2007).

5. Pharmacological activities

Through extensive modern pharmacological experimental researchs indicated that *Alstonia* played an essential part in the cytotoxicity, anticancer, vasodilatory, β_2-adrenergic receptor (β_2AR) activity, antiplasmodial, anti-inflammatory, antibacterial, antifungal, antioxidant, analgesic and radioprotective activities, etc. The pharmacological activities of genus *Alstonia* can be found in Table 5. Fig. 2 shows the different pharmacological activities of *Alstonia* plants.

Table 5 Pharmacological activities of the genus *Alstonia*.

pharmacological activities	Name	Description	*In vivo*/ *In vitro*	Reference
Antifertility activity	β-amyrin α-amyrin	oral administration of the exact at a dose of 200 mg/day in 60 days did not cause weight loss, while the weight of the test, epididymis, seminal vesicles, and abdominal prostate decreased	*In vivo*	(Gupta et al., 2002)
	Llupiolacetate Rhazine	oral administration of the exact at a dose of 200 mg/day in 60 days did not cause weight loss, while the weight of the test, epididymis, seminal vesicles, and abdominal prostate decreased	*In vivo*	(Gupta et al., 2002)
	Venenative Yohimbine	oral administration of the exact at a dose of 200 mg/day in 60 days did not cause weight loss, while the weight of the test, epididymis, seminal vesicles, and abdominal prostate decreased	*In vivo*	(Gupta et al., 2002)
Anticancer activity	ASE	the combination of 180 mg/kg of ASE and 8 mg/kg of BCLL showed the maximum antitumor effect	*In vivo*	(Jagetia and Baliga, 2004)
		significant increase in reduced glutathione, superoxide dismutase and catalase but decrease in lipid peroxidation was measured in ASE administered experimental groups than the carcinogen treatedcontrol.	*In vivo*	(Jahan et al., 2009)
	ASERS	tumors were relieved at 240 mg/kg body weight, where the maximum antitumor effect was observed. As 240 mg/kg ASERS showed toxic manifestations, the next lower dose of 210 mg/kg was considered as the best effective dose	*In vitro*	(Jagetia and Baliga, 2006)
	Echitamine	*in vivo* researchs with methylanthracene-induced fibroid rats showed that the anticancer activity of echidna extended to the *in vivo* system and a significant decrease in tumor growth was observed	*In vivo*	(Baliga, 2010)
Cytotoxic activity	Alstobrogalin	alstobrogalin was weakly cytotoxic towards MDA-MB-231 and MCF7 cells (IC_{50} 25.3 and 24.1 μM, respectively), but inactive towards MDA-MB-468, SKBR3, and T47D cells (IC_{50} > 30 μM)	*In vitro*	(Krishnan et al., 2019)
	15-hydroxyangustilobine A	15-hydroxyangustilobine A was the active component (IC50 of 26 μ M in MCF-7 cells). 15 hydroxyangustilobine A was shown to cause cell cycle arrest in the G2/M phase (MCF-7 cells) and to trigger apoptosis	*In vitro*	((Spiegler et al., 2021)
	Alstomairine B	demonstrated cytotoxic activity against all tumor cell lines tested (IC_{50} = 9.2 μM)	*In vitro*	(Yan et al., 2017)
	Alstomairine C	exhibited cytotoxic activity against all tumor cell lines tested with an IC_{50} value of 13.0 μM	*In vitro*	(Yan et al., 2017)
	Angustilobine C	had moderate cytotoxicity towards drug-sensitive KB and vincristine-resistant at IC_{50} of 7.76 and 7.33 μg/mL, respectively	*In vitro*	(Ku et al., 2011)
	ScholarisinⅥ	possessed significant cytotoxicities against all tumor cell lines tested, with low IC_{50} values (< 30 μM)	*In vitro*	(Wang et al., 2013)
	Perakine N_4-oxide Raucaffrinoline N_4-oxide Vinorine N_4-oxide	possessed higher cytotoxic activities against astrocytoma and glioma cell (CCF-STTG1, CHG-5, SHG-44 and U_{251}) with lower IC_{50} value than against human skin cancer (SK-MEL-2) and human breast cancer (MCF-7 cells)	*In vitro*	(Cao et al., 2012)0
pharmacological activities	Name	Description	*In vivo*/ *In vitro*	Reference
	Scholarisin I	possessed significant cytotoxicities against all tumor cell lines tested, with low IC_{50} values (< 30 μM)	*In vitro*	(Wang et al., 2013)
	Angustilobine B	angustilobine B was cytotoxic to KB cells	*In vitro*	(Tan et al., 2010)
	Alstonine	alstonine was reported to have antitumor effects in transplantable YC8 lymphoma ascites-bearing mice (BALB/C mice) and in Ehrlich ascites carcinoma-bearing swiss mice	*In vivo*	(Baliga, 2010)
	Vincadifformine Echitoveniline	displayed cytotoxicity against A549 lung cancer cells and the IC_{50} values ranged from 5.6 to 77.1 μM	*In vitro*	(Li et al., 2022a, 2022b)
	Tabersonine Tetrahydroalstonine	displayed cytotoxicity against A549 lung cancer cells and the IC_{50} values ranged from 5.6-77.1 μM	*In vitro*	(Li et al., 2022a, 2022b)
	16- methoxytabersonine 19-acetoxy-11-methoxytabersonine	displayed cytotoxicity against A549 lung cancer cells and the IC_{50} values ranged from 5.6-13.1 μM	*In vitro*	(Li et al., 2022a, 2022b)
	19-hydroxytabersonine Vandrikidine	displayed cytotoxicity against A549 lung cancer cells and the IC_{50} values ranged from 5.6-77.1 μM	*In vitro*	(Li et al., 2022a, 2022b)

Table 5 (*continued*)

