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Review

Medicinal plants of the genus *Gelsemium* (Gelsemiaceae, Gentianales)—A review of their phytochemistry, pharmacology, toxicology and traditional use

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ABSTRACT

Ethnopharmacological relevance: In the genus *Gelsemium*, *Gelsemium elegans* (Gardn. & Champ.) Benth. has been recognized as a toxic plant that is widely distributed in Southeast Asia and has been used as traditional Chinese medicine for the treatment of rheumatoid pain, neuropathic pain, spasticity, skin ulcers and cancers for many years. *Gelsemium sempervirens* (L.) J.St.-Hil. has been used since the nineteenth century in homeopathy for treating anxiety, neuralgia, migraine and spasmodic disorders, such as asthma and whooping cough in North America. This review aims to provide comprehensive information on the botany, traditional uses, phytochemistry, pharmacological research and toxicology of medicinal plants in the genus *Gelsemium*. The overall objective is to explore the evidence supporting its ethnopharmacological effectiveness.

Materials and methods: A literature survey was performed by searching the scientific databases Pubmed, Google Scholar, SciFinder, Scopus, Web of Science and the Chinese CNKI, in addition to traditional Chinese medicine and homeopathic texts for information on *Gelsemium*.

Results: Plants of the genus *Gelsemium* have been used in traditional medicine for the treatment of migraines, neuralgia, sciatica, cancer and various types of sores. Studies into the phytochemical composition of this genus have shown that all of the species are rich sources of monoterpene indole alkaloids and that they have attracted the attention of many researchers due to their markedly diverse and complex architecture. To date, a total of 121 alkaloids have been isolated and identified from the genus. The crude extracts, as well as the monomeric compounds, from the genus possess anti-tumor, analgesic, anxiolytic, anti-inflammatory and immunomodulating pharmacological activities.

Conclusion: It is evident from the available literature that *Gelsemium* species possess potential for use as a beneficial therapeutic remedy. However, the analysis of previous pharmacological research suggests that a clear assignment of active molecules and mechanisms of action is remain lacking. Due to their high toxicity, the studies available on toxicity and safety are inadequate for providing information on clinical utilization.

Contents

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1. Introduction

Gelsemium is a genus of flowering plants in the Gelsemiaceae family (previously classified in the Loganiaceae family; Struwe et al., 1994). The genus comprises three species: the Asian *Gelsemium elegans* (Gardn. & Champ.) Benth. (Fig. 1) and two North American species, *Gelsemium sempervirens* (L.) J.St.-Hil. and *Gelsemium rankinii* Small (Ornduff, 1970; Robert and Broyles, 1993). *Gelsemium elegans* and *Gelsemium rankinii* grow well in damp, rich, clay soil, while *Gelsemium sempervirens* prefers dry upland habitats, which makes the plant popular among hill tribes (Ornduff, 1970). All three of the species are well-known for their toxicity. *Gelsemium rankinii* is a rare species from the southeastern region of the United States with scarce pharmacological reports (Pascarella, 2007). *Gelsemium elegans* is known as Gou Wen, Da Cha Yao or Duan Chang Cao in China (Kimura and Unesco, 1998). This species is distributed in the Fujian, Yunnan, Guizhou, Guangdong and Guangxi provinces in southern China and over southeastern Asia (Wu et al., 1996). It has been used in traditional Chinese medicine to treat certain types of skin ulcers, headaches and cancer pain (Editorial Committee of Zhonghua Bencao National Traditional Chinese Herb Administration, 1999). *Gelsemium sempervirens*, commonly known as yellow jasmine in North America, is not a close relative to the jasmines (*Jasminum* spp.) and is native to the southern regions of the United States spanning from Virginia to Florida. *Gelsemium sempervirens* is listed in traditional homeopathic materials as a well-known remedy for the treatment of neuralgia, migraines, uterine pain, rheumatism, influenza, nausea and whooping cough (Dewey, 1921; Grieve, 1971; Gutman, 1972; King, 1900; Bousta et al., 2001; Bellavite, 2011a; Paris et al., 2012). It is also frequently used as a mild sedative for a variety of anxiety-like psychological and behavioral symptoms (Bellavite et al., 2009; Dutt et al., 2010a).

Recently, a number of studies have been conducted on the phytochemical, pharmacological and toxicological aspects of *Gelsemium*. Phytochemical studies of *Gelsemium* plants have identified more than 190 compounds, including alkaloids, iridoids and steroids. Of these compounds, alkaloids and iridoids are regarded as the two active groups that are most likely to be responsible for the observed pharmacological effects (Takayama and Sakai, 1997; Su et al., 2011; Zhang et al., 2011a). Moreover, both *in vivo* and *in vitro* experiments have demonstrated that *Gelsemium* exhibits a diverse set of anti-tumor, analgesic, anti-inflammatory, immunomodulating, anxiolytic and protective neurotropic biological effects (Bhattacharyya et al., 2008; Cai et al., 2009; Dutt et al., 2010a; Liu et al., 2011; Xu et al., 2012a). These studies will be evaluated in detail in this review.

In a 2010 review, Dutt et al. (2010b) summarized the current ethnopharmacological knowledge of the genus *Gelsemium*. Several

Fig. 1. (A) Flowers and leaves from *Gelsemium elegans*. (B) Figure from *Materia medica* illustrating the roots of *Gelsemium elegans*.

important studies have been published in the intervening years, which have prompted us to reassess *Gelsemium*. In the current review, we provide a comprehensive overview on the ethnopharmacology, phytochemistry, pharmacological activities and toxicology of the species of *Gelsemium*.

2. Botanical descriptions

The genus *Gelsemium* is classified in the division Spermatophyta, class Magnoliopsida, subclass Asteridae and order Gentianales (Struwe et al., 1994). The position of *Gelsemium* Juss. has been in dispute since the genus was created (Moore, 1947). The earliest authors first placed it in the Apocynaceae (Moore, 1947). Bureau (1856) revised the genus and placed *Gelsemium* in the tribe Gelsemieae, family Loganiaceae, this relationship has been supported by several scholars (Bentham, 1857; Klett, 1924; Moore, 1947). Struwe et al. (1994) classified *Gelsemium* in its own family, the Gelsemiaceae; however, the Gelsemiaceae family has not yet been widely recognized. Currently, *Gelsemium* is often classified in either the Loganiaceae or the Gelsemiaceae families (Leege and Wolfe, 2002; Jiao and Li, 2007).

The three species of the genus are the Asian *Gelsemium elegans* and two North American species, *Gelsemium sempervirens* and *Gelsemium rankinii. Gelsemium* species are evergreen woody vines that thrive in warm and humid climates (Table 1). *Gelsemium elegans* is a well-known, toxic plant in China and Southeastern Asia, and has been used in traditional Chinese medicine since ancient times. *Gelsemium elegans* is widely distributed with populations reported in Laos, Malaysia, Vietnam, India, Thailand, Myanmar, Taiwan and the Chinese provinces of Fujian, Jiangxi, Hunan, Guangdong, Xianggang, Hainan, Guangxi, Guizhou, Yunnan and Zhejiang (Wu et al., 1996).

Gelsemium elegans has a smooth and twining stem that contains a milky latex. Its leaves are evergreen, opposite, entire and glabrous. The leaf shape is variable and may be shining, ovate, lanceolate, or verticillate on rare occasion. Stipules are reduced to an interpetiolar line. The flowers are produced in axillary clusters in fascicles with $1-\infty$ flowers. The calyx is composed of sepals with 3–4 mm long lanceolate lobes. The corolla is 12–19 mm long, dark yellow and funnel-shaped. The androecium contains five stamens that are 3.5–4 mm long and are inserted between the base and the middle of the corolla tube. The filaments are strap-shaped to filiform. The anthers are 2-locular with a sagittate base. The fruit is an oval or elliptical pod 10–15 mm long consisting of two separable jointed pods containing numerous flat-winged seeds. The flowering and fruiting season is during the months of May to December (Wu et al., 1996).

Gelsemium sempervirens is an evergreen woody vine of southern North America that is commonly cultivated. It grows well in rich moist soils that naturally occur along the seacoast from Virginia to the southern Florida extending into Mexico. Separate populations of *Gelsemium sempervirens* also occur in the mountains of southern Mexico and Guatemala (Miranda and Sharp, 1950; Ornduff, 1970). *Gelsemium sempervirens* stems may grow up to 6 m long. The reddish-brown stems are slender but tough with much of the epidermis coated with a waxy covering. Its leaves are opposite, entire, lanceolate to narrowly ovate, 2–6 cm long and 1–2 cm thick. Flowers form in axillary clusters of only a few dimorphous flowers with a five-parted calyx. The corolla is 2.5–3.5 cm long and funnel-shaped with 5 obtuse lobes. The fruit is 1.5–2.5 cm long with a 1–2 mm beak. The brownish seeds are 1.2–1.5 cm with a 1 cm wing (Cullen, 2000).

The third species, *Gelsemium rankinii*, occurs in swamps of the outer Coastal Plain from North Carolina to Louisiana. It is morphologically similar to *Gelsemium sempervirens* with a few differences; its leaf-bases are more rounded, its flowers are unscented, its stems are scaly only at the base, the calyx-lobes are 3–6 mm and acuminate. *Gelsemium rankinii* is persistent in fruit, and the fruit is 1–1.6 cm with a 2 mm beak and a 3–4 mm wingless seed (Cullen, 2000).

3. Traditional uses

Gelsemium species have a long history as traditional remedies (Editorial Committee of Zhonghua Bencao National Traditional Chinese Herb Administration, 1999). The two widespread species have been used in the areas where they are naturally distributed. *Gelsemium elegans* is mainly used in China and other Asian countries, while *Gelsemium sempervirens* is mainly used in North America and Europe as a homeopathic remedy. Interestingly, both *Gelsemium elegans* and *Gelsemium sempervirens* have been used to treat neuralgia.

Table 1
The species of *Gelsemium* and its traditional uses.

Species	Synonyms	Common/vernacular names	Traditional uses	Reference
Gelsemium elegans (Gardn. & Champ.) Benth.	*Gelsemium sumatranum* (Blume) Boerl. *Leptopteris sumatrana* Blume *Medicia elegans* Gardner & Champ.	Humanten, Dachayao, Duanchangcao, Dapaoye, Yeman, Huangmengcai	Mainly externally used for treating eczema; tinea corporis or tinea pedis; traumatic injury, fracture; Hemorrhoids; Leprosy; boils and pyodermas; pretibial ulcer; myiasis; scrofula.	http://www.theplantlist.org/tpl/record/kew-2818730, Sung et al. (1998), Xie et al. (1996), Editorial Committee of Zhonghua Bencao National Traditional Chinese Herb Administration (1999)
Gelsemium sempervirens (L.) J.St.-Hil.	*Gelsemium sempervirens* (L.) Pers. *Gelsemium sempervirens* (L.) W.T. Aiton *Gelsemium nitidum* var. *inodorum* Nutt. *Gelsemium nitidum* Michx. *Gelseminum sempervirens* Catesby *Lisianthius sempervirens* Mill. ex Steud.	Yellow jessamine, Jasmine, Carolina jasmine, Jessamine, Evening trumpet flower, Gelsemium, Woodbine	Treating facial and neuralgias, malarial fever, cancer; root tincture used for fevers, inflammation of the spinal column; diminish blood to the cerebrospinal centers, reducing spasmodic action. roots used as a blood purifier and healing salve	http://www.theplantlist.org/tpl/record/kew-2818735, Butler (1900), Khan and Abourashed (2009), King et al. (1900), Grieve. (1971), Bellavite et al. (2011b), Magnani et al. (2010), Bousta et al., 2001, Gutman (1972), Paris et al. (2012), Dewey (1921), Tantaquidgeon and Commission (1942)
Gelsemium rankinii Small	*Gelsemium sempervirens* var. *inodorum* Nutt.	Rankin's Jessamine, Swamp Jessamine, Rankin's trumpetflower	The traditional use is rarely report.	http://www.theplantlist.org/tpl/record/kew-2818734

3.1. Gelsemium elegans

The first recorded use of *Gelsemium elegans* is in the classic Chinese herbal medicine, *The Shennong Emperor's Classic of Materia Medica* (Shen-nong Ben-cao jing). According to legend, Shennong was poisoned by *Gelsemium elegans*; hence, the plant is also known as Duan Chang Cao in China. Although *Gelsemium elegans* is very toxic, it is widely used to treat various diseases based on the traditional Chinese medicine principle of 'like cures like'. *Gelsemium elegans* is used to treat malignant skin problems, such as malignant boils, abscesses, sores, carbuncles, leprosy and psoriasis (Xie et al., 1996). The dried and powdered root, stem and/or leaf of *Gelsemium elegans* are applied externally for the treatment of these skin diseases (Editorial Committee of Zhonghua Bencao National Traditional Chinese Herb Administration, 1999). Because it is an effective analgesic, *Gelsemium elegans* is commonly used to treat neuralgia, sciatica, rheumatoid arthritis and acute pain (Tan et al., 1988; Rujjanawate et al., 2003). Additionally, the Hani people of Yunnan Province, China, use the roasted and crushed roots and the leaves of *G. elegans* to treat bone fractures, stomach-ache and kidney disease (Ghorbani et al., 2011). The Yao ethnic group uses the whole plant of *Gelsemium elegans* in medicinal baths to cure eczema, scrofula, carbuncles, furuncles, injuries incurred from falling and rheumatalgia (Li et al., 2006).

Other Asian countries have been influenced by traditional Chinese medicine, and *Gelsemium elegans* has been used as an external medication to treat several types of ailments. In northern Thailand, the roots of *Gelsemium elegans* are used to treat venereal disease (Srithi et al., 2012). In Japan, the plant is mainly used as an external medication for dermatitis (Yamada et al., 2008). Interestingly, a study demonstrated that an ancient medicine conserved in the Shosoin Repository in Japan for more than 1250 years was the plant 'Yakatsu' which is now known as *Gelsemium elegans* (Kitajima et al., 1998).

3.2. Gelsemium sempervirens

Gelsemium sempervirens is a toxic plant indigenous to North America. The recorded medical use of *Gelsemium sempervirens* dates back to the nineteenth century when the plant was mistakenly identified as an alternative herb for the treatment of a man with "bilious fever" (Garland, 1888). Physicians prepared it as a nostrum called "Electrical Febrifuge" (Club, 1883). During 1863–1926, *Gelsemium* was listed in the U.S.Ph. as *Extractum gelsemii* and *Tinclura gelsemiii* and in the *Eclectic Materia Medica* as *Tinclura Gelemini* (Millspaugh, 1892). The Delaware in New England used *Gelsemium* roots as a blood purifier and healing salve (Tantaquidgeon and Commission, 1942). *Gelsemium* is considered to be an important homeopathic remedy when used in highly diluted solutions to treat a variety of neurological and behavioral symptoms (Bellavite et al., 2011b), especially those symptoms that are similar to those caused by *Gelsemium* poisoning. The homeopathic preparation is a tincture made from the bark of the fresh root of *Gelsemium sempervirens* (Club, 1883). *A Text-Book of Materia Medica, Pharmacology and Therapeutics* states that *Gelsemium* has a distinct effect on sensory nerves and that is useful for the treatment of pain (Butler, 1900). Interestingly, the drug appears to be most effective in treating trifacial neuralgia and neuralgia involving the inferior dental nerve (Butler, 1900). In addition, it was suggested to be efficacious for the treatment of discomfort related to dysmenorrhea, pruritus and eczema (Butler, 1900). It was also widely used by traditional practitioners in the nineteenth century as a root tincture to cure fevers, diminish neuralgia, reduce inflammation and blood to the cerebrospinal centers and to reduce spasmodic action (Khan and Abourashed, 2009). The reference *King's American Dispensatory* describes the medicinal usage of *Gelsemium* for the treatment of restlessness, mental irritability, insomnia, headache, irritation of the urinary tract, hyperemia and convulsions (King et al., 1900). *Gelsemium sempervirens* is noted for both producing and curing fatigue of the extrinsic ocular muscles, the autonomic pupillary reflex and the ciliary muscle of accommodation (King et al., 1900). In addition, it was also used for other typical flu symptoms, such as photophobia, blurred vision and a glassy expression (King et al., 1900). Grieve (1971) suggested that the homeopathic preparation of *Gelsemium sempervirens* should be used as a drug for treating irritated nerve centers; Symptomatically these irritations present as a flushed face, bright eyes, contracted pupils, fever, a "full, bounding pulse" insomnia, thirst, pain and soreness in the back and limbs. In the United States, a homeopathic preparation of *Gelsemium sempervirens* is recommended for the treatment of headache and spasmodic disorders, such as asthma and whooping cough; it is further useful in treating dysmenorrhea, hysteria, chorea and epilepsy. Otherwise, a *Gelsemium* homeopathic tincture was found useful in cases of urine retention. Although *Gelsemium sempervirens* was formerly extensively used to treat fevers, it is now mainly used to treat neuralgic pains, especially those involving the facial nerves (Grieve, 1971). Recently, several studies have tested its homeopathic effects. Magnani et al. (2010) reported that series of centesimal dilutions of *Gelsemium sempervirens*, prepared according to the homeopathic pharmacopeia, has anxiolytic-like effects in mice. *In vitro* experiments revealed that *Gelsemium sempervirens* changes the emotional responses of mice to novel environments, which increases exploratory behavior and decreases thigmotaxis or neophobia (Magnani et al., 2010; Bellavite et al., 2011b).

4. Phytochemistry

To date, a total of 121 alkaloids, 25 iridoids and a number of other compounds from a wide spectrum of secondary metabolite classes have been found in *Gelsemium*. Phytochemical studies have revealed that all of the species are rich in alkaloids, especially the indole alkaloids. These alkaloids are found throughout the plant but are especially concentrated in the roots. Indole alkaloid such as gelsemine, koumine, gelsenicine and gelsevirine are the major active components in *Gelsemium* (Zhang et al., 2007; Su et al., 2011; Liu et al., 2013). The compounds isolated from each species are documented in Table 2, while the chemical structures of the alkaloids and iridoids are shown in Figs. 3 and 4.

4.1. Alkaloids

The indole alkaloids extracted from *Gelsemium* have attracted a great deal of attention from chemists and pharmacologists due to their complex structural features and multiple biological effects. Currently, a total of 121 alkaloids have been isolated and identified (Fig. 3) and have either an indole or oxindole nucleus. Based on their chemical structures, the diverse and complex alkaloids have been classified into the following six types: the gelsedine-type, gelsemine-type, humantenine-type, koumine-type, sarpagine-type and yohimbane-type (Fig. 2). The alkaloid groups found in *Gelsemium* will be discussed in the following paragraphs.

4.1.1. Gelsedine-type alkaloids

Compounds 1–47 isolated from the *Gelsemium* genus are gelsedine-type alkaloids. These types of alkaloids are oxindoles with a novel skeleton similar to that of the humantenine-type oxindole alkaloids but lacking their C-21 carbon (Takayama and Sakai, 1997). Some of these alkaloids are novel forms and have shown cytotoxic effects. Gelsedilam (18) and 14-acetoxygelsedilam (20) were obtained from the leaves of *Gelsemium elegans* and are

Table 2
A comprehensive list of the chemical constituents isolated from *Gelsemium* species.

No.	Chemical component	Plant	Part of plant	References
	Alkaloids			
	Gelsedine-type Alkaloids			
1	14β-Hydroxygelsedine	Stems	*Gelsemium sempervirens*	Schun and Cordell (1985)
2	14-Hydroxygelsemicine	Roots	*Gelsemium sempervirens*	Kogure et al. (2007)
3	Gelsedine	Leaves	*Gelsemium elegans*	Kitajima et al. (2006)
		Roots	*Gelsemium elegans*	Zhang et al. (2012)
4	Gelsemicine	Leaves	*Gelsemium elegan*	Kitajima et al. (2006)
		Roots	*Gelsemium elegan*	Kogure et al. (2007)
5	Gelsenicine	Branches	*Gelsemium elegans*	Ponglux et al. (1988a)
		Roots	*Gelsemium elegans*	Sun et al. (2013)
	Gelegamine D	Stems	*Gelsemium sempervirens*	Kitajima et al. (2003b)
	11-Methoxyhumantenmine	Whole plant	*Gelsemium elegans*	Zhao et al. (2010b)
6	4,20-Dehydrogelsemicine	Stems	*Gelsemium elegans*	Kitajima et al. (2003b)
		Roots	*Gelsemium elegans*	Kogure et al. (2007)
7	Gelegamine E	Roots	*Gelsemium elegans*	Zhang et al. (2009c)
8	19-Oxogelsenicine	Leaves	*Gelsemium elegans*	Ponglux et al. (1988b)
		Roots	*Gelsemium elegans*	Zhang et al. (2012)
9	GS-1	Stems	*Gelsemium sempervirens*	Kitajima et al. (2003b)
10	GS-2	Leaves and stems	*Gelsemium sempervirens*	Kitajima et al. (2003b)
		Roots	*Gelsemium elegans*	Kogure et al. (2007)
11	11-Hydroxygelsenicine	Stems	*Gelsemium elegans*	Zhang et al. (2009a)
12	11,14-Dihydroxygelsenicine	Stems	*Gelsemium elegans*	Zhang et al. (2009a)
13	14-Hydroxygelsenicine	Seeds	*Gelsemium elegans*	Ponglux et al. (1988b)
	Humantenidine	Stems and leaves	*Gelsemium elegans*	Xu et al. (2006)
		Aerial parts	*Gelsemium elegans*	Ouyang et al. (2011)
		Roots	*Gelsemium elegans*	Zhang et al. (2009c)
14	14-Acetoxygelsenicine	Leaves	*Gelsemium elegans*	Kitajima et al. (2006)
15	14,15-Dihydroxygelsenicine	Leaves	*Gelsemium elegans*	Kitajima et al. (2003a)
16	14-Acetoxy-15-hydroxygelsenicine	Leaves	*Gelsemium elegans*	Kitajima et al. (2006)
17	14-Hydroxy-19-oxogelsenicine	Leaves	*Gelsemium elegans*	Kitajima et al. (2006)
18	Gelsedilam	Leaves	*Gelsemium elegans*	Kogure et al. (2006)
19	14-Hydroxygelsedilam	Leaves and branches	*Gelsemium elegans*	Yamada et al. (2008)
20	14-Acetoxygelsedilam	Leaves	*Gelsemium elegans*	Kogure et al. (2006)
21	N_b-Methylgelsedilam	Roots	*Gelsemium elegans*	Yamada et al. (2011)
22	15-Hydroxy-N_b-methylgelsedilam	Roots	*Gelsemium elegans*	Yamada et al. (2011)
23	Gelsecrotonidine	Leaves and branches	*Gelsemium elegans*	Yamada et al. (2008)
24	14-Hydroxygelsecrotonidine	Leaves and branches	*Gelsemium elegans*	Yamada et al. (2008)
25	11-Methoxygelsecrotonidine	Leaves and branches	*Gelsemium elegans*	Yamada et al. (2008)
26	Gelsamydine	Whole plant	*Gelsemium elegans*	Lin et al. (1989a)
27	14α-Hydroxygelsamydine	Stems and leaves	*Gelsemium elegans*	Xu et al. (2006)
28	19α-Hydroxygelsamydine	Whole plant	*Gelsemium elegans*	Lin et al. (1996)
29	Gelselegine	Whole plant	*Gelsemium elegans*	Lin et al. (1990a)
30	11-Methoxygelselegine	Stems	*Gelsemium elegans*	Xu et al. (2012b)
31	11-Methoxy-19-(R)-hydroxygelselegine	Whole plant	*Gelsemium elegans*	Lin et al. (1990a)
	Gelegamine C	Roots	*Gelsemium elegans*	Zhang et al. (2009c)
32	14-Acetoxygelselegine	Leaves	*Gelsemium elegans*	Kitajima et al. (2006)
33	Elegansamine	Branches	*Gelsemium elegans*	Ponglux et al. (1988a)
34	14α-Hydroxyelegansamine	Stems and leaves	*Gelsemium elegans*	Xu et al. (2006)
35	Gelseoxazolidinine	Roots	*Gelsemium elegans*	Yamada et al. (2009)
36	Gelseziridine	Aerial parts	*Gelsemium elegans*	Ouyang et al. (2011)
37	Gelsemoxonine	Leaves	*Gelsemium elegans*	Kitajima et al. (2003a)
38	GS-3	Dried stems	*Gelsemium sempervirens*	Kitajima et al. (2003b)
39	Gelselenidine	Aerial parts	*Gelsemium elegans*	Ouyang et al. (2011)
40	Gelsesyringalidine	Roots	*Gelsemium elegans*	Yamada et al. (2011)
41	Gelsevanillidine	Roots	*Gelsemium elegans*	Yamada et al. (2009)
42	Gelsefuranidine	Leaves	*Gelsemium elegans*	Kogure et al. (2006)
43	14-Dehydroxygelsefuranidine	Roots	*Gelsemium elegans*	Yamada et al. (2011)
44	Gelsemolenine A	Aerial parts	*Gelsemium elegans*	Ouyang et al. (2011)
45	Gelsemolenine B	Aerial parts	*Gelsemium elegans*	Ouyang et al. (2011)
46	Gelseiridone	Leaves	*Gelsemium elegans*	Kogure et al. (2006)
47	Gelseganine D	Leaves and stems	*Gelsemium elegans*	Yin et al. (2008)
	Gelsemine-type Alkaloids			
48	Gelsemine	Aerial parts	*Gelsemium sempervirens*	Kitajima et al. (2003b)
		Roots	*Gelsemium sempervirens*	Kogure et al. (2007)
		Leaves	*Gelsemium elegans*	Kitajima et al. (2006)
		Stems	*Gelsemium elegans*	Zhang et al. (2009a)
49	Gelsevirine	Whole plant	*Gelsemium elegans*	Jin and Xu (1982)
		Roots	*Gelsemium elegans*	Sun et al. (2013)
		Roots	*Gelsemium sempervirens*	Kogure et al. (2007)
		Leaves and branches	*Gelsemium rankini*	Kitajima et al. (2010)
50	21-Oxogelsemine	Stems	*Gelsemium sempervirens*	Schun et al. (1986)
		Leaves	*Gelsemium elegans*	Kitajima et al. (2006)
51	21-Oxogelsevirine	Leaves and branches	*Gelsemium rankini*	Kitajima et al. (2010)
		Stems	*Gelsemium sempervirens*	Schun et al. (1986)