pharmacological activities	Name	Description	*In vivo*/ *In vitro*	Reference
	Isovallesiachotamine	had potent cytotoxicity against A549 lung cancer cells and the IC_{50} values ranged from 5.6-13.1 μM	*In vitro*	(Li et al., 2022a, 2022b)
	Angustilongine A Angustilongine B	displayed significant *in vitro* growth inhibitory activity against a range of human cancer cell lines, including KB, vincristine-resistant KB, PC-3, LNCaP, MCF7, MDA-MB-231, HT-29, HCT 116, and A549 cells within the range of 0.3-8.3 Mm	*In vitro*	(Yeap et al., 2018)
	Alstomairine D Alstomairine G	displayed cytotoxicity against A549 lung cancer cells and IC_{50} values ranged from 5.6 to 77.1 μM	*In vitro*	(Li et al., 2022a, 2022b)
	Lochnericine Alstomairine E	displayed cytotoxicity against A549 lung cancer cells and IC_{50} values ranged from 5.6 to 13.1 μM	*In vitro*	(Li et al., 2022a, 2022b)
	Yohimbine-17-*O*-3′,4′,5′-Trimethoxybenzoate	displayed cytotoxicity against A549 lung cancer cells and IC_{50} values ranged from 5.6 to 13.1 μM	*In vitro*	(Li et al., 2022a, 2022b)
	(*E*)-16-formyl-5α-Methoxystrictamine	displayed marked cytotoxicities against all the tumor cell lines tested and IC_{50} value was low (< 30 μM)	*In vitro*	(Wang et al., 2013)
	Alstomairine D Alstomairine E	showed cytotoxicity against A549 lung cancer cells tested. The IC_{50} of alstomairines D and E ranged from 5.6 to 77.1 μM and 5.6 to 13.1 μM, respectively	*In vitro*	(Li et al., 2022a, 2022b)
pharmacological activities	Name	Description	*In vivo*/*In vitro*	Reference
Vasorelaxant activity	Undulifolin	with uleine skeleton showed moderate activity (33.3% at 3×10^{-5} M)	*In vitro*	(Koyama et al., 2008)
	Alstilobanine A	possessing angustilodine skeleton without an ether linkage showed more potent activity (44.3% at 3×10^{5} M)	*In vitro*	(Koyama et al., 2008)
	Alstilobanine C	showed moderate activity (28.0% at 3×10^{-5} M) with uleine skeleton	*In vitro*	(Koyama et al., 2008)
	Alstilobanine B	with uleine skeleton showed moderate activity (21.2% at 3×10^{-5} M)	*In vitro*	((Koyama et al., 2008)
	Alstilobanine E	with an ether linkage showed moderate activity the weakest activity (6.8% at 3×10^{-5} M)	*In vitro*	(Koyama et al., 2008)
	Alstilobanine D	showed weak activity (10.0% at 3×10^{-5} M) against phenylephrine (PE, 3×10^{7} M)-induced contractions ofthoracic rat aortic rings with endothelium	*In vitro*	(Koyama et al., 2008)
	Alstonamic acid	possessing *seco* skeleton showed a weak activity (35.0% at 3×10^{-5} M)	*In vitro*	(Koyama et al., 2008)
	6,7-secoangustilobine B	showed weak activity (7.0% at 3×10^{-5} M) against phenylephrine (PE, 3×10^{7} M)-induced contractions ofthoracic rat aortic rings with endothelium	*In vitro*	(Koyama et al., 2008)
	Alstiphyllanine A	showed vasorelaxant activity against phenylephrine induced contraction of isolated rat aorta (70% at 3×10^{-5} M)	*In vitro*	(Hirasawa et al., 2009)
	Alstiphyllanine B	had vasorelaxant activity against phenylephrine-induced constriction in isolated rat aorta (35% at 3×10^{-5} M)	*In vitro*	(Hirasawa et al., 2009)
	Alstiphyllanine C	showed vasorelaxant activity against phenylephrine-induced constriction in isolated rat aorta (40% at 3×10^{-5} M)	*In vitro*	(Hirasawa et al., 2009)
	Alstiphyllanine D	had vasorelaxant activity against phenylephrine-induced constriction in isolated rat aorta (42% at 3×10^{-5} M)	*In vitro*	(Hirasawa et al., 2009)
	Vincamajine-17-*O*-veratrate	showed that they relaxed phenylephrine (PE)-induced contractions	*In vitro*	(Arai et al., 2012)
	Vincamajine-17-*O*-3′,4′,5′-Trimethoxybenzoate	showed that they relaxed phenylephrine (PE)-induced contractions	*In vitro*	(Arai et al., 2012)
	AlstiphyllanineI	showed that they relaxed phenylephrine (PE)-induced contractions	*In vitro*	(Arai et al., 2012)
	AlstiphyllanineJ	showed that they relaxed phenylephrine (PE)-induced contractions	*In vitro*	(Arai et al., 2012)
	AlstiphyllanineL	showed that they relaxed phenylephrine (PE)-induced contractions	*In vitro*	(Arai et al., 2012)

(*continued on next page*)

Table 5 (*continued*)

pharmacological activities	Name	Description	*In vivo*/*In vitro*	Reference
	AlstiphyllanineM	showed that they relaxed phenylephrine (PE)-induced contractions	*In vitro*	(Arai et al., 2012)
	AlstiphyllanineN	showed that they relaxed phenylephrine (PE)-induced contractions	*In vitro*	(Arai et al., 2012)
	AlstiphyllanineO	showed that they relaxed phenylephrine (PE)-induced contractions	*In vitro*	(Arai et al., 2012)
pharmacological activities	Name	Description	*In vivo*/*In vitro*	Reference
	Alstolarine A	exhibited promising vasorelaxant activities against KCl-induced contraction of rat renal arteries with EC_{50} values of 4.6 μM	*In vitro*	(Zhang et al., 2020)
	Alstolarine B	exhibited promising vasorelaxant activities against KCl-induced contraction of rat renal arteries with EC_{50} values of 6.7 μM	*In vitro*	(Zhang et al., 2020)
	Melosline C	exhibited potent vasorelaxant activityon renal arteries with EC_{50} value of 38.62 $\mu mol \cdot L^{-1}$	*In vitro*	(Zhang et al., 2019)
	Melosline D	exhibited potent vasorelaxant activityon renal arteries with EC_{50} value of 41.43 $\mu mol \cdot L^{-1}$	*In vitro*	(Zhang et al., 2019)
	Alstoschonoid A	showed significant vasorelaxant activity with relaxation rates above 90% at 200 μM and exhibited moderate vasorelaxant activity with IC_{50} values between 41.87 and 93.30 μM by further studies	*In vitro*	(Zhang et al., 2022)
	Alstochonine B		*In vitro*	(Zhang et al., 2022)
	Methyl 4- [2-hydroxy-2-(4-hydroxy-3-methoxyphenyl) -l (hydroxymethyl) ethyl] ferulate	exhibited significant vasodilatory activity at 200 μM with a relaxation rate of > 90% and by further studies showed moderate vasodilatory activity having IC50 values between 41.87 and 93.30 μM	*In vitro*	(Zhang et al., 2022)
	(-) - (7R,7′R,7″R,8S,8′S,8″S)-4′,4″-dihydroxy-3,3′,3″,5-tetramethoxy-7, 9′:7′,9-diepoxy-4,8″-oxy-8, 8′-sesquineolignan-7″,9″-diol	exhibited significant vasodilatory activity at 200 μM with a relaxation rate of > 90% and by further studies showed moderate vasodilatory activity having IC50 values between 41.87 and 93.30 μM	*In vitro*	(Zhang et al., 2022)
	(-) - (7R,7′R,7″R,8S,8′S,8″S)-4′,4″-dihydroxy-3,3′,3″,5,5′-pentamethoxy-7,9′:7′,9-diepoxy-4,8″-oxy-8,8′-sesquineolignan-7″,9″-diol	exhibited significant vasodilatory activity at 200 μM with a relaxation rate of > 90% and by further studies showed moderate vasodilatory activity having IC50 values between 41.87 and 93.30 μM	*In vitro*	(Zhang et al., 2022)
	Alstochonine A	showed moderate vasorelaxant activity (IC_{50} values of 93.30 ± 10.81)	*In vitro*	(Zhang et al., 2022)
Antifungal activity	Δ^3-alstovenine	Δ^3-alstovenine at 250–1000 mg/L inhibited the spore germination of most of the tested fungi	*In vitro*	(Singh et al., 1999)
	Tricin-4′-O-β-L-arabinoside	showed significant antifunga activity against salmonella typhimurium (MTCC-98), candida albicans (IAO-109)	*In vitro*	(Parveen et al., 2010)
	The leaves extract of *A. scholaris*	the extract was applied against eight five fungal strains	*In vitro*	Altaf et al., 2019
pharmacological activities	Name	Description	*In vivo*/*In vitro*	Reference
	The leaves and bark of *A. venenata*	Fungal studies were conducted on crude extracts of plants to test their fungicidal properties against human pathogens, plant pathogens and industrially important strains of fungi	*In vitro*	(Ray and Dutta, 1973)
	Scholarisin I	demonstrated antifungal activity for two fungi (*G. pulicaris* and *C. nicotianae*) and the MIC values were 0.64–0.69 mM	*In vitro*	(Wang et al., 2013)
	ScholarisinⅡ	demonstrated antifungal activity for two fungi (*G. pulicaris* and *C. nicotianae*) and the MIC values were	*In vitro*	(Wang et al., 2013)

Table 5 (*continued*)

pharmacological activities	Name	Description	*In vivo*/ *In vitro*	Reference
		1.37-1.44 mM		
	ScholarisinIII	demonstrated antifungal activity for two fungi (*G. pulicaris* and *C. nicotianae*) and the MIC values were 1.80-1.91 mM	*In vitro*	(Wang et al., 2013)
	(3R,5S,7R,15R,16R,19E)-scholarisine F	demonstrated antifungal activity for two fungi (*G. pulicaris* and *C. nicotianae*) and the MIC values were 1.55-1.71 mM	*In vitro*	(Wang et al., 2013)
Antibacterial activity	The crude methanolic extracts of ASE	exhibiting improved and broader spectrum of antibacterial activity	*In vitro*	(Khan et al., 2013)
	Scholarisine T	exhibited significant antibacterial effects on Escherichia coli and MIC value was 0.78 μg/mL.	*In vitro*	(Yu et al., 2018)
	Scholarisine U	showed remarkable antibacterial activity against Bacillus subtilis and MIC value was 3.12 μg/mL	*In vitro*	(Yu et al., 2018)
	Scholarisine V	exhibited significant antibacterial effects on Escherichia coli and MIC value was 0.78 μg/mL exhibited significant antibacterial effects on Escherichia coli and MIC value was 0.78 μg/mL.	*In vitro*	(Yu et al., 2018)
	Tricin-4′-*O*-*β*-L-arabinoside	showed antibacterial activity against staphylococcus aureus (IAO-SA-22), escherichia coli (K-12)	*In vitro*	(Parveen et al., 2010)
Antimicrobial activity	Tricin-4′-*O*-*β*-L-arabinoside	showed significant antimicrobial activity using agar well diffusion method	*In vitro*	(Parveen et al., 2010)
	The crude extract of AM	antimicrobial activity was exhibited against various strains of *Escherichia coli*, *Staphylococcus aureus, Staphylococcus saprophyticus*, *Proteus mirabilis*, *Trichophyton mentagrophytes* var *mentagrophytes, MicrosporμM gypseum, Streptococcus faecalis* and *Trichophyton rubrum*. The minimum inhibitory concentration (MIC) values range from 64 to 1000 μg/ml for bacteria and 32-128 mg/ml for dermatophytes However, the strains of *Pseudomonas* aeruginosa, *Klebsiella sp*. and *Vibrio cholerae* demonstrated resistance to the extract treatment up to 2000 μg/ml, while two yeasts were resistant even at a concentration of 128 mg/ml	*In vitro*	(Chattopadhyay et al., 2004)
	ASE	the current study on *A. scholaris* revealed valuable phytochemical constituents with significant antimicrobial properties and further suggested that the minimum inhibitory concentration (MIC) values of the extracts should be investigated in future studies	*In vitro*	(Altaf et al., 2019)
pharmacological activities	Name	Description	*In vivo*/ *In vitro*	Reference
Marginal activity	Crude alkaloidal extracts from the roots	crude extracts of alkaloids obtained from plant roots exhibited weak activity against experimental U14 tumors in mice	*In vivo*	(Chen et al., 1983)
SGLT inhibitory activity	Alstiphyllanine E	indicated inhibitory activity against SGLT1 and SGLT2 with 60.3% and 80.5% inhibition values	*In vitro*	(Arai et al., 2010)
	Burn-amine-17-*O*-3′,4′,5′-trimethoxybenzoate	indicated inhibitory activity against SGLT1 and SGLT2 with 53.0% and 87.3% inhibition values	*In vitro*	(Arai et al., 2010)
	Alstiphyllanine F	indicated inhibitory activity against SGLT1 and SGLT2 with 65.2% and 103.8% inhibition values	*In vitro*	(Arai et al., 2010)
	AlstiphyllanineD	indicated inhibitory activity agains $SGLT_1$ and $SGLT_2$ with 89.9% and 101.4% inhibition values	*In vitro*	(Arai et al., 2010)
	10-methoxy-N_1-methylburnamine-17-*O*-veratrate	indicated inhibitory activity agains $SGLT_1$ and $SGLT_2$ with 98.5% and 102.6% inhibition values	*In vitro*	(Arai et al., 2010)
β_2AR activity	*Z*-alstoscholarine	compared with the control, *Z*-alstoscholarine showed significant effects	*In vitro*	(Hou et al., 2012a)
	Akuammidine	compared with the control, akuammidine showed significant effects	*In vitro*	(Hou et al., 2012a)
	19,20-(*E*)-vallesamine	compared with the control, 19,20-(*E*)-vallesamine showed significant effects	*In vitro*	(Hou et al., 2012a)
	E-alstoscholarine	compared with the control, *E*-alstoscholarine showed significant effects	*In vitro*	(Hou et al., 2012a)
	12-hydroxy-echitamidine	compared with the control, HENO showed significant effects	*In vitro*	(Hou et al., 2012a)