Table 2 (*continued*)

No.	Chemical component	Plant	Part of plant	References
52	N_b-Demethylgelsevirine	Leaves and branches	*Gelsemium rankini*	Kitajima et al. (2010)
53	Gelsevirine N-oxide	Leaves and branches	*Gelsemium rankini*	Kitajima et al. (2010)
54	19R-Hydroxydihydrogelsevirine	Whole plant	*Gelsemium elegans*	Lin et al. (1991b)
		Roots	*Gelsemium sempervirens*	Kogure et al. (2007)
55	19S-Hydroxydihydrogelsevirine	Whole plant	*Gelsemium elegans*	Lin et al. (1991b)
56	19R-Acetyldihydrogelsevirine	Stems	*Gelsemium sempervirens*	Lin et al. (1991b)
57	19R-Hydroxydihydrogelsemine	Whole plant	*Gelsemium sempervirens*	Lin et al. (1991b)
58	4*S*- Gelsemine N-oxide	Aerial parts	*Gelsemium elegans*	Zhang et al. (2011c)
59	4*R*- Gelsemine N-oxide	Leaves	*Gelsemium elegans*	Ponglux et al. (1988b)
60	4R-Gelsevirine N4-oxide	Aerial parts	*Gelsemium elegans*	Ouyang et al. (2011)
61	Gelsebanine	Stems and leaves	*Gelsemium elegans*	Xu et al. (2006)
	Humantenine -type Alkaloids			
62	Gelseganine A	Leaves and stems	*Gelsemium elegans*	Yin et al. (2008)
63	Gelseganine B	Leaves and stems	*Gelsemium elegans*	Yin et al. (2008)
64	Humantenine N4-oxide	Leaves and stems	*Gelsemium elegans*	Yin et al. (2008)
65	*N*-Desmethoxyrankinidine	Whole plant	*Gelsemium elegans*	Lin et al. (1989d)
		Roots	*Gelsemium elegans*	Zhang et al. (2012)
66	11-Hydroxyrankinidine	Whole plant	*Gelsemium elegans*	Lin et al. (1989d)
67	11-Hydroxyhumantenine	Whole plant	*Gelsemium elegans*	Lin et al. (1989d)
68	11-Methoxyhumantenine	Whole plant	*Gelsemium elegans*	Lin et al. (1989d)
		Roots	*Gelsemium sempervirens*	Kogure et al. (2007)
69	6-Hydroxyhumantenine	Leaves and branches	*Gelsemium rankini*	Kitajima et al. (2010)
70	19(E)-Humantenine	Leaves and branches	*Gelsemium rankini*	Kitajima et al. (2010)
71	Humantenine	Roots	*Gelsemium elegans*	Yang and Chen (1984)
		Leaves and branches	*Gelsemium rankini*	Kitajima et al. (2010)
72	Humantenirine	Roots	*Gelsemium elegans*	Yang and Chen (1984)
		Leaves	*Gelsemium elegans*	Kitajima et al.(2006)
73	Rankiniridine	Leaves and stems	*Gelsemium rankini*	Kogure et al. (2008b)
74	Humanteniridine	Leaves and stems	*Gelsemium elegans*	Kogure et al. (2008b)
75	4,5-Dehydrorankinidine	Leaves and branches	*Gelsemium rankini*	Kitajima et al.(2010)
76	14-Hydroxyrankinidine	Leaves and branches	*Gelsemium rankini*	Kitajima et al. (2010)
77	15-Hydroxyrankinidine	Leaves and branches	*Gelsemium rankini*	Kitajima et al. (2010)
78	Rankinidine	Stems	*Gelsemium rankini*	Schun et al. (1986)
		Whole plant	*Gelsemium elegans*	Lin et al. (1989b)
79	20-Hydroxydihydrorankinidine	Whole plant	*Gelsemium elegans*	Lin et al. (1991a)
80	*N*-Desmethoxyhumantenine	Whole plant	*Gelsemium elegans*	Lin et al. (1991a)
81	l5-Hydroxyhumantenine	Whole plant	*Gelsemium elegans*	Lin et al. (1991a)
82	19,20-Dihydrorankinidine	Leaves and branches	*Gelsemium rankini*	Kitajima et al. (2010)
83	(4R)-Humantenine N_4-oxide	Aerial parts	*Gelsemium elegans*	Ouyang et al. (2011)
84	Humantenoxenine	Roots	*Gelsemium elegans*	Yamada et al.(2011)
85	15-Hydroxyhumantenoxenine	Roots	*Gelsemium elegans*	Yamada et al. (2011)
86	Gelegamine A	Roots	*Gelsemium elegans*	Zhang et al. (2009c)
87	Gelegamine B	Roots	*Gelsemium elegans*	Zhang et al.(2009c)
88	Gelsemamide	No recorded	*Gelsemium elegans*	Lin et al. (1989b)
89	11-Methoxygelsemamide	No recorded	*Gelsemium elegans*	Lin et al. (1989b)
		Roots	*Gelsemium elegans*	Zhang et al. (2009c)
	Koumine -type Alkaloids			
90	Kounaminal	Roots	*Gelsemium elegans*	Yamada et al. (2011)
91	Koumine		*Gelsemium elegans*	Khuong-Huu et al. (1981)
92	21-(2-oxopropyl)-koumine	Stems	*Gelsemium elegans*	Xu et al. (2012b)
93	19-(R)-Hydroxydihydrokoumine	Whole plant	*Gelsemium elegans*	Lin et al. (1990b)
	(19R)-Kouminol	Roots	*Gelsemium elegans*	Sun et al. (1989)
94	19-(S)-Hydroxydihydrokoumine	Whole plant	*Gelsemium elegans*	Lin et al. (1990b)
	(19S)-Kouminol	Roots	*Gelsemium elegans*	Sun et al. (1989)
95	Koumine N-oxide	Leaves	*Gelsemium elegans*	Ponglux et al. (1988b)
96	Gelseganine C	Leaves and stems	*Gelsemium elegans*	Yin et al. (2008)
97	Dihydrokoumine	Roots	*Gelsemium elegans*	Zhang et al. (1991)
98	21-Oxokoumine	Roots	*Gelsemium elegans*	Sun et al. (2013)
99	Furanokoumine	Roots	*Gelsemium elegans*	Sun et al. (2013)
	Sarpagine -type Alkaloids			
100	Gelsempervine A	Roots	*Gelsemium sempervirens*	Kogure et al. (2005)
101	Gelsempervine B	Roots	*Gelsemium sempervirens*	Kogure et al. (2005)
102	Gelsempervine C	Roots	*Gelsemium sempervirens*	Kogure et al. (2005)
103	Gelsempervine D	Roots	*Gelsemium sempervirens*	Kogure et al. (2005)
104	19Z-16-epi-Voacarpine	Roots	*Gelsemium sempervirens*	Kogure et al. (2005)
		Roots	*Gelsemium elegans*	Zhang et al. (2009c)
105	19E:16-epi-Voacarpine	Roots	*Gelsemium elegans*	Ponglux et al. (1988b)
		Roots	*Gelsemium sempervirens*	Kogure et al. (2005)
106	Koumidine	Stems	*Gelsemium sempervirens*	Schun and Cordell (1987)
		Roots	*Gelsemium elegans*	Zhang et al. (2012)
107	3-Hydroxykoumidine	Leaves and branches	*Gelsemium rankini*	Kitajima et al. (2010)
108	*N*-Methoxyanhydrovobasinediol	Whole plant	*Gelsemium elegans*	Lin et al. (1989c)
		Roots	*Gelsemium elegans*	Zhang et al. (2009c)
109	Anhydrovobasindiol	Stems and leaves	*Gelsemium elegans*	Xu et al. (2006)

Table 2 (*continued*)

No.	Chemical component	Plant	Part of plant	References
110	19-(Z)-Taberpsychine	Roots	*Gelsemium elegans*	Ponglux et al. (1988b)
111	19-(Z)-Akuammidine	Roots	*Gelsemium elegans*	Sakai et al. (1987)
112	Koumicine N-oxide	Roots	*Gelsemium elegans*	Ponglux et al. (1988b)
113	Dehydrokoumidine	Roots	*Gelsemium elegans*	Yamada et al. (2011)
	Yohimbane-type Alkaloids			
114	Sempervilam	Roots	*Gelsemium sempervirens*	Kogure et al. (2005)
115	Sempervirine	Aerial parts	*Gelsemium sempervirens*	Zhang et al. (2008)
		Stems and leaves	*Gelsemium elegans*	Xu et al. (2006)
116	Ourouparine	Roots	*Gelsemium sempervirens*	Kogure et al. (2007)
	Other types of Alkaloids			
117	Gelsebamine	Stems and leaves	*Gelsemium elegans*	Xu et al. (2006)
118	Gelsenine	Whole plant	*Gelsemium elegans*	Zhao et al. (2010b)
119	Gelebolines A	Roots	*Gelsemium elegans*	Zhang et al. (2012)
120	Gelebolines B	Roots	*Gelsemium elegans*	Zhang et al. (2012)
121	Gelebolines C	Roots	*Gelsemium elegans*	Zhang et al. (2012)
	Iridoids			
122	Gelsemide	Leaves	*Gelsemium sempervirens*	Jensen et al. (1987)
123	7-Deoxygelsemide	Leaves	*Gelsemium elegans*	Takayama et al. (1994)
		Leaves and stems	*Gelsemium sempervirens*	Kitajima et al. (2003b)
124	9-Deoxygelsemide	Leaves	*Gelsemium elegans*	Takayama et al. (1994)
125	Gelemide-7-glucoside	Leaves	*Gelsemium sempervirens*	Jensen et al. (1987)
126	Gelsemiol	Leaves	*Gelsemium sempervirens*	Jensen et al. (1987)
127	Gelsemiol-1-glucoside	Leaves	*Gelsemium sempervirens*	Jensen et al. (1987)
128	Gelsemiol-3-glucoside	Leaves	*Gelsemium sempervirens*	Jensen et al. (1987)
129	9-Hydroxysemperoside	Leaves	*Gelsemium sempervirens*	Jensen et al. (1987)
130	Semperoside	Leaves	*Gelsemium sempervirens*	Jensen et al. (1987)
131	Geleganoid A	Leaves	*Gelsemium elegans*	Zhang et al. (2011a)
132	Geleganoid B	Leaves	*Gelsemium elegans*	Zhang et al. (2011a)
133	Geleganoid C	Leaves	*Gelsemium elegans*	Zhang et al. (2011a)
134	Geleganosides A	Leaves	*Gelsemium elegans*	Zhang et al. (2011a)
135	Geleganosides B	Leaves	*Gelsemium elegans*	Zhang et al. (2011a)
136	GRIR-1	Aerial parts	*Gelsemium rankini*	Kogure et al. (2008a)
		Leaves	*Gelsemium elegans*	Zhang et al. (2011a)
137	GEIR-2	Leaves	*Gelsemium elegans*	Kogure et al. (2008a)
		Leaves	*Gelsemium sempervirens*	Jensen et al. (1987)
138	Geleganoid D	Leaves	*Gelsemium elegans*	Zhang et al. (2011a)
139	Geleganoid F	Leaves	*Gelsemium elegans*	Zhang et al. (2011a)
140	Geleganoid E	Leaves	*Gelsemium elegans*	Zhang et al. (2011a)
141	GEIR-3	Leaves	*Gelsemium elegans*	Kogure et al. (2008a)
142	GEIR-1	Leaves	*Gelsemium elegans*	Kogure et al. (2008a)
143	GSIR-1	Leaves and stems	*Gelsemium sempervirens*	Kitajima et al. (2003b)
		Roots	*Gelsemium sempervirens*	Kogure et al. (2007)
144	Gouwenoside A	Aerial parts	*Gelsemium elegans*	Zhang et al. (2011b)
145	Sweroside	aerial parts	*Gelsemium elegans*	Zhang et al. (2011b)
146	Brasoside	Leaves	*Gelsemium sempervirens*	Jensen et al. (1987)
	Megastigmane Glycosides			
147	(3R, 5S, 6S, 7E, 9R)-Megastigman-7-ene-3,5,6,9-tetrol-9-*O*-β-Dglucopyranoside	Aerial parts	*Gelsemium elegans*	Zhang et al. (2011c)
148	(6R, 7E, 9R)-9-Hydroxy-4,7-megastigmadien-3-one-9-*O*-[α-L-arabinopyranosyl-(1- ≥ 6)-β-Dlucopyranoside]	Aerial parts	*Gelsemium elegans*	Zhang et al. (2011c)
149	(6S, 7E, 9R)-6,9-Dihydroxy-4,7-megastigmadien-3-one-9-*O*-[α-L-arabinopyranosyl-(1- ≥ 6)-β-Dglucopyranoside]	Aerial parts	*Gelsemium elegans*	Zhang et al. (2011c)
150	Eleganosides A	Aerial parts	*Gelsemium elegans*	Zhang et al. (2011b)
151	Eleganosides B	Aerial parts	*Gelsemium elegans*	Zhang et al. (2011b)
152	Foliasalacioside B1	Aerial parts	*Gelsemium elegans*	Zhang et al. (2011b)
	Steroides			
153	12β-Hydroxy-5α-pregn-16-ene-3,20dione	Stems	*Gelsemium sempervirens*	Schun and Cordell (1987)
154	12β-Hydroxy-pregna-1,16-diene-3,20-dione	Stems	*Gelsemium sempervirens*	Schun and Cordell (1987)
155	21-Hydroxy-5α-pregn-16-ene-3,20-dione	Aerial parts	*Gelsemium sempervirens*	Zhang et al. (2008)
156	3-Oxoandrosta-16-ene-17-carboxylic acid	Aerial parts	*Gelsemium sempervirens*	Zhang et al. (2008)
157	3-Oxoandrosta-4,16-diene-17-carboxylic acid	Aerial parts	*Gelsemium sempervirens*	Zhang et al. (2008)
158	β-Sitosterol	Whole plant	*Gelsemium elegans*	Zhao et al. (2009)
159	Stigmasterol	Whole plant	*Gelsemium elegans*	Zhao et al. (2009)
160	Daucosterol	Whole plant	*Gelsemium elegans*	Zhao et al. (2009)
161	Stigmasterol-3-*O*-β-D-glucopyranoside	Whole plant	*Gelsemium elegans*	Zhao et al. (2009)
	Lignin			
162	(+)-8-Hydroxypinoresinol	Whole plant	*Gelsemium elegans*	Zhao et al. (2010a)
163	Cleomiscosin C	Whole plant	*Gelsemium elegans*	Zhao et al. (2010a)
164	Cleomiscosin A	Whole plant	*Gelsemium elegans*	Zhao et al. (2010a)
165	Gelsemiunoside A	Whole plant	*Gelsemium elegans*	Hua et al. (2008)
166	Gelsemiunoside B	Whole plant	*Gelsemium elegans*	Hua et al. (2008)