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Table 5 (*continued*)

pharmacological activities	Name	Description	*In vivo*/ *In vitro*	Reference
	N_b-oxide (HENO)			
	Scholaricine	displayed much poorer β_2 AR activation	*In vitro*	(Hou et al., 2012a)
	Picrinine	displayed much poorer β_2 AR activation	*In vitro*	(Hou et al., 2012a)
	11-methoxygelsemamide	indicated potential activity for β_2 AR	*In vitro*	(Hou et al., 2012b)
	Alstomaline	displayed potential activity for β_2 AR	*In vitro*	(Hou et al., 2012b)
	Alloyohimbine	displayed potential activity for β_2 AR	*In vitro*	(Hou et al., 2012b)
	19*E*-Vallesamine	displayed potential activity for β_2 AR	*In vitro*	(Hou et al., 2012b)
	Pseudoyohimbine	indicated potential activity for β_2 AR	*In vitro*	(Hou et al., 2012b)
	Picrinine	indicated potential activity for β_2 AR	*In vitro*	(Hou et al., 2012b)
	Picralinal	indicated potential activity for β_2 AR	*In vitro*	(Hou et al., 2012b)
Spasmolytic activity	The crude extract of *A. scholaris*	in isolated rabbit jejunum preparation, the As. Cr produced inhibition of spontaneous and high K^+ (80 mM) -induced contractions, with respective EC_{50} values of 1.04 (0.73-1.48) and 1.02 mg/mL (0.56-1.84; 95% CI), thus showing spasmolytic activity mediated possibly through calcium channel blockade (CCB)	*In vitro*	(Shah et al., 2010)
pharmacological activities	Name	Description	*In vivo*/ *In vitro*	Reference
	Akuammidine	the EC_{50} value for the spasmolytic activity was 243.9 μmol/L	*In vitro*	(Hou et al., 2012a)
	The total alkaloidal extract of *A. scholaris*	the EC_{50} value for the spasmolytic activity of the total alkaloidal extract (500 μg/mL) was 267.5 μmol/L	*In vitro*	(Hou et al., 2012a)
	Z-alstoscholarine	the EC_{50} value for the spasmolytic activity was 137.5 μmol/L	*In vitro*	(Hou et al., 2012a)
	19,20-(*E*)-vallesamine	the EC_{50} value for the spasmolytic activity was 74.8 μmol/L	*In vitro*	(Hou et al., 2012a)
Immunostimulating activity	Ethanol extractions of *A. scholaris* bark	*A. scholaris* bark aqueous extracts at 50 and 100 mg/kg of bw were able to stimulate non– specific immune response	*In vivo*	(Iwo et al., 2000)
	Alstiphyllanine A	displayed intermediate-level antiplasmodial activity against *Plasmodium falciparum*	*In vitro*	(Hirasawa et al., 2009)
	Echitamine	exhibited moderate activity against *P. falciparum* K-1 (IC_{50} < 30 μM); showed moderate activity against *P. falciparum* NF54 A19A (IC_{50} values of 11.07 μM)	*In vitro*	(Kanyanga et al., 2019)
	6,7-seco-angustilobine B	exhibited moderate activity against *P. falciparum* K-1 (IC_{50} < 30 μM); showed moderate activity against *P. falciparum* NF54 A19A (IC_{50} values of 21.26 μM)	*In vitro*	(Kanyanga et al., 2019)
	β-amyrin	exhibited moderate activity against *P. falciparum* K-1 (IC_{50} < 30 μM); showed moderate activity against *P. falciparum* NF54 A19A (IC_{50} values of 40.70 μM)	*In vitro*	(Kanyanga et al., 2019)
	The combination stem barks of *K. ivorensis* and *A. boonei*	exhibited antimalarial activity in a mouse model of malaria. In mice treated with the combination therapy at 200 mg/kg/day, parasitemia values were 6.2% ± 1.7 and 6.5% ± 0.8 compared to 10.8% ± 1.3 and 12.0% ± 4.0 in the control group ($p < 0.01$). Doubling the dose of the extract did not significantly increase the parasitemia inhibition	*In vitro*	(Tepongning et al., 2011)
	Alstiphyllanine B	displayed intermediate-level antiplasmodial activity against *Plasmodium falciparum*	*In vitro*	(Hirasawa et al., 2009)
	Alstiphyllanine C	displayed intermediate-level antiplasmodial activity against *Plasmodium falciparum*	*In vitro*	(Hirasawa et al., 2009)
	Alstiphyllanine D	displayed intermediate-level antiplasmodial activity against *Plasmodium falciparum*	*In vitro*	(Hirasawa et al., 2009)
	Boonein	boonein exhibited anti-*P. falciparum* K-1 activity with IC50 >64μM; boonein did not response to *P. falciparum* NF54 A19A	*In vitro*	(Kanyanga et al., 2019)
	Akuammicine *N*-oxide	had antiplasmodial activityagainst *Plasmodium falciparum* (K1, multidrug-resistance strain) with IC_{50} = 63.2 μg/mL	*In vitro*	(Salim et al., 2004)
	N_b-demethylalstogustine	had antiplasmodial activityagainst *Plasmodium falciparum* (K1, multidrug-resistance strain) with IC_{50} = 6.75 μg/mL	*In vitro*	(Salim et al., 2004)
pharmacological activities	Name	Description	*In vivo*/ *In vitro*	Reference

Table 5 (*continued*)