Table 2 (*continued*)

No.	Chemical component	Plant	Part of plant	References
	Phenolic acids			
167	caffeic acid	Whole plant	*Gelsemium elegans*	Zhao et al. (2010a)
168	1-*O*-Caffeoylquinic acid	Whole plant	*Gelsemium elegans*	Zhao et al. (2010a)
169	4-*O*-Caffeoylquinic acid	Whole plant	*Gelsemium elegans*	Zhao et al. (2010a)
170	1-*O*-Caffeoylquinicacid Me thylester	Whole plant	*Gelsemium elegans*	Zhao et al. (2010a)
171	3,4-Dihydroxyphenylaldehyde	Whole plant	*Gelsemium elegans*	Zhao et al. (2010a)
172	Caffeic acid ethyl ester	Branches	*Gelsemium elegans*	Zhang et al. (2009b)
173	Ferulic acid ethyl ester	Branches	*Gelsemium elegans*	Zhang et al. (2009b)
174	Ursolic acid	Whole plant	*Gelsemium elegans*	Zhao et al. (2009)
175	Gallic acid	Whole plant	*Gelsemium elegans*	Zhao et al. (2009)
176	Ferulic acid	Whole plant	*Gelsemium elegans*	Zhao et al. (2009)
177	Protocatechuic acid	Whole plant	*Gelsemium elegans*	Zhao et al. (2009)
	Flavonoids			
178	Tamarixin	Leaves	*Gelsemium elegans*	Zhang et al. (2009b)
179	Tamarixetin 3-*O*-β-D-galactopyranoside	Leaves	*Gelsemium elegans*	Zhang et al. (2009b)
180	7-*O*-β-D-Glucopyranosylscopoletin	Aerial parts	*Gelsemium sempervirens*	Zhang et al. (2008)
	Coumarin			
181	Scopoletin	Leaves	*Gelsemium elegans*	Zhang et al. (2009b)
182	Scopolin	Leaves	*Gelsemium elegans*	Zhang et al. (2009b)
		Aerial parts	*Gelsemium sempervirens*	Zhang et al. (2008)
		Roots	*Gelsemium sempervirens*	Kogure et al. (2007)
183	Fabiatrin	Leaves	*Gelsemium sempervirens*	Jensen et al. (1987)
184	7-*O*-β-D-Apiofuranosyl-(1→6)-β-D-glucopyranosylscopoletin	Aerial parts	*Gelsemium sempervirens*	Zhang et al. (2008)
185	Scoparone	Whole plant	*Gelsemium elegans*	Hua et al. (2007)
	Terpenoids			
186	Uvaol	Aerial parts	*Gelsemium sempervirens*	Zhang et al. (2008)
187	3-Hydroxy-27-p-(Z)-coumaroyloxy ursan-12-en-28-oic acid	Whole plant	*Gelsemium elegans*	Hua et al. (2007)
188	3-Hydroxy-27-p-(E)-coumaroyloxy ursan-12-en-28-oic acid	Whole plant	*Gelsemium elegans*	Hua et al. (2007)
189	Uncarinic acid E	Whole plant	*Gelsemium elegans*	Hua et al. (2007)
	Fructose and its derivative			
190	n-Butyl-α-D-Fructofuranoside	Aerial parts	*Gelsemium elegans*	Zhang et al. (2011c)
191	Ethyl-α-D-Fructofuranoside	Leaves	*Gelsemium elegans*	Zhang et al. (2009b)
192	Ethyl-β-D-Fructopyranoside	Leaves	*Gelsemium elegans*	Zhang et al. (2009b)
	Others			
193	Uridine	Leaves	*Gelsemium elegans*	Zhang et al. (2009b)
194	2-(4-hydroxyphenyl)ethyl heptadecanoate	Aerial parts	*Gelsemium sempervirens*	Zhang et al. (2008)
195	Di(2-ethylhexyl) phthalate	Whole plant	*Gelsemium elegans*	Hua et al. (2007)

the first examples of naturally occurring 18, 19-nor-type monoterpenoid indole alkaloids (Kogure et al., 2006). Yamada et al. (2008) isolated four gelsedine-type oxindole alkaloids from the leaves and branches of *Gelsemium elegans*, and among these alkaloids were gelsecrotonidine (23), 14-hydroxygelsecrotonidine (24) and a form of 11-methoxygelsecrotonidine (25), which possesses an additional C-2 unit with an acetic acid residue. Another isolate is 14-hydroxygelsedilam (19), an 18, 19-nor-type monoterpenoid indole alkaloid. The 14-acetoxygelsenicine (14), 14, 15-dihydroxygelsenicine (15), gelsedine (3) and gelsemicine (4) alkaloids showed potent cytotoxic effects against the A431 human epidermoid carcinoma cell line (Kitajima et al., 2006). Gelsenicine (5) was obtained from *Gelsemium elegans* and was found to have an effect on inflammatory and neuropathic pain (Liu et al., 2011). Gelsemolenines A (44) and B (45) are the first examples of *Gelsemium* alkaloids with an additional acetyl orformyl unit at the N4 position (Ouyang et al., 2011). Gelseiridone (46) and gelseganine D (47) have a nitrogen-carbon linkage between a gelsenicine-type monoterpenoid indole alkaloid and a monoterpene unit with an iridoid skeleton (Kogure et al., 2006).

4.1.2. Gelsemine-type alkaloids

Gelsemine (48) was the first alkaloid isolated from *Gelsemium* plant material in 1959, and subsequent investigations have led to the isolation of 14 additional gelsemine-type alkaloids (48–61). The gelsemine-type alkaloids contain an oxindole unit and have an additional bond between the C-6 and C-20 positions when compared to the humantenine-type alkaloids. Gelsemine (44) is one of the principal alkaloidal constituents of the *Gelsemium* genus (Kitajima et al., 2006; Kogure et al., 2007).

4.1.3. Humantenine-type alkaloids

Humantenine-type alkaloids are oxindole derivatives of the *C*/*D* ring cleaved sarpagine-type indole alkaloids. Currently, there are 28 humantenine-type alkaloids (62–89) that have been isolated from *Gelsemium*. Among these, humantenoxenine (84) and 15-hydroxyhumantenoxenine (85) contain a novel β-amino-α, β-unsaturated ketone residue (Yamada et al., 2011). 6-hydroxyhumantenine (69) is the first example of a *Gelsemium* alkaloid with an oxygen at the C-6 position, and it is a plausible biogenetic precursor of gelsemine-type alkaloids (Kitajima et al., 2010).

4.1.4. Koumine-type alkaloids

Koumine-type alkaloids have attracted the attention of many researchers because of their novel hexacyclic cage structure. Only 10 koumine-type alkaloids (90–99) have been isolated from *Gelsemium elegans*. Koumine (91) was first isolated from *Gelsemium elegans* in 1931, and its structure was determined in 1981 (Khuong-Huu et al., 1981). Several studies have shown that koumine is highly cytotoxic to cancer cell lines and has an

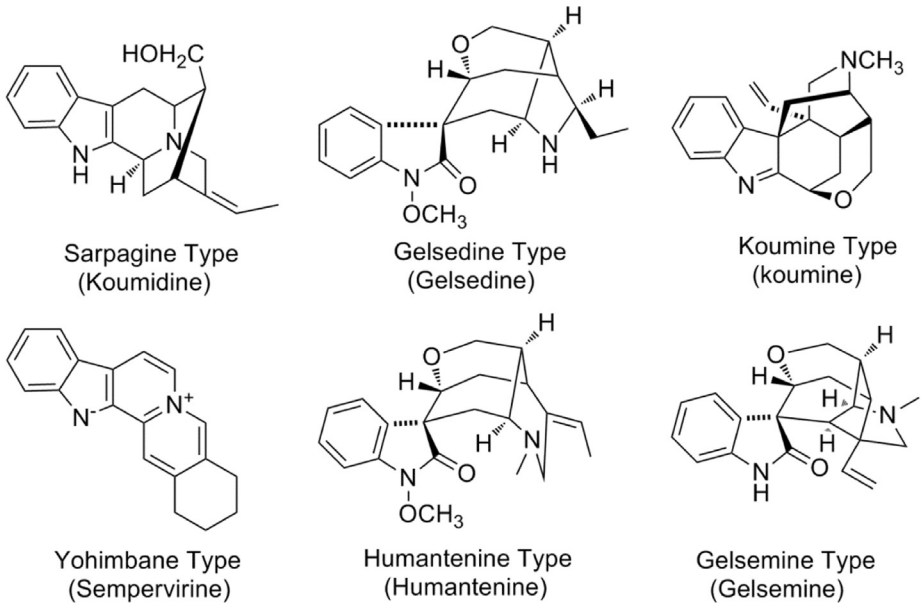

Fig. 2. Six classes of alkaloids present in *Gelsemium* and representative compounds.

analgesic activity with no additive side effects. Koumine N-oxide (95), a highly oxidized alkaloid, was isolated from the leaves of *Gelsemium elegans* (Ponglux et al., 1988b). The koumine-type alkaloids 19-(R)-hydroxydihydrokoumine (93) and 19-(S)-hydroxydihydrokoumine (94) were found in *Gelsemium elegans* (Lin et al., 1990b). Gelseganines C (96) represents a rare class of monoterpenoid indole alkaloids that bear an N4-iridoid unit, which was found in *Gelsemium elegans* (Yin et al., 2008). Kounaminal (90) was isolated from *Gelsemium elegans* and is the first koumine-type alkaloid to possess a residue at the C-21 position (Yamada et al., 2011).

4.1.5. Sarpagine-type alkaloids

Sarpagine-type indole alkaloids are especially high in the Apocynaceae and Rubiaceae plant families and have been found in many other plants. Fourteen sarpagine-type alkaloids (100–113) have been identified from the genus *Gelsemium*. However, only the 3-Hydroxykoumidine (107) alkaloid has been isolated from the leaves and branches of *Gelsemium rankinii* (Kitajima et al., 2010). This compound is similar to the Corynanthe-type monoterpenoid indole alkaloid in that they both have an additional bond between the C-5 and C-16 positions. Kogure et al. (2005) isolated five sarpagine-type alkaloids from the root of *Gelsemium sempervirens* and found that 2-acyl sarpagine-type alkaloids possess an N_b-methyl group with a keto-amino structure or a trans-annular form in solution depending on the solvent.

4.1.6. Yohimbane-type alkaloids

The yohimbane-type alkaloids are a rather rare and unique type of alkaloid. Only three yohimbane-type indole alkaloids have been isolated from *Gelsemium sempervirens*, which are sempervilam (114), sempervirine (115) and ourouparine (116) (Kogure et al., 2005; Kogure et al., 2007).

4.1.7. Other types of alkaloids

Gelsebamine (117) selectively inhibits the A-549 human lung adenocarcinoma cell line; however, Gelsebamine was shown to be an artifact and does not exist among the crude alkaloids (Xu et al., 2006). Gelebolines A–C (118–121) exhibit a unique degraded monoterpenoid moiety and are the first reported β-carboline from the genus (Zhang et al., 2012).

4.2. Iridoids

In addition to alkaloids, the *Gelsemium* genus has proven to be a rich source of iridoids. There are currently 24 iridoids (122–145) that have been reported from the genus. Jensen et al. (1987) isolated seven iridoids from *Gelsemium sempervirens* including gelsemide (122), gelemide-7-glucoside (125), gelsemiol (126), gelsemiol-1-glucoside (127), gelsemiol-3-glucoside (128), 9-hydroxysemperoside (129) and semperoside (130). All of these iridoids are lactones of the asperuloside type. Kogure et al. (2008a) recovered four new iridoids from the leaves of *Gelsemium elegans* and *Gelsemium rankinii*. GRIR (136) was the only iridoid recovered from *Gelsemium rankinii*, and GEIR-1 (142) has a novel tetracyclic caged structure. Zhang et al. (2011a) isolated six aglycones (geleganoids A-F) and two glycosides (geleganosides A (134) and B (135)) from the leaves of *Gelsemium elegans*. Among these isolates, the geleganosides B (135) compounds possess a rare α-D-glucopyranose unit and the geleganoids D (138) compounds are a noriridoid due to the absence of C-3. These compounds were tested for PC12 neurite cell outgrowth activity but were found to be inactive (Zhang et al,. 2011a).

4.3. Megastigmane glycosides

The megastigmane derivatives are commonly reported as natural products in plants, yet there have only been six megastigmane glycoside compounds isolated from *Gelsemium*. Zhang et al. (2011c) isolated two new megastigmane glycosides and four previously known megastigmane glycosides from the aerial parts of *Gelsemium elegans*.

4.4. Steroids and other constituents

Two pregnane derivatives, 12β-hydroxy-5α-pregn-16-ene-3, 20-dione and 12β-hydroxy-pregna-4, 16-diene-3,20-dione have been isolated from the MeOH extract of the stem from *Gelsemium sempervirens*. These derivatives displayed activity in human mouth epidermal carcinoma (KB) and murine leukemia (P388) cell lines (Schun and Cordell, 1987). Zhang et al. (2008) isolated three new steroids (155–157) from *G. sempervirens*, and their structures were determined to be 21-hydroxy-5α-pregn-16-ene-3, 20-dione, 3-oxoandrosta-16-ene-17-carboxylicacid, and 3-oxoandrosta-4,

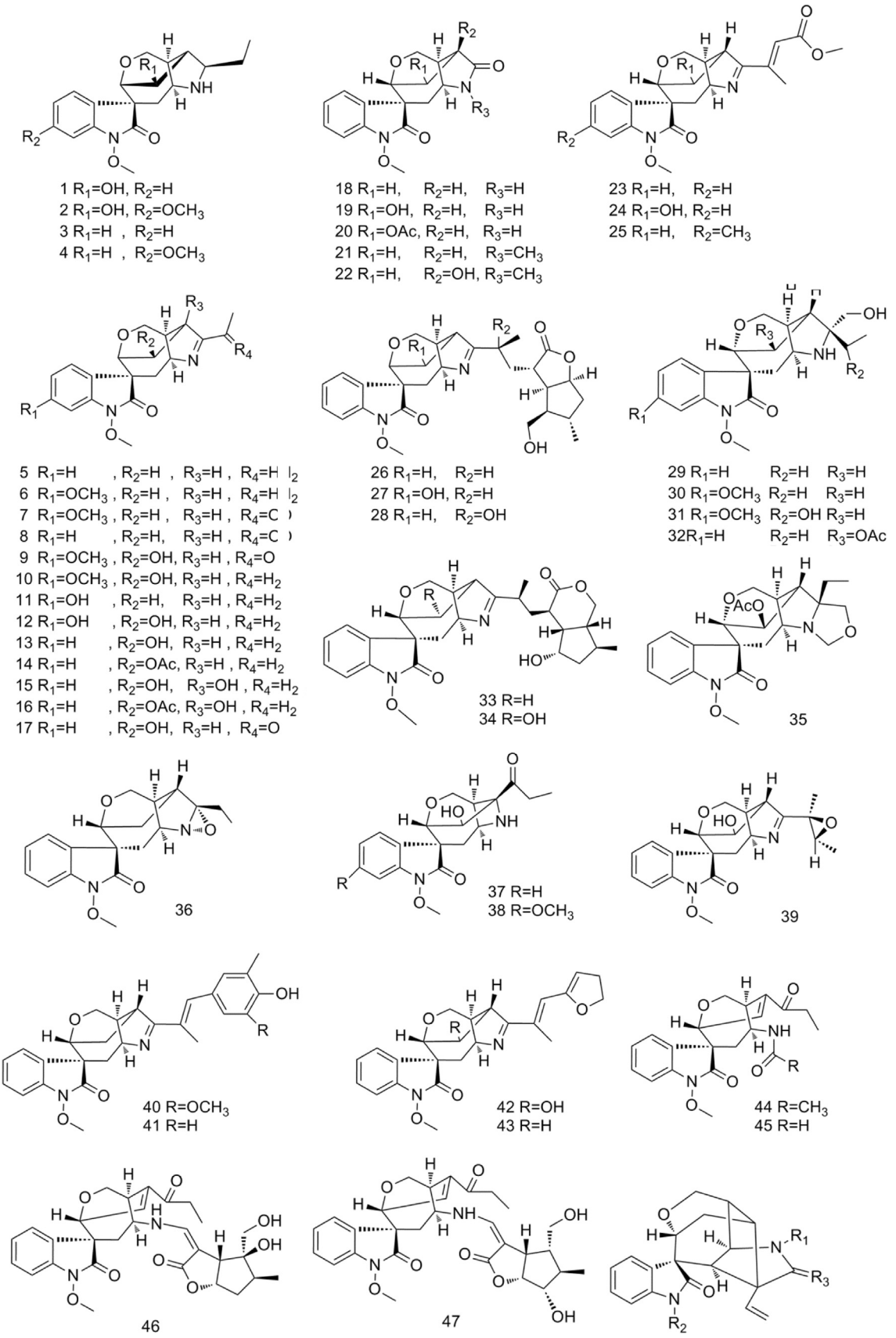

Fig. 3. Alkaloids isolated from the species of the genus *Gelsemium* (compounds 1–121).

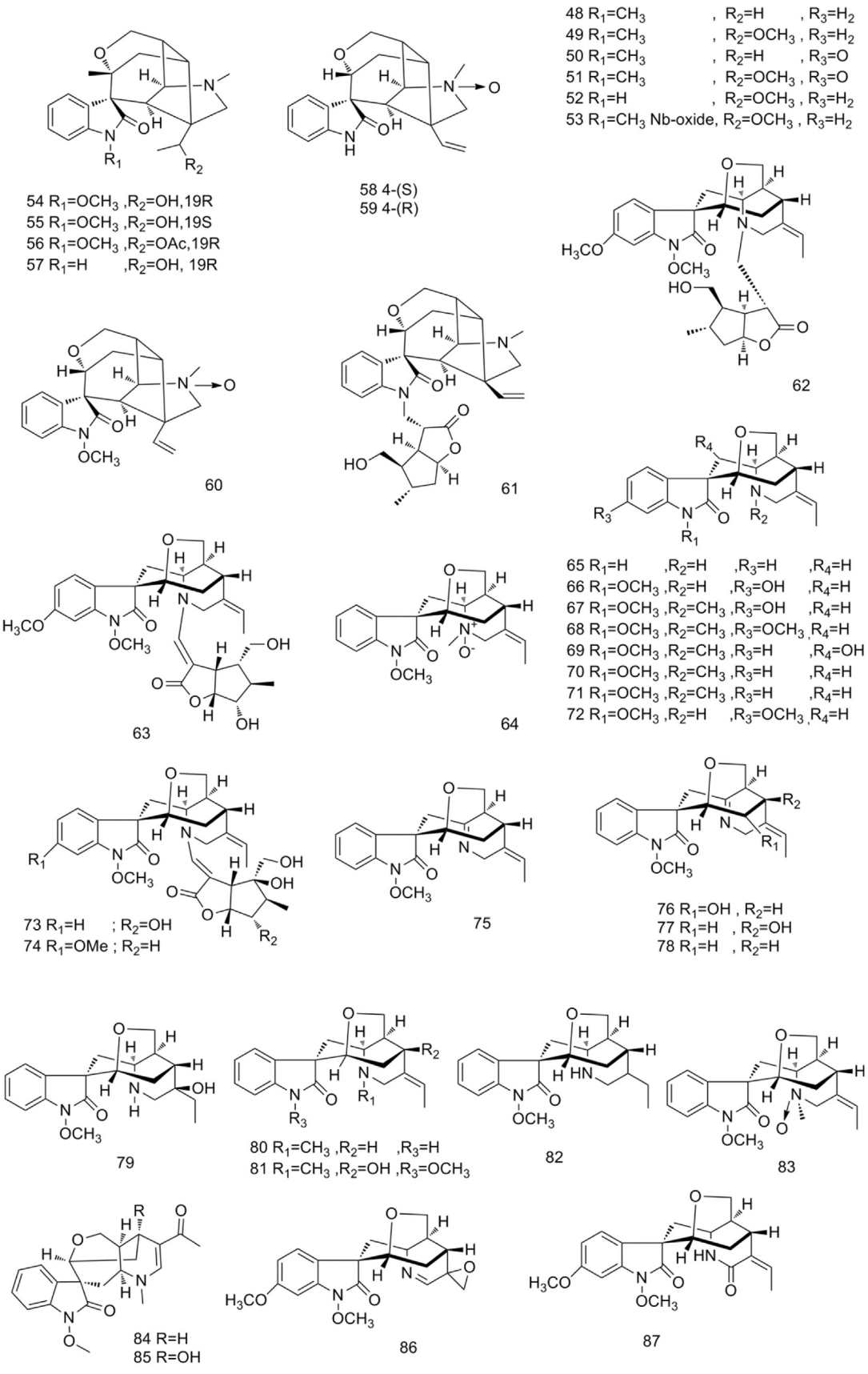

Fig. 3. (*continued*)

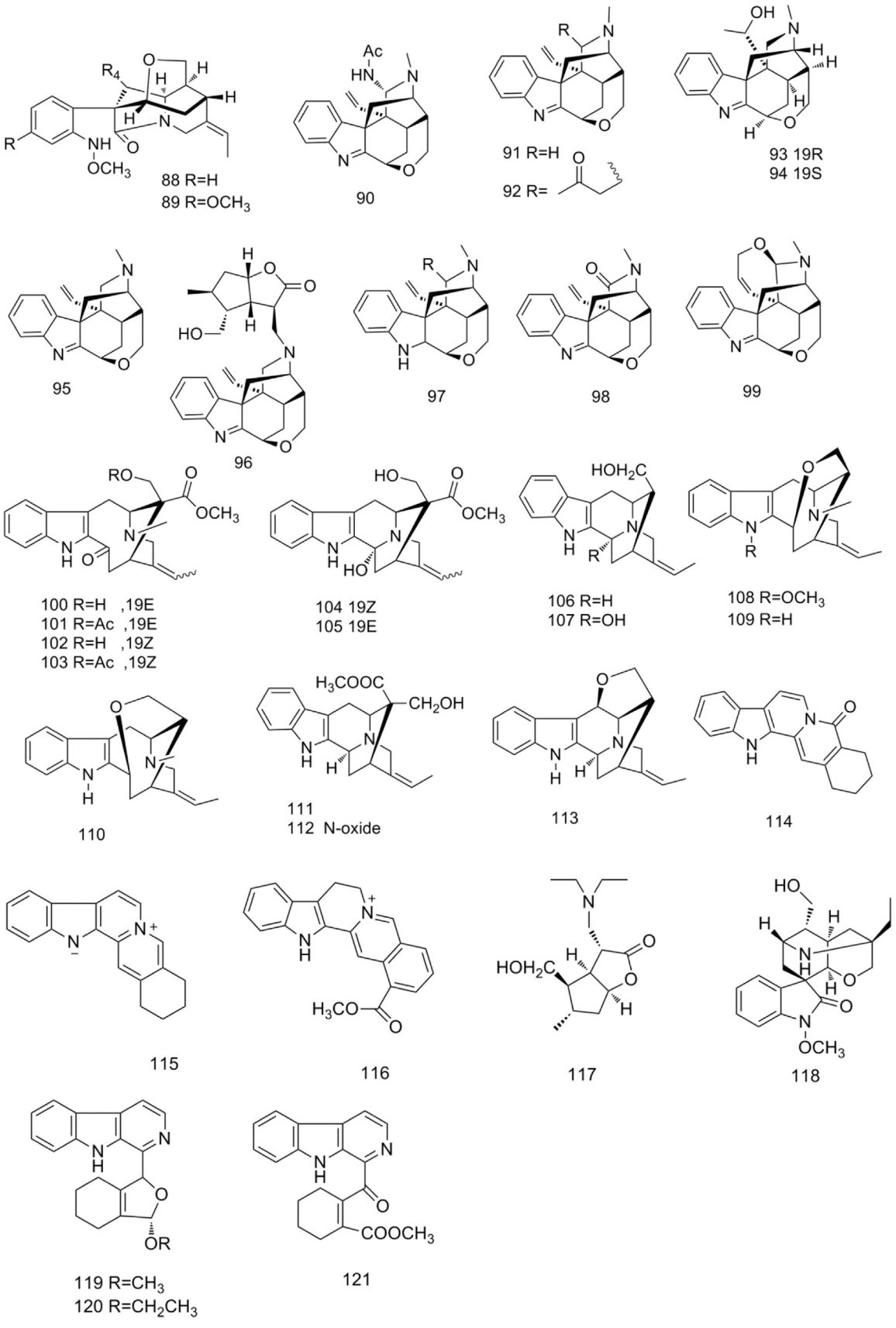

Fig. 3. (*continued*)