pharmacological activities	Name	Description	*In vivo*/*In vitro*	Reference
AChE inhibitory activity	Alstolarine B	displayed moderate AChE inhibitory activity at an IC_{50} value of 19.3 μM (IC50 for control tacrine = 0.3 μM).	*In vitro*	(Zhang et al., 2020)
	Naresuanoside	displayed moderate AChE and butyrylcholinesterase (BChE) inhibitory effects	*In vitro*	(Changwichit et al., 2011)
Anti-inflammatory activity	12-ursene-2,3,18,19-tetrol,28 acetate	triterpenoidesters and glycosides showed anti-inflammatory activity	*In vivo*	(Sultana et al., 2020)
	Alstoprenyol	triterpenoidesters and glycosides showed anti-inflammatory activity	*In vivo*	(Sultana et al., 2020)
	3*β*-hydroxy-28-*β*-acetoxy-5-olea triterpene	triterpenoidesters and glycosides showed anti-inflammatory activity	*In vivo*	(Sultana et al., 2020)
	TA Picrinine Scholaricine 19-epischolaricine Vallesamine	the aggregation and invasion of inflammatory cells in lung tissue were inhibited, and lung tissue damage was alleviated. Oxygen saturation was increased and interleukin-1*β*, monocyte-chemo attractive peptide 1, interleukin −11, matrixmetalloproteinase-12, transforming growth factor-*β* and vascular endothelial growth factor were significantly decreased. The levels of elastin were significantly increased and fibronectin was decreased. the expression of Bcl-2 was significantly increased and the levels of nuclear factor-κB and *β*-catenin were decreased	*In vivo*	(Zhao et al., 2020a)
	Perakine N_4-oxide Raucaffrinoline N_4-oxide Vinorine N_4-oxide	perakine N_4-oxide, rauffrin N_4-oxide and vinorine N_4-oxided selectively inhibited Cox-2 with 94.07%, 88.09% and 94.05% inhibition rates, respectively	*In vitro*	(Cao et al., 2012)
	Scholarisin I	exhibited inhibition of Cox-2 selectively (> 90%) comparable to the standard drug NS-398	*In vitro*	(Wang et al., 2013)
	Methanolic extract of dried leaves of AM	the extract at a concentration of 200 mg/kg and 400 mg/kg, p.o. and its fractions at 25 mg/kg and 50 mg/kg, p.o. showed the significant dose depen-dent antiinflammatory activity in carrageenan and dextran-induced rats hind paw edema (acutemodels) as well as in cotton pellet-induced granuloma (chronic model) in rats	*In vivo*	Arunachalam et al., 2002
	24-ethyl-3-*O*-*β*-D-glucopyranoside	triterpenoidesters and glycosides showed anti-inflammatory activity	*In vivo*	(Sultana et al., 2020)
	Lanosta,5ene,24-ethyl-3-*O*-*β*-D-glucopyranosideester	triterpenoidesters and glycosides showed anti-inflammatory activity	*In vivo*	(Sultana et al., 2020)
	Lupeol acetate	triterpenoidesters and glycosides showed anti-inflammatory activity	*In vivo*	(Sultana et al., 2020)
pharmacological activities	Name	Description	*In vivo*/*In vitro*	Reference
	3*β*-hydroxy-24-nor-urs-4,12,28-triene triterpene	triterpenoidesters and glycosides showed anti-inflammatory activity	*In vivo*	(Sultana et al., 2020)
	(±)-scholarisine II	(±)-scholarisine II selectivelyinhibited the inducible COX-2 but not COX-1, also significantly inhibited 5-LOX, comparable to positive controls	*In vivo*	(Cao et al., 2012)
	The methanol extract of the stem bark of *A. boonei*	extract showed significant inhibition of carrageenan-induced paw edema and cotton ball granuloma in rats, and exhibited anti-arthritic activity ($P < 0.05$). Acetic acid-induced peritoneal vascular permeability in mice was also inhibited.	*In vivo*	(Olajide et al., 2000)
	The ethanolic bark extract of ASE	ASE exerted a powerful anti-inflammatory activity, with ASE-treated cells showing MCP-1 levels 928.8 ± 64.0 pg/mL (at 100 ppm) and 1074.0 ± 82.2 pg/mL (at 500 ppm) lower than control cells	*In vitro*	(Chandrashekar et al., 2012)
	ScholarisinⅥ	exhibited inhibition of Cox-2 selectively (> 90%) comparable to the standard drug NS-398	*In*	(Wang et al., 2013)

(*continued on next page*)

Table 5 (*continued*)

pharmacological activities	Name	Description	*In vivo*/*In vitro*	Reference
			vitro	
	(*E*)-16-formyl-5α-methoxystrictamine	exhibited inhibition of Cox-2 selectively (>90%) comparable to the standard drug NS-398	*In vitro*	(Wang et al., 2013)
α-glucosidase inhibitory activity	Quercetin 3-*O*-β-D-xylopyranosyl (1‴ → 2″)-*β*-D-galactopyranoside	showed the high inhibitory activity only against maltase at an IC_{50} value of 1.96 mM	*In vitro*	(Nilubon et al., 2007)
	(-)-lyoniresinol 3α-*O*-β-D-glucopyranoside	exhibited inhibitory activity against not only sucrase but also maltase as well with IC_{50} values of 1.95 and 1.43 mM, respectively	*In vitro*	(Nilubon et al., 2007)
	(+)-lyoniresinol 3α-*O*-β-D-glucopyranoside	showed far lower inhibition against sucrase and maltase	*In vitro*	(Nilubon et al., 2007)
Anti-melanogenesis activity	Alpneumine E	showed anti-melanogenesis in B16 mousemelanoma cells with IC_{50} values of 71.4 μM	*In vitro*	(Koyama et al., 2010a)
	AlpneumineG Vincamine Apovincamine	demonstrated an anti-melanogenic activity in B16 mouse melanoma cells at IC50 values of 58.3, 68.9 and 49.8 μM.	*In vitro*	(Koyama et al., 2010a)
Antidiabetic and antihyperlipidemic activities	EEAS	streptozotocin-induced diabetic rats were treated orally with EEAS (100, 200 and 400 mg/kg). Moreover, EEAS not only significantly reduced blood glucose levels, glycated hemoglobin and lipid peroxidation ($P < 0.001$)	*In vivo*	(Arulmozhi et al., 2010)
DRAK2 inhibitory activity	Alstonlarsine A	demonstrated DRAK2 inhibitory activity at an IC_{50} value of 11.65 ± 0.63 μM	*In vitro*	(Zhu et al., 2019)
pharmacological activities	Name	Description	*In vivo*/*In vitro*	Reference
	Alstoscholarisine K	alstoscholarisine K had superior antibacterial activity than berberine (37.50 μg/mL), indicating an MIC value of 18.75 μg/mL againstis *Escherichia coli*	*In vitro*	(Yu et al., 2021)
Reversed multidrug resistance	Alstolucine A Alstolucine B	were found to reverse multidrug resistance in vincristine-resistant KB (VJ300) cells	*In vitro*	(Tan et al., 2010)
	Alstolobine A Alstolucine F	were found to reverse multidrug resistance in vincristine-resistant KB (VJ300) cells	*In vitro*	(Tan et al., 2010)
	N_4-demethylalstogustine *19-epi-*N_4-demethylalstogustine	were found to reverse multidrug resistance in vincristine-resistant KB (VJ300) cells	*In vitro*	(Tan et al., 2010)
	Scholaricine	were found to reverse multidrug resistance in vincristine-resistant KB (VJ300) cells	*In vitro*	(Tan et al., 2010)
Analgesic activity	Scholarisine I (±)-scholarisine II	at 10, 20, 40 and 80 mg/kg, scholarisine I and (±)-scholarisine II reduced the writhing reflex in mice by 48.4, 40.1, 36.6 and 49.5%, respectively, comparable to aspirin at 200 mg/kg (57.2%). At doses of 50 and 100mg/kg, scholarisine I and (±)-scholarisine II decreased xylene-induced ear edemain mice by 46.0 and 41.2%, comparable to aspirin at 200 mg/kg (45.7%)	*In vitro*	(Cao et al., 2012)
	The methanol extract of the Stem bark of *A. boonei*	the extract of *A. boonei* produced significant analgesic effect in non-inflammatory pain and inflammatory pain	*In vivo*	(Olajide et al., 2000)
	methanol extract of *A. macrophylla* leaves (MEAML)	MEAML also exhibited significant dose-dependent analgesic activity, with a significant increase in response time for all doses tested in both tests	*In vitro*	(Chattopadhyay et al., 2004)
Antioxidant	EEAS	significantly reduced the levels of lipid peroxidation and bone marrow peroxidation in joint tissues and	*In vivo*	(Arulmozhi et al., 2011)