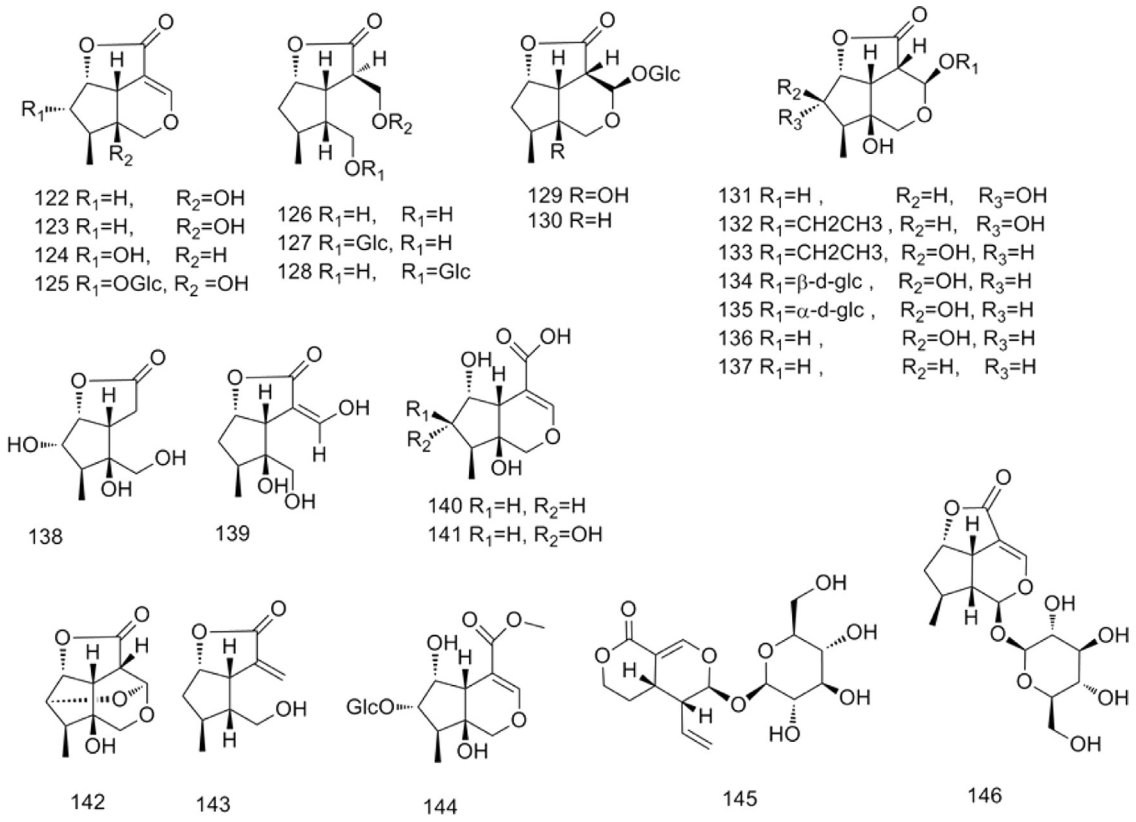

Fig. 4. Iridoids isolated from the species of the genus *Gelsemium* (compounds 122–146).

16-diene-17-carboxylic acid. Hua et al. (2008) isolated two new benzofuran lignan glycosides (gelsemiunoside A and B) from the whole plant of *Gelsemium elegans*, which showed a potent cytotoxic activity by suppressing the proliferation of A375-S2 cells. To study the non-alkaloid chemical constituents of *Gelsemium elegans*, Zhang et al. (2009b) isolated and identified the following 10 compounds: tamarixin, tamarixetin 3-*O*-β-D-galactopyranoside, uridine, caffeic acid, caffeic acid ethyl ester, ferulic acid ethylester, ethyl-α-D-fructofuranoside, ethyl-β-D-fructopyranoside, scopoletin and scopolin. Zhao et al. (2009) was the first study to isolate and identify 16 non-alkaloid constituents from the *Gelsemium elegans* genus.

5. Pharmacological properties

The traditional medicinal applications of *Gelsemium* species have inspired many pharmacological investigations. Several extracts of *Gelsemium* spp. and isolated compounds have been evaluated for their anti-tumor, anti-inflammatory, analgesic, anxiolytic and immunostimulatory activity (Tan et al., 1988; Rujjanawate et al., 2003; Dutt et al., 2010a; Liu et al., 2011; Xu et al., 2012a; Zhang et al., 2013a). The *Gelsemium* extracts and monomeric compounds were highly cytotoxic to several cancer cell lines (Kitajima et al., 2006; Zhao et al., 2006a; An et al., 2008; Bhattacharyya, 2009; Huang et al., 2010; Gao et al., 2012). There seems to be an interest in developing new anti-tumor drugs from these plants. However, the molecular mechanisms that drive the effects of these compounds are not sufficiently understood. Thus, a more detailed pharmacological explanation is needed for the further development of these compounds. In addition to its anti-tumor activity, the analgesic and anxiolytic properties of *Gelsemium* have also been well studied. Koumine, gelsemine and gelsevirine are efficacious in several inflammatory and pain models (Tan et al., 1988; Rujjanawate et al., 2003; Liu et al., 2011; Xu et al., 2012a; Zhang et al., 2013a, b). Table 3 lists the available pharmacological studies with detailed study methods and conditions.

5.1. Anti-tumor activity

Several studies have demonstrated that *Gelsemium* sp. possess anti-tumor effects *in vivo* and *in vitro*. An alkaloid extract of *Gelsemium elegans* (10 μg/ml) has a significant dose and time dependent inhibitory effect on hepatic carcinoma HepG2 cells *in vitro*, and the mechanism of this anti-tumor action may be related to their apoptosis-inducing activities (Wang et al., 2001). These results were similar in Abdul et al. (2004) in which a methanol extraction of *Gelsemium elegans* exhibited a strong cytotoxic effect on CaOV-3 cells (human ovarian cancer cell line) with an IC_{50} value of 5 μg/ml and to a lesser extend in MDAMB-231 cells (human estrogen receptor negative breast cancer cells) with an IC_{50} value of 40 μg/ml. These effects were both dose and time dependent in both of these tests. The 95% ethanol extract of *Gelsemium sempervirens* has been reported to inhibit human DNA topoisomerase I (Topo I). Sempervirine, which intercalates DNA and inhibits Topo I by modulating enzyme activity with an IC_{50} of 54.5 ± 15.9 μM, was identified as the active ingredient following phytochemical analysis (Zhang et al., 2008). Among the active components isolated from *Gelsemium elegans*, uncarinic acid E reportedly inhibits the cellular growth of HCT-15 (colon), MCF-7 (breast), A549 (lung), and HT-1197 (bladder) by over expressing PLCγ1 with IC_{50} values of 0.5–6.5 μM (Lee et al., 2000). It has also been reported that uncarinic acid E (6–48 μM) exerts potent inhibitory effects on HepG2 cells in a time and dose dependent manner. Its molecular mechanism of action may be related to an

Table 3
Pharmacological effects of the *Gelsemium* species.

Pharmacological effects	Detail	Extracts/compounds	Minimal active concentration/ dose	*In vitro*/ *in vivo*	Reference
Antitumor activity	Cytotoxic effects on HepG2 cells	Uncarinic acid E	6–48 μM	*In vitro*	Zhao et al. (2006b)
		Alkaloidal fraction from *Gelsemium elegans*	10 μg/ml	*In vitro*	Wang et al. (2001)
		Gelsenicine	IC_{50} = 184.55 μg/ml	*In vitro*	Gao et al. (2012)
		Gelsenicine	IC_{50} = 1.79 ± 0.54 mmol/L	*In vitro*	Huang et al. (2010)
		Koumine	IC_{50} = 1.26 ± 0.32 mmol/L	*In vitro*	Huang et al. (2010)
		Gelsemine	IC_{50} = 1.82 ± 0.35 mmol/L	*In vitro*	Huang et al. (2010)
	Inhibit TE-11 cell proliferation	Gelsenicine	IC_{50} = 1.73 ± 0.35 mmol/L	*In vitro*	Huang et al. 2010)
		Koumine	IC_{50} = 0.74 ± 0.05 mmol/L	*In vitro*	Huang et al. (2010)
		Gelsemine	IC_{50} = 1.94 ± 0.30 mmol/L	*In vitro*	Huang et al. (2010)
	Inhibit SW480 cell proliferation	Gelsenicine	IC_{50} = 0.52 ± 0.22 mmol/L	*In vitro*	Huang et al. (2010)
		Koumine	IC_{50} = 0.45 ± 0.10 mmol/L	*In vitro*	Huang et al. (2010)
		Gelsemine	IC_{50} = 0.76 ± 0.28 mmol/L	*In vitro*	Huang et al. (2010)
		Gelsevirine	IC_{50} = 1.41 ± 0.06 mmol/L	*In vitro*	Huang et al. (2010)
	Inhibit MGC80-3 cell proliferation	Gelsenicine	IC_{50} = 1.14 ± 0.23 mmol/L	*In vitro*	Huang et al. (2010)
		Koumine	IC_{50} = 0.82 ± 0.19 mmol/L	*In vitro*	Huang et al. (2010)
		Gelsemine	IC_{50} = 1.20 ± 0.33 mmol/L	*In vitro*	Huang et al. (2010)
		Gelsevirine	IC_{50} = 1.22 ± 0.11 mmol/L	*In vitro*	Huang et al. (2010)
	Induce HepG2 and HeLa cell death	4-N-demethylgelsemine	IC_{50} = 340.3 and 338.9 μM, respectively	*In vitro*	Zhao et al. (2010b)
		21-oxogelsemine	IC_{50} = 107.1 and 338.9 μM, respectively	*In vitro*	Zhao et al. (2010b)
		Gelsemine	600 μM	*In vitro*	Zhao et al. (2010b)
	Inhibit HeLa cell growth and proliferation	Ethanol and chloroform extraction of *Gelsemium elegans*	1 μl/ml	*In vitro*	An et al. (2008)
	Cytotoxic activity for A431 Epidermoid Carcinoma Cells	14-acetoxygelsenicine	ED_{50} = 0.25 μM	*In vitro*	Kitajima et al. (2006)
		14-acetoxy-15-hydroxygelsenicine	ED_{50} = 36 μM	*In vitro*	Kitajima et al. (2006)
		14,15-dihydroxygelsenicine	ED_{50} = 1.3 μM	*In vitro*	Kitajima et al. (2006)
		Gelsenicine	ED_{50} = 37 μM	*In vitro*	Kitajima et al. (2006)
		Gelsedine	ED50 = 0.35 μM	*In vitro*	Kitajima et al. (2006)
		Gelsemicine	ED_{50} = 0.75 μM	*In vitro*	Kitajima et al. (2006)
	Inhibit A375-S2 cell proliferation	Non-alkaloid and alkaloidal fraction from *Gelsemium elegans*	IC_{50} = 38.6 and 87.5 μg/ml, respectively	*In vitro*	Zhao et al. (2006a)
		Gelsemiunoside A	IC_{50} = 193.4	*In vitro*	Hua et al. (2008)
		Gelsemiunoside B	IC_{50} = 69.4	*In vitro*	Hua et al. (2008)
	Inhibit KB cell proliferation	Non-alkaloid and alkaloidal fraction from *Gelsemium elegans*	IC_{50} = 78.6 and 109.8 μg/ml, respectively	*In vitro*	Zhao et al. (2006a)
	Inhibit SGC7901 cell proliferation	Non-alkaloid and alkaloidal fraction from *Gelsemium elegans*	IC_{50} = 125.9 and 283.3 μg/ml respectively	*In vitro*	Zhao et al. (2006a)
	Inhabit H22 tumor growth in mice	The component 2 of non-alkaloid from *Gelsemium elegans*	1.5–6 mg/kg for 10 days	*In vitro*	Zhao et al. (2006a)
	Cytotoxicity against A549 cells	Koumine and its metabolites M1, M2, M3, M4	100 μM, inhibition ratio was 15.4%, 14.4%, 14.5%, 13.7%, and 9.6%, respectively	*In vitro*	Zhang et al. (2013)
	Anticancer against DMBA induced skin cancer in mice	4-Methyl-7 hydroxy coumarin	50 mg/kg (b.w.)	*In vitro*	Bhattacharyya et al. (2009)
		Scopoletin	50 mg/kg (b.w.)	*In vitro*	Bhattacharyya et al. (2010)

Table 3 (*continued*)

Pharmacological effects	Detail	Extracts/compounds	Minimal active concentration/ dose	*In vitro*/ *in vivo*	Reference
	Cytotoxicity against CaOV3 cells	Methanol extracts of *Gelsemium elegans* leaves	IC_{50}=5 μg/ml	*In vitro*	Wu et al. (2006)
	Cytotoxicity against MDA-MB-231 cells	Methanol extracts of *Gelsemium elegans* leaves	IC_{50}=40 μg/ml	*In vitro*	Wu et al. (2006)
	Cytotoxicity against AGZY-83-α	Injection of *Gelsemium elegans*	IC_{50}=50 μg/ml	*In vitro*	Lu et al. (1990)
	Inhibit Bel7402 cell proliferation	Koumine	IC_{50}=74.39 μg/ml	*In vitro*	Wu et al. (2006)
	Inhibit Lovo cell proliferation	Koumine	IC_{50}=58.68 μg/ml	*In vitro*	Wu et al. (2006)
	Antitumor activity on mice beared Bel7402, H22, Lewis asctic type solid tumor	Koumine	1.2 mg/kg	*In vivo*	Wu et al. (2006)
	Antitumor activity on mice beared sarcoma 180 type tumor	Extracts from *Gelsemium elegans*	0.11 g/kg/day for 14 days	*In vivo*	Yang et al. (2004)
	Inhabit the rabbit platelet aggregation induced by arachidonic acid, Thrombin and Ca^{2+}	Koumine	IC_{50}=0.45, 0.22 and 0.0015 g/L, respectively	*In vitro*	Fang et al. (1998)
Analgesic effect	Effect on bone cancer inoculation in rats	Gelsemine	ED_{50}=0.5 μg (i.t.)	*In vivo*	Zhang et al., 2013a, b
	Effect on hot plate test in mice	Parenteral solution of crude alkaloidal extraction from *Gelsemium elegans*	ED_{50}=0.28 mg/kg (i.p.)	*In vivo*	Tan et al. (1988)
	Effect on acetic acid induced nociceptive in mice.	Koumine	ED_{50}=5.85 mg/kg	*In vivo*	Xu et al. (2012a)
		Alkaloidal fraction from *Gelsemium elegans*	1.0 mg/kg (i.p.)	*In vivo*	Rujjanawate et al. (2003)
		Parenteral solution of crude alkaloidal extraction from *Gelsemium elegans*	ED_{50}=0.28 mg/kg (i.p.) and 0.39 mg/kg (p.o.)	*In vivo*	Tan et al. (1988)
	Effect on tail flick test	Parenteral solution of crude alkaloidal extraction from *Gelsemium elegans*	ED_{50}=0.5 mg/kg (i.p.)	*In vivo*	Tan et al. (1988)
		Gelsenicine	ED_{50}=10.4 μg/kg	*In vivo*	Liu et al. (2011)
	Formalin induced tonic pain in mice and rats	Gelsemine	ED_{50}=13.3 μg (i.t.)	*In vivo*	Zhang et al., 2013a, b
	Formalin test in mice (early phase)	Alkaloidal fraction of *Gelsemium elegans*	1.0 mg/kg (i.p.)	*In vivo*	Rujjanawate et al. (2003)
	Formalin test in mice (late phase)	Koumine	2.0 mg/kg	*In vivo*	Xu et al. (2012a)
		Alkaloidal fraction of *Gelsemium elegans*	1.0 mg/kg (i.p.)	*In vivo*	Rujjanawate et al. (2003)
		Gelsenicine	ED_{50}=7.4 μg/kg	*In vivo*	Liu et al. (2011)
	Inhabit CFA induced nociceptive in mice.	Koumine	0.8 mg/kg	*In vivo*	Xu et al. (2012a)
	Effect on CCI and SNL models of neuropathic pain	Koumine	0.28 mg/kg, twice/day for 7 days	*In vivo*	Xu et al. (2012a)
				In vivo	Xu et al. (2012a)
	Rat SNL model of neuropathic pain	Gelsemine	ED_{50}=0.5 μg (i.t.)	*In vivo*	Zhang et al., 2013a, b
	Rat CCI model of neuropathic pain	Gelsenicine	ED_{50}=9.8 μg/kg	*In vivo*	Liu et al. (2011)
Antiinflammatory activity	Inhabit EPP induced ear edema in rats	Alkaloidal fraction from *Gelsemium elegans*	2.5 mg/ear	*In vivo*	Rujjanawate et al. (2003)
	Inhabit the edema of hind paw induced by carrageenin or fresh egg white in rat	Crude alkaloidal fraction of *Gelsemium elegans*	1 mg/kg (i.p.)	*In vivo*	Xu et al. (1991)
Antianxiety activity	Elevated plus-maze	Gelsemine	10^{-10} M	*In vivo*	Meyer et al. (2013)
		Methanol extract of *Gelsemium sempervirens*	150 mg/kg	*In vivo*	Dutt et al. (2010a)
		A fraction (F9.4) derived from the methanol extract of *Gelsemium sempervirens*	10 mg/kg	*In vivo*	Dutt et al. (2010a)
		Koumine,	0.4 mg/kg	*In vivo*	Liu et al. (2013)
		Gelsemine,	2 mg/kg	*In vivo*	Liu et al. (2013)
		Gelsevirine	0.4 mg/kg	*In vivo*	Liu et al. (2013)
	Light–dark transition model	Koumine,	0.4 mg/kg	*In vivo*	Liu et al. (2013)
		Gelsemine,	2 mg/kg	*In vivo*	Liu et al. (2013)

Table 3 (*continued*)

Pharmacological effects	Detail	Extracts/compounds	Minimal active concentration/ dose	*In vitro*/ *in vivo*	Reference
		Gelsevirine	0.4 mg/kg	*In vivo*	Liu et al. (2013)
Anti-stress activity	Stress tests such as weight bearing swimming, antihypoxia, high temperature resistance and low temperature resistance	Koumine	2.4 mg/kg/day for 7 days	*In vivo*	Cai et al. (2007)
Effects on skin disease	Effect on psoriasis in mouses models	koumine	6–150 mg/kg for 5 days	*In vivo*	Zhang et al. (2005)
Immunoregulatory effects	Cytotoxicity on murine spleen cells and inhibitory activity on T cell and B cell proliferation	21-(2-oxopropyl)-koumine, 11-methoxygelsegine, koumine, gelselegine	0.1 –10 μM	*In vivo*	Xu et al. (2012b)
	Inhabit mixed lymphocyte	Alkaloids abstract of *Gelsemium sempervirens*	MIC=2.5 μg/ml	*In vitro*	Lei et al. (1996)
		Koumine	MIC=10.5 μg/ml	*In vitro*	Sun et al. (1999)
	Inhabit C_{57}BL/6j mouse splenocytes induced by LPS, Con A	Alkaloids abstract of *Gelsemium sempervirens*	MIC=40 μg/ml (by LPS); 20 μg/ml (by Con A)	*In vitro*	Lei et al. (1996)
		Koumine	MIC=40 μg/ml (by LPS); 5 μg/ml (by Con A)	*In vitro*	Sun et al. (1999)
	Effect on proliferation of murine CD4+ T cells	Koumine	20 μg/ml	*In vitro*	Wang et al. (2005)

increase in the expression of p53, which alters the protein expression ratio of Bcl-xL/Bax leading to caspase activation and cytochrome *c* release from the mitochondria (Zhao et al., 2006b). Gelsemiunoside A and B, two benzofuran lignan glycosides, were isolated from *G. elegans* and exhibit potent cytotoxic activity by suppressing the proliferation of A375-S2 cells with IC_{50} values of 193.4 and 69.4 μM, respectively (Hua et al., 2008). Koumine (50 μM) has been reported to both induce apoptosis of LoVo cells in a time-dependent manner and inhibit DNA synthesis *in vitro* (Chi et al., 2004). Koumine (1.2, 2.4 and 4.8 mg/kg) was also reported to inhibit the growth of H22 solid tumors in BALB/c athymic mice in a dose-dependent manner without any inhibitory effect on the immune system (Cai et al., 2009). An *in vitro* study using the MTT assay focused on the inhibitory effects of gelsemine and its metabolites M1 (4-N-demethylgelsemine) and M2 (21-oxogelsemine) on tumor cell proliferation. These two metabolites exhibit potent inhibitory effects on HepG2 and HeLa cell growth from 40 to 160 μM. However, gelsemine alone exerted no effects on either cell in the same concentration range. The IC_{50} values of 24 h M1-treated HepG2 cells and HeLa cells were 340.3 and 338.9 μM, respectively; M2-treated cells were 107.1 and 169.8 μM, respectively (Zhao et al., 2010b). Gelsebanine, an extraction artifact, was isolated from the stems and leaves of *Gelsemium elegans* and was cytotoxic to A-549 (human lung adenocarcinoma cell line) cells with an IC_{50} value of 6.34×10^{-7} M (Xu et al., 2006). Gelsemicine isolated from *Gelsemium sempervirens* and five alkaloids isolated from the leaves of *Gelsemium elegans* including gelsedine, 14-acetoxygelsenicine, 14-acetoxy-15-hydroxygelsenicine, 14,15-dihydoxygelsenicine and gelsenicine showed relatively strong cytotoxic effects on the A431 human epidermoid carcinoma cell line with EC_{50} values of 0.35, 0.25, 36, 1.3, 37 and 0.75 μM, respectively (Kitajima et al., 2006). Scopoletin is an analog of coumarin that was separated from the ethanolic extract of *Gelsemium sempervirens*, which has a considerable inhibitory potential in HeLa cells (Bhattacharyya et al., 2008). Additionally, 4-Methyl-7-hydroxy coumarin, a synthetic coumarin that is structurally similar to scopoletin, has been evaluated for potential anti-tumor effects on DMBA (7, 12-Dimethylbenz[α]anthracine) induced skin cancer in mice. Its major mechanism of action in reducing tumor formation is by mediating Aryl hydrocarbon receptors and increasing the production of PCNA (Proliferating Cell Nuclear Antigen) in mice (Bhattacharyya et al., 2010).

5.2. Anti-inflammatory and analgesic activity

A parenteral introduction of a crude alkaloidal extract solution from *Gelsemium elegans* (0.5, 1.0 and 2.0 mg/kg) significantly increased the pain thresholds of mice in both hot plate and writhing tests. The alkaloidal extract also increased the pain threshold of rats in a tail flick test with an ED_{50} of 0.5 mg/kg (Tan et al., 1988). Rujjanawate et al. (2003) also demonstrated the analgesic and anti-inflammatory effects of a crude alkaloidal fraction from *Gelsemium elegans*. The crude alkaloidal fraction showed a significant decrease in the writhing test in mice at sub lethal doses of 1.0 and 2.5 mg/kg. However, the reaction time in the tail immersion test failed to increase at the same dose; thus, demonstrating that the analgesic activity of the crude alkaloidal fraction is peripheral. The formalin test demonstrated that the crude alkaloidal fraction has analgesic activity at doses of 1.0 and 2.5 mg/kg in both the early and late phases. The ear edema test induces inflammation with ethyl phenylpropiolate and suggests that the crude alkaloidal fraction has an effect on acute inflammation at a dose of 2.5 mg per ear. Gelsenicine was found to produce dose-dependent analgesic effects in both inflammatory and neuropathic pain models. Pretreatment of mice with 4 and 20 μg/kg gelsenicine inhibited writhing by 40.9–58.5% with an ED_{50} of 10.4 μg/kg. Writhing decreased by 78.1% in comparison with the control group. Gelsenicine inhibited formalin-induced nociceptive behavior only in the second phase with an ED_{50} value of 7.4 μg/kg. The analgesic effect of gelsenicine was further studied by using the chronic constriction injury (CCI) method with an ED_{50} of 9.8 μg/kg (Liu et al., 2011). Koumine, one of the main alkaloidal constituents of *Gelsemium elegans*, has a significant effect on both inflammatory and neuropathic pain. Several animal models of inflammatory and neuropathic pain were used to evaluate the analgesic activity of koumine., The ED_{50} of koumine in a writhing response test was 5.85 mg/kg in mice. A formalin-induced nociceptive behavior test showed that koumine significantly reduces nociceptive behavior at 2 and 10 mg/kg doses in the second phase. In the CFA model, koumine also reversed thermal hyperalgesia after the administration of koumine (4, 20 mg/kg) once per day for 10 consecutive days. Further studies of koumine in neuropathic pain models have shown a reduction in both thermal hyperalgesia and mechanical allodynia in the CCI and L5SNL models with twice a day administration of koumine (7 mg/kg) beginning from post-operative day

Table 4
Toxicological effects of the *Gelsemium* species.