Table 5 (*continued*)

pharmacological activities	Name	Description	*In vivo*/ *In vitro*	Reference
activity		increasing the levels of superoxide dismutase, glutathione peroxidase and antioxidant enzymes glutathione		
	AM	AM crude extracts were found to be effective free radical scavengers given that the IC_{50} value was low at 0.71 mg/mL	*In vivo*	(Tan et al., 2019)
	The root bark extract of *A. boonei*	ethyl acetate fraction displayed superior antioxidant activity with an IC_{50} of 54.25 µg/mL compared to 121.79 and 141.67 µg/mL for acetone and methanol fractions, respectively. The crude precipitate and isolated compound revealed IC_{50} of 364.39 and 354.94 µg/mL, respectively	*In vivo*	(Obiagwu et al., 2014)
Antipyretic activity	The methanol extract of the stem bark of *A. boonei*	the extract also significantly reduced hyperthermia in mice.	*In vivo*	(Olajide et al., 2000)
Anti-HBV activity	The crude extract of *A. venenata* bark	shows activity against HBV in HepG2.2.15 cell line	*In vitro*	(Bagheri et al., 2020)
pharmacological activities	Name	Description	*In vivo*/ *In vitro*	Reference
CNS activity	MEAML	it was confirmed by spontaneous activity, touch, pain and vocal responses that the methanolic extract of MEAML at doses not < 100 mg/kg affects the general behavioral characteristics of the treated animals. The same effect was observed for its fractions, such as fraction B	*In vivo*	(Chattopadhyay et al., 2004)
Anti-HSV and	17-nor-excelsinidine	strictamine was found to possess better activity against HSV and adenovirus than those of 17-nor-	*In vitro*	(Zhang et al., 2014)
Anti-HDV activity	Strictamine	excelsinidine, with EC_{50} values of 0.36 and 0.28 l g/mL and CC_{50} values of 5.01 and 3.31 l g/mL, which led to SI values of 13.93 and 11.82, respectively	*In vitro*	(Zhang et al., 2014)
Antidiarrhoeal activity	ASE	at doses of 100–1000 mg/kg, it exerted 31–84% protection against castor oil-induced diarrhea in mice, similar to that of loperamide	*In vivo*	(Shah et al., 2010)
		regarding both the 100 and 200 mg/kg bw at all oral doses, significant dose-dependent antidiarrheal activity was shown for all *A. congensis* samples, with a significant increase in time to onset and varying decreases in all other diarrheal parameters in both models compared to the untreated group	*In vitro*	(Lumpu et al., 2012)
Radioprotective activity	The hydro-alcoholic extracted material from the bark of ASE	the results showed more favorable postirradiation changes in the number of peripheral blood constituents in animals treated with ASE before irradiation in comparison with irradiated control mice	*In vivo*	(Gupta et al., 2008)
	The bark of ASE	the extract was found to re store the total leucocytes and differential leucocytes (lymphocytes, monocytes, neutrophils, and non-neutrophilic granulocytes) count in the *A. scholaris* extract pretreated animals as compared to the irradiated control group. The data clearly indicate that the *A. scholaris* extract significantly reduced the deleterious bioeffects of radiation on peripheral blood	*In vivo*	(Gupta et al., 2011)
Anti-pulmonary fibrosis	TA	the administration of TA significantly improved pathological changes in the lungs, reducing levels of Krebs von den Lungen-6, lactate dehydrogenase, transforming growth factor-β, hydroxyproline, type I collagen, and malondialdehyde, and increasing superoxide dismutase activity in serum and lung tissue	*In vivo*	(Zhao et al., 2020c; Zhao et al., 2020a)

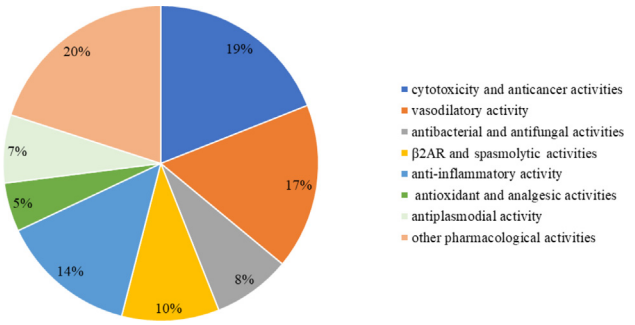

Fig. 2 The different pharmacological activities of *Alstonia* plants.

5.1. Cytotoxicity and anticancer activities

In 2017, cancer was the second most common cause of mortality worldwide and a major load on wellness systems. Several researches reported that in laboratory animal models, compounds possessing antioxidant or anti-inflammatory properties, sunch as certain phytochemicals, had been found to inhibit tumorigenesis, promotion and development (Chesson and Collins, 1997; Hocman, 1989). According to the statistics of literature, the crude extracts and compounds of *Alstonia* plants had anti-cancer effects in numerous *in vivo* and *in vitro* experiments. ASERS (the alkaloid fraction of *A. scholaris*) was considered the most efficientt doses of 210 mg/kg (Jagetia and Baliga, 2006). This opens the way for the genus *Alstonia* to be an anti-tumor, attracting the attention of many scholars. Moreover, Baliga reported that echitamine (**35**) had cytotoxic effects on HeLa, HepG2, HL60 and other models (Baliga, 2010). Moreover, one recent study (Spiegler et al., 2021) further demonstrated that *A. boonei* extracts were effective for common pediatric tumor types (leukemias and Ewing sarcoma). 15-hydroxyglutathione A (**78**) was identified as the effective ingredient of *A. boonei* extract using bioassay-guided approach. The IC_{50} value for MCF-7 cells was 26 μM. This is the first time that compounds of *A. boonei* are mentioned. Preliminary mechanistic studies demonstrated that in G2/M phase, apoptosis increased and cell cycle arrested.

5.2. Vasodilatory activity

Vasodilators help treat cerebral vasospasm and hypertension as well as improve peripheral circulation. More and more species of genus *Alstonia* are being identified to have vasorelaxant activities. Arai et al. found that vincamedine (**185**) showed potent vasodilatory activity. The mechanism of vincamedine (**185**) might be the inhibition of Ca^{2+} influx through volte-dependent Ca^{2+} channels (VDCs) and/or receptor-operated Ca^{2+} channels (ROCs) (Arai et al., 2012). In addition to the above, they observed the presence of two substituents at the N-1 and C-17 positions, which may be critical in showing vasodilatory activity (Arai et al., 2012)(). Obviously, the activity of compounds varies with their structure.

5.3. Antibacterial and antifungal activities

Multidrug resistance is a leading challenge in both developed and developing countries. There is an urgent need to tackle multi-drug resistance. Through many experiments, some scholars found that *Alstonia* species had antibacterial and antifungal activity. Khan et al. found that there was excellent antimicrobial activity and broad antimicrobial spectrum in crude methanolic extracts made from leaves, stems and root barks of *A. scholaris*, in particular the butanol part of *A. scholaris*. However, all fractions were inactive against the tested moulds (Khan et al., 2003). Singh et al. demonstrated that Δ^3-alstovenine (**155**) was a quaternary alkaloid. At concentrations of 250–1000 mg/L, spore germination of the tested fungi was mostly inhibited (Singh et al., 1999). In addition to alkaloids with antifungal activity, flavonoid glycosides had the same activity. For example, a compound with antibacterial activity named tricin-4′-*O*-*β*-L-arabinoside (**363**) was obtained from the leaves of *A. macrophylla* (Parveen et al., 2010).