Extracts/Compounds	Animals	Route	LD_{50}/Dose range	Toxic symptom	Reference
Parenteral solution of crude alkaloidal extraction	Rat (male)	i.p.	LD_{50}=1.2 mg/kg	Dyspnea, convulsions, death occurs between 3–12 h	Tan et al. (1988)
Parenteral solution of crude alkaloidal extraction	Mice (female)	i.m.	LD_{50}=1.5 mg/kg	Dyspnea, convulsions, convulsions followed by death	Tan et al. (1988)
Parenteral solution of crude alkaloidal extraction	Mice	i.m.	LD_{50}=3.6 mg/kg	Dyspnea, convulsions, convulsions followed by death	Tan et al. (1988)
Parenteral solution of crude alkaloidal extraction	Mice	i.v.	LD_{50}=1.56 mg/kg	Dyspnea, convulsions, convulsions followed by death	Tan et al. (1988)
Parenteral solution of crude alkaloidal extraction	Rabbit (female)	i.v.	$LD_{50}=76\pm22$ mg/kg	Exciting, dyspnea, convulsions followed by death	Tan et al. (1988)
Parenteral solution of crude alkaloidal extraction	Monkey	s.c.	1.6 mg/kg	Muscular weakness, respiratory depression, recovered 1 h later	Tan et al. (1988)
Crude alkaloidal fraction	Rat	p.o.	LD_{50}=15 mg/kg	Asphyxia, respiratory arrest, convulsions and death	Rujjanawate et al. (2003)
Crude alkaloidal fraction	Rat	i.p.	LD_{50}=4 mg/kg	Asphyxia, respiratory arrest, convulsions and death	Rujjanawate et al. (2003)
		i.v.(in tail)	LD_{50} =3.07 ml/kg	Asphyxia, respiratory arrest, convulsions and death	Zhou et al. (1995)
Gelsemine	Mice	i.p.	LD_{50}=56.2 mg/kg	Stimulates respiration, tremors and convulsions followed by death	Chen et al. (1987)
Gelsevirine N-oxide	Mice	i.p.	LD_{50}=63.1 mg/kg	Increase in motor activity, stimulates respiration, tremors and convulsions followed by death	Chen et al. (1987)
Koumicine	Mice	i.p.	>125 mg/kg	Decrease in motor activity, ataxia, dyspnea, disappearance of pain response	Chen et al. (1987)
Koumidine	Mice	i.p.	>125 mg/kg	Shortness of breath, disappearance of pain response, death occurs after 30 min, surviving animals paralyzed more than 3 h	Chen et al. (1987)
Koumine	Mice	i.p.	99 mg/kg	Respiration became labored, and brief coordinated, clonic convulsions occurred immediately before death.	Chen et al. (1987), Xu et al. (2012a)
Gelsenicine	Mice	i.p.	LD_{50}=0.165 mg/kg	Death	Chen et al. (1987)
	Mice	s.c.	LD_{50}: 0.1–0.2 mg/kg	Death	Liu et al. (2011)
		i.p.	LD_{50} =0.185 mg/kg	death.	Chen et al. (1987)
Kouminicine	Mice	i.p.	2.83 mg/kg	Death	Chen et al. (1987)
	Rat	i.v.	0.7 mg/kg	Head fibrillation, tonic convulsions, and died of respiratory depression	Chen et al. (1987)
Humantendine	Mice	i.p.	0.21 mg/kg	Respiration became labored, convulsions, death occurs between 5–10 m	Zhou et al. (1995)
	Mice	i.v.	0.128 mg/kg	Respiration became labored, convulsions, death occurs between 5–10 m	Zhou et al. (1995)
	Rat	i.p.	0.26 mg/kg	Respiration became labored, convulsions, death occurs between 5–10 m	Zhou et al. (1995)
	Rat	i.v.	0.15 mg/kg	Respiration became labored, convulsions, death occurs between 5–10 m	Zhou et al. (1995)
Gelsemicine	Frog	i.p.(in saccus lymphaticus)	20–30 mg/kg	Respiratory depression, convulsions	Brossi (1988)
	Rat	i.p. or i.v.	0.1–0.3 mg kg	Respiratory depression, convulsions	Brossi (1988)
	Rabbit	i.v.	0.05–0.06 mg/kg	Respiratory depression, convulsions	Brossi (1988)
	Dog	i.v.	0.05–0.10 mg/kg	Respiratory depression, convulsions	Brossi (1988)

4 and concluding on day 10 (Xu et al., 2012a). Zhang et al., 2013a, b demonstrated that gelsemine produces potent and specific anti-nociception effects in chronic pain states by the activation of spinalα3 GlyRs.

5.3. Anxiolytic activity

A methanol extract prepared from the roots and rhizome of *Gelsemium sempervirens* affects the behavior of mice in an elevated plus maze model. At a dosage of 150 mg/kg the mice significantly increased the number of entries and mean time spent in the open arms in the maze. In comparison, petroleum, chloroform and water extracts did not show any significant effects on mouse behavior (Dutt et al., 2010a). A fraction (F9.4) derived from the methanol extract also exhibited a significant anxiolytic activity at a 10 mg/kg dosage level in the elevated plus maze test. Alkaloids and iridiods are the main constituents found in the F9.4 fraction (Dutt et al., 2010a). Bellavite et al. (2009) carried out a series of behavioral tests on dilutions/dynamizations of *Gelsemium sempervirens*, and they observed that *Gelsemium sempervirens* treated mice exhibit non-anxious behavior in the light–dark and open-field tests (Magnani et al., 2010; Bellavite et al., 2012). Venard et al. (2011) observed the anxiolytic and analgesic effects of *Gelsemium sempervirens* by demonstrating that centesimal dilutions (5, 9 and 15 cH) of *Gelsemium sempervirens* and gelsemine stimulate the synthesis of 3α, 5α-THP in the limbic system and spinal circuit through modulating glycine receptors. A possible explanation for these effects is that gelsemine antagonizes glycine receptors and stimulates the biosynthesis of allopregnanolone (Venard et al 2011). In a recent study, low doses of gelsemine were reported

to exhibit anxiolytic effects, and this study may provide new perspectives for the development of safe and effective anxiolytic drugs (Meyer et al., 2013).

5.4. Immunostimulatory and immunosuppressive activities

Koumine (20–320 μg/ml) dose-dependently inhibits the proliferation of murine $CD4^+$ cells induced by cancanavalin A (5 mg/ml) or phytahematoagglutinin (1 mg/ml). Koumine also significantly decreases the levels of IL-2 at doses of 20, 100 and 200 μg/ml, respectively (Wang et al., 2005). Furthermore, koumine was shown to significantly inhibit the proliferation of murine splenocytes *in vitro*. This effect was induced by a mixed lymphocyte response and cancanavalin A (2 μg/mg) or lipopolysaccharide (10 μg/ml). Additionally, koumine pretreatment of mice with 10, 20 and 40 mg/kg for 7 days reduced the activities of serum hemolysin by 19.2%, 34.4% and 37%, respectively. Koumine delivered at high concentrations slightly suppressed complement-mediated-hemolysis *in vitro* (Sun et al., 1999).

5.5. Effects on skin disease

Gelsemium sempervirens, one of the constituents in drug formulations, has been used for the treatment of psoriasis and neurodermatitis (Calarasu, 1988). The vaginal mucous and squamous epidermis from mice tails were used to study the therapeutic effects of koumine on psoriasis. Treatment with koumine (6, 30 and 150 mg/kg/day for 6 days) showed a significant inhibitory effect on the mitosis of vaginal epithelial cells and promoted the formation of an epidermal granular layer. Furthermore, koumine decreased serum IL-2 levels dose-dependently in mice. These findings suggest that the therapeutic effects of koumine on psoriasis are related to an immunomodulatory effect (Zhang et al., 2005).

6. Toxicology

All three species of *Gelsemium* are highly poisonous. The leaves, stems and roots are equally toxic, and consuming the plant has been used as a method to commit suicide and homicide (Zhang and Huang, 1988). Experimental work indicates that typical symptoms of intoxication include sweating, dizziness, nausea, vomiting, blurred vision, muscular weakness, limb paralysis, dilated pupils, breathing difficulty, coma and convulsion. In instances of severe poisoning, the nervous system is depressed and death is caused by respiratory depression (Tan et al., 1988; Zhou et al., 1995; Rujjanawate et al., 2003).

The high concentration of alkaloids appears to be responsible for the toxic effects of the plant, and the typical symptoms exhibited by someone who has overdosed on *Gelsemium* are similar to the symptoms of alkaloid poisoning. We have summarized the toxic information of the extract and alkaloids in Table 4. The acute toxicity of a crude alkaloidal extraction isolated from *Gelsemium elegans* was assessed by determining 50% of the lethal dose (LD_{50}), when given to mice (female, im; male and female, intravenously) and rats (male, intraperitoneally). The LD_{50} was determined to be 1.5, 1.2 and 1.56 mg/kg, respectively. The mean lethal dose of a crude alkaloidal extract in female rabbits was estimated to be 76 ± 22 mg/kg after parenteral administration of a 1% solution (Tan et al., 1988). The toxicity of a crude alkaloidal fraction (CAF) from the leaves of *Gelsemium elegans* was also evaluated. Oral administration of a CAF at doses of 5, 10, 15 and 20 mg/kg was lethal in 0, 11%, 50%, 72% and 100% in mice, respectively. At a dose of 7 mg/kg, a CAF caused 100% mortality when administered by intraperitoneally. The LD_{50} is 15 and 4 mg/kg when administered orally and intraperitoneally, respectively (Rujjanawate et al., 2003). Among the monomer alkaloids from *Gelsemium sempervirens*, gelsemicine is the most toxic compound ($LD_{50} \sim 0.2$ mg/kg, rat, intraperitoneally), and gelsemine is the most abundant compound ($LD_{50} \sim 56$ mg/kg, mice, intraperitoneally). In contrast, gelsenicine is the most toxic alkaloid in *Gelsemium elegans* ($LD_{50} \sim 0.128$ mg/kg, mice, intraperitoneally; 0.26 mg/kg, rat, intraperitoneally; 0.15 mg/kg, rat, intravenously). Koumine is the most abundant alkaloid in *Gelsemium elegans* and exhibits mild toxicity ($LD_{50} \sim 100$ mg/kg, mice, intraperitoneally) (Chen et al., 1987; Xu et al., 2012a, b).

7. Conclusions

In this review, we document the existing traditional uses of the species of the genus *Gelsemium* and summarize recent research into the phytochemistry, pharmacology and toxicology of the genus. Previous studies have documented that *Gelsemium* species have traditionally been used to treat neuralgia, anxiety, cancer and various skin diseases. Some of these traditional uses have been validated by phytochemical and modern pharmacological studies. The extracts and single compounds derived from the genus have been found to possess various biological activities, especially in the areas of anti-tumor, anxiolytic and anti-nociceptive activities. Even more promising is that the therapeutic effects of some of the active ingredients, such as koumine and gelsevirine, exhibit therapeutic effects at levels far below their LD50 values, suggesting these alkaloids may be therapeutically safe for the treatment of certain diseases.

Although increased interest has prompted more studies on the phytochemistry, pharmacology and toxicology of the genus *Gelsemium*, there are still many areas where our current knowledge could be improved. (i) According to traditional Chinese medicine, all parts of *Gelsemium* plants are toxic, including the flower and nectar, and its medical use has therefore been limited due to safety concerns. Thus, detailed investigations on the toxic components and toxicological mechanisms of *Gelsemium* are needed. (ii) The genus *Gelsemium* is a rich source of indole alkaloids, many with the same skeletal structure. Therefore, it would be interesting to investigate the structure-activity relationships of these alkaloids. We would expect to find high efficiency and low toxicity compounds from these alkaloids. (iii) Several traditional uses of the genus have been validated in recent pharmacological studies; however, some of these pharmacological activities were only tested *in vitro*. Thus, the effectiveness of these compounds *in vivo* needs to be further investigated. Taken together, the importance of genus *Gelsemium* has been highlighted based on their wide usage in traditional medicine as well as potential in beneficial therapeutic remedy. Nevertheless, there is clearly a need for further studies focusing on *in vivo* and eventually clinical trials.

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