5.4. β_2AR and spasmolytic activities

β_2AR agonist is one of the most commonly used drugs for asthma and chronic obstructive pulmonary disease. Hou et al. used a liquid chromatography with ion trap time-of-flight mass spectrometry (LCMS-IT-TOF) system to isolate alkaloids with β_2AR agonists activity from *A. scholaris*. In addition, the alkaloids were identified to have a synergistic effect in an isolated guinea pig model (Hou et al., 2012a). *In vitro* experiments proved that akuammidine (**161**) and *Z*-alstoscholarine (**299**) were new indole alkaloid-type β_2AR agonists. Shah et al. showed that the *A. scholaris* extract (ASE) possessed spasmolytic effect. This mechanism might be mediated by calcium channel block (CCB) (Shah et al., 2010).

5.5. Anti-inflammatory activity

Alkaloids are potent anti-inflammatory compounds found in the genus *Alstonia*. Cao et al. obtained eight compounds from *A. yunnanensis*, including raucaffrinoline N_4-oxide (**181**), vinorine N_1, N_4-dioxide (**182**), and vinorine N_4-oxide (**183**) exhibited selective inhibition of Cox-2 with 94.77%, 88.09% and 94.05% inhibition, respectively (Cao et al., 2012). Wang et al. obtained three monoterpene indole alkaloids from 70% ethanol extract of *Alstonia rupestris* Kerr leaves. Scholarisin I (**1**), scholarisinVI (**26**) and *E*-16-formyl-5α-methoxystricta mine (**39**) had elective inhibition of Cox-2 with inhibition rates of 96.4%, 95.5%, and 92.0% (Wang et al., 2013). A recent study (Zhao et al., 2020a, 2020c) suggested that TA obtained from *A. scholaris* leaves had the potential to be an effective new drug to treat emphysema. TA not only inhibited airway wall inflammation and airflow resistance, as well as improved pulmonary elasticity and protease/antiprotease balance.

5.6. Antioxidant and analgesic activities

Oxidative damage can lead to various diseases. Therefore, the study of antioxidant drugs has attracted the attention of medical workers. Studies demonstrated (Arulmozhi et al., 2011) that the ethanol extract of *A. scholaris* leaves (EEAS) significantly decreased lipid peroxidation and myeloperoxidase levels in the joint tissue. The bark of the Philippine *A. macrophylla* (AM) and the root bark extract of *A. boonei* demonstrated antioxidant activity against DPPH radical (Tan et al., 2019;

Obiagwu et al., 2014). Similarly, the analgesic activity of *Alstonia* plants has also been identified through a large number of experiments. Compared to aspirin, alkaloids from *A. scholaris* leaves, especially scholarisine I (**1**) and (±)-scholarisine II (**2**), had the same analgesic efficacy at 200 mg/kg (Cai et al., 2010). Acetic acid-induced writhing and early and late paw licking in mice were observed to be reduced, indicating that the methanolic extract of *A. boonei* stem bark produced significant analgesic activity (Olajide et al., 2000).

5.7. Antiplasmodial activity

Malaria remains a stubborn disease, ravishing communities in about 100 countries. The cause of this disease-*Plasmodium* parasites transmitted by *Anopheles* mosquitoes-had been widely understood since the late 19th century (Cox, 2010). Consequently, it is exceptionally critical to recognize a new drug against the malaria parasite. In many African countries, *Alstonia congensis* Engl. is a medicinal plant. Crude extracts and single compounds obtained from the root bark of *A. congensis* displayed antimalarial activity when tested *in vitro* and *in vivo* (Kanyanga et al., 2019). In addition, the combination of the genus *Alstonia* with other traditional Chinese medicines were identified to exhibit antiplasmodial activity. Tepongning et al. reported that the stem bark combination of the *K. ivorensis* and *A. boonei* showed antiplasmodial activity with large dose intervals between therapeutic and toxic doses in the murine malaria model, which was used as an antimalarial prophylactic (Tepongning et al., 2011).

5.8. Other pharmacological activities

Other than those listed above, *Alstonia* had been proved to possess a variety of other pharmacological activities. Alstiphyllanines E (**20**) and F (**12**) showed moderate Na^+-glucose cotransporter (SGLT) inhibitory activity. 10-methoxy-N_1-methylburnamine-17-*O*-veratrate (**15**) exhibited potent inhibitory activity (Arai et al., 2010). Compound alstonlarsine A (**128**) was isolated from *A. scholaris* and had death associated protein related apoptotic kinase (DPAK2) inhibitory activity (Zhu et al., 2019). *A. scholaris* bark aqueous extracts in the 50 and 100 mg/kg body weight were able to stimulate non-specific immune response inhibitory activity (Iwo et al., 2000). Weiming et al. found that the crude alkaloidal extracts from *A. yunnanensis* root exhibited marginal activity against experimental tumour U_{14} in mice (Weiming et al., 1983). Hirasawa et al. found that isolated constituents of *A. pneumatophora* showed antimelanogenesis in B16 mouse melanoma cells, specifically alpneumine E (**125**), alpneumine G (**242**), vincamine (**243**) and apovincamine (**244**) (Hirasawa et al., 2009).

In addition, extracts with α-glucosidase inhibitory activity were acquired by drying the methanolic water of *A. scholaris* (Nilubon et al., 2007). Antidiabetic and antihyperlipidemic activities of *A. scholaris* leaves were also reported (Arulmozhi et al., 2010). Chattopadhyay et al. revealed CNS activity of *A. macrophylla* leaf extracts (Chattopadhyay et al., 2004). Alstolarine B (**292**) showed moderate acetylcholinesterase (AChE) inhibitory activity (Zhang et al., 2020). 17-nor-excelsinidine (**109**) and strictamine (**43**) were isolated from *A. scholaris* and showed significant inhibitory activity against herpes simplex virus (HSV) and adenovirus (ADV) (Zhang et al., 2014). A recent research (Bagheri et al., 2020) demonstrated that *Alstonia venenata* R. Br. bark was effective against hepatitis B virus (HBV) in benzene, isopropanol and methanol fractions. ASE also showed significant radioprotective activity. Compared with irradiated animals, ASE pretreatment significantly increased glutathione levels in the serum and liver (Gupta et al., 2008).

6. Toxicity

In recent years, some diseases, such as cancer, bacterial infections, etc., have developed multi-drug resistance to the drugs used, which makes it more difficult to treat these diseases. The excellent pharmacological activity of genus *Alstonia*, particularly *A. scholaris*, can be used as a natural drug treasure trove for clinical use. However, there is limited knowledge of its potential toxicity and therefore toxicity studies are essential.

Baliga et al. administered different doses of hydroalcoholic extracts of *A. scholaris* to rats and observed the acute and subacute toxic effects of the extracts on rats. They found that oral administration of the hydroalcoholic extracts of *A. scholaris* were not toxic to mice at a dose of 2000 mg/kg body weight. However, the highest number of animals died after intraperitoneal injection at a dose of 1100 mg/kg body weight. Interestingly, they also observed that the acute toxicity of the mice depended on the season in which the plants were collected. The acute toxicity was highest for plants collected in summer, followed by those collected in winter (Baliga et al., 2004). Baliga and Shrinath further studied *A. scholaris*. It was demonstrated that extracts of *A. scholaris* stem bark and leaves did not cause death or adverse effects at a dose of 2000 mg/kg body weight. However, when injected intraperitoneally at high concentrations, mice demonstrated systemic and developmental toxicity (Baliga and Shrinath, 2012). The alkaloids isolated from the leaves of *A. scholaris* were also proved to be non-toxic (Zhao et al., 2020b, 2020d). While the safety of *A. scholaris* stem bark has been evaluated, the lack of rigorous toxicological studies and the diversity of experimental animals are necessary to further demonstrate the pharmacology and safety of high concentrations of *A. scholaris* stem bark extracts prior to clinical use. Zhao et al. conducted a comprehensive preclinical program including acute and subchronic studies with beagle dogs as a model. Research revealed that indole alkaloids at 20, 60 and 120 mg/kg body weight showed no signs of toxicity except for vomiting and drooling in most dogs. Alkaloid extracts of *A. scholaris* leaves did not cause adverse effects or death in beagle dogs (Zhao et al., 2020e). In addition, indole alkaloids are not genotoxic in the Ames test, mammalian chromosome aberration test, as well as in the micronucleus test (Zhao et al., 2020d).

Therefore, the current study indicates that the stem and leaves extract of *A. scholaris* are safe and provides toxicological data for conducting clinical trials.

7. Clinical research

On the basis of these findings, together with a series of preclinical studies and safety assessments, the genus *Alstonia*, with special reference to *A. scholaris*, has been developed as a new botanical drug and further approved by the Chinese Food

and Drug Administration for Phase I/II clinical trials (Shang et al., 2010a, 2010b).

Li et al. evaluated the safety of *A. scholaris* leaves alkaloids capsule (CALAS) (No. 2011L01436), when administered orally at different doses. The clinical study was conducted in 40 healthy volunteers who were divided into four groups (n = 10 per group) and received different doses of CALAS ranging from 20 mg, 40 mg, 80 mg to 120 mg. On August 26, 2015, the trial was registered (https://www.chictr.org.cn/showproj.aspx?proj=11736) with the number ChiCTR-IPR-15006976 (Li et al., 2019). During the trial, two minor adverse events were observed, although both were related to individual physiological variability and were safe for volunteers at the current dosing regimen (Li et al., 2019). Gou et al. further assessed the clinical safety and tolerability of CALAS. In distinction to Li et al., subjects were randomized to receive either CALAS or then placebo in one of single ascending dose of 8, 40, 120, 240, 360, 480, or in one of multiple ascending dose of 40 or 120 mg, three times daily for 7 days. The results showed that in healthy Chinese volunteers, CALAS from the *Alstonia scholaris* leaves proved to be safe and tolerated with no unexpected or clinically relevant safety concerns at a single dose of 360 mg and up to 120 mg three times daily (Gou et al., 2021). In addition, clinical population pharmacokinetic, metabolomic and therapeutic data are also crucial to provide guidance on patient dosing. Li et al. performed a metabolomic analysis to determine biomarkers associated with treatment efficacy in CALAS from the *Alstonia scholaris* leaves and to assess efficacy and safety depending on symptoms and adverse events in the clinic (Li et al., 2022a, 2022b). This study identified changes in lysophosphatidylcholine, lysophosphatidylethanolamine, and amino acids as possible indirect markers in the treatment of acute bronchitis, and there were no serious adverse effects in clinical trials (Li et al., 2022a, 2022b). Pharmacokinetic, metabolomic, and therapeutic data as well as clinical safety and tolerability evaluations of CALAS from the *Alstonia scholaris* leaves in clinical populations have demonstrated a reliable safety profile, only showing minor, transient adverse reactions.

In conclusion, the excellent pharmacological activity and clinical Phase I data of *A. scholaris* further support the Phase II clinical trial. *A. scholaris* can be further developed into products used to treat patients who have respiratory diseases.

8. Conclusion and future perspectives

Alstonia genus is traditionally used to heal human diseases. Because of its remarkable pharmacological activity, it has attracted the attention of many scholars. In the current work, we comprehensively review the composition and pharmacological activities of genus *Alstonia* and discussed its toxicity for further study and clinical application. So far, over 400 chemical compounds have been obtained from genus *Alstonia*, such as alkaloids, triterpenes, flavonoids, fatty acids, phenolic acids, lignans, and volatile oils. Alkaloids are considered to be the main effective components, with the most widespread being MIAs among *Alstonia* plants. Nonetheless, compared with alkaloids, non-alkaloid components such as flavonoids and triterpenes have not been studied in depth. And some species have been less studied, such as *A. pneumatophora* and *Alstonia balansae* Guillaumin, etc. It is promising to deploy a bioactivity-oriented isolation strategy to locate additional bioactive components. Because the diversity of chemical structures determines the difference in biological activity and determines the clinical application, phytochemical research focuses on chemical components with fewer studies or better efficacy.

The exploration of bioactive molecules and multi-component interactions is important for the clinical application in *Alstonia* plants. For example, 15-hydroxyangustilobine A (**78**) is identified in *A. boonei* leaves as an effective constituent for the treatment of tumors. *Alstonia* plants have a variety of bioactivities, but their mechanism research is not in-depth, and the structure–activity relationship is not clear. In order to further make drugs from the compounds contained in *Alstonia* plants into drugs, the mechanisms involved in the biological activity and structure–activity relationships of chemical composition must be studied in depth.

In summary, the aim of this review is not only to contribute to a basis for analyzing the bioactive mechanisms of important natural products, but also to provide potential development value for studying new drugs. Further research on the molecular and cellular mechanisms as well as clinical applications is needed for the exploitation of *Alstonia* plants. Only by bridging the gap between bioactivity-related mechanisms and structure–activity relationships of chemical components can the development of *Alstonia* plants be further promoted.

Author contributions

Mi-xue Zhao collected the information and drafted the manuscript; Jing Cai and Ying Yang helped to modify the format of the manuscript; Wen-yuan Liu and Jian Xu were involved in the preparation of tables; Wei Li and Toshihiro Akihisa edited the pictures; Jie Zhang analyzed the manuscript. All authors approved the final submitted version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.arabjc.2023.104857.

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