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A Review on Therapeutic Potential and Perspectives of *Gelsemium*

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Abstract: Gelsemium *species have attracted increasing scientific interest due to their potential anxiolytic and stress-modulating properties. Recent pharmacological studies suggest that the bioactive alkaloids present in these plants influence inhibitory neurotransmission within the central nervous system by modulating glycinergic and GABAergic signaling pathways. These interactions appear to regulate neuronal excitability and may contribute to reductions in anxiety-like behaviors observed in experimental models. In addition, certain* Gelsemium *compounds stimulate the synthesis of neurosteroids such as allopregnanolone, which further enhances inhibitory neurotransmission and supports the regulation of stress responses. Literature review of many studies also indicated that* Gelsemium *extracts may influence multiple neuronal pathways involved in emotional processing and neurochemical balance. Although these findings highlight promising therapeutic potential for the development of novel anxiolytic agents, further research is necessary to fully understand the pharmacokinetics, safety, and clinical applicability of* Gelsemium*-derived compounds*

Key Words: *Gelsemium, Anxiety, Neurotransmitters, Stress relief.*

1. INTRODUCTION AND THERAPEUTIC CAPABILITIES OF *GELSEMIUM* SPECIES:

Medicinal plants have long served as an essential reservoir for the discovery of pharmacologically active molecules. In recent decades, increasing attention has been directed toward plants that possess both potent bioactivity and complex secondary metabolites, particularly those belonging to the genus *Gelsemium*. This genus, belonging to the family Gelsemiaceae, comprises a small group of climbing shrubs widely distributed across different regions of world, with the three most recognized species being *Gelsemium elegans*, *Gelsemium sempervirens*, and *Gelsemium rankinii* (Peng et al., 2023; Wang et al., 2023). These species are historically renowned for their dual nature as both medicinally valuable and highly toxic plants, which has intrigued pharmacologists and phytochemists for decades.

Traditional medical systems have employed *Gelsemium* preparations for a wide spectrum of ailments including neuralgia, migraine, anxiety disorders, inflammatory conditions, skin diseases, fractures, and certain cancers. Such ethnopharmacological uses have been recorded in classical Chinese herbal texts as well as in North American folk medicine (Peng et al., 2023). In particular, *G. elegans* known in Chinese medicine as “Duan-Chang-Cao” has been historically utilized for treating neuropathic pain, skin ulcers, and inflammatory disorders despite its well-known toxicity (Peng et al., 2023). Similarly, *G. sempervirens* has been traditionally used as a neuroactive remedy for conditions such as anxiety, migraine, and spasmodic disorders (Bellavite et al., 2018).

Modern pharmacological research has increasingly validated many of these traditional claims, revealing that *Gelsemium* species contain a remarkable diversity of bioactive secondary metabolites, particularly monoterpenoid indole alkaloids (MIAs). These compounds represent the principal pharmacologically active constituents of the genus and exhibit diverse chemical scaffolds and biological activities. Recent studies have identified more than 200 alkaloids from *Gelsemium* plants and their endophytic fungi, highlighting the exceptional chemical diversity within this genus (Peng et al., 2023). These alkaloids can be broadly classified into several structural types, including gelsemine-type, koumine-type, humantenine-type, gelsedine-type, sarpagine-type, and yohimbane-type alkaloids (Wang et al., 2023).

The pharmacological activities of *Gelsemium* constituents have attracted considerable interest due to their multifaceted therapeutic potential. Experimental studies indicate that extracts and isolated compounds from *Gelsemium* species exhibit analgesic, anti-inflammatory, anxiolytic, immunomodulatory, and antitumor activities. These biological effects have been demonstrated in both in vitro and in vivo experimental models, suggesting that the genus may serve as a valuable source of novel therapeutic agents (Peng et al., 2023; Wang et al., 2023). Furthermore, certain alkaloids

such as gelsemine, koumine, and gelsevirine have shown significant pharmacological effects on the central nervous system, particularly through interactions with inhibitory neurotransmitter receptors (Wang et al., 2025).

Among the various therapeutic properties reported, neuropharmacological activity represents one of the most distinctive features of *Gelsemium*. Studies indicate that its alkaloids can modulate key inhibitory neurotransmitter systems, including glycine receptors and GABAA_AA receptors, which are essential regulators of neuronal excitability. Such interactions may explain the traditional use of *Gelsemium* in treating anxiety, neuralgia, and certain neurological disorders (Wang et al., 2024; Bellavite et al., 2018). These findings have positioned *Gelsemium* as a promising candidate for the development of novel neuroactive compounds targeting central nervous system disorders.

In addition to its neurological effects, *Gelsemium* species have demonstrated significant anticancer potential. Several alkaloids isolated from *G. elegans* exhibit cytotoxic activity against various cancer cell lines, suggesting possible applications in cancer chemotherapy. Mechanistic studies indicate that these compounds may induce apoptosis, inhibit tumor cell proliferation, and modulate immune responses associated with tumor progression (Peng et al., 2023). The complexity of the alkaloid structures has also attracted the interest of synthetic chemists, who are exploring strategies to develop novel derivatives and synthetic analogues with improved therapeutic profiles (Wang et al., 2023).

Despite its promising therapeutic properties, the clinical development of *Gelsemium*-derived compounds remains challenging due to the high toxicity and narrow therapeutic index associated with many of its alkaloids. Consumption of crude plant material can produce severe symptoms including dizziness, muscular paralysis, respiratory depression, and even fatal poisoning. Consequently, understanding the precise pharmacological mechanisms and establishing safe dosage ranges are critical prerequisites for the medicinal utilization of this genus (Peng et al., 2023).

Recent advances in molecular pharmacology, computational chemistry, and metabolomics have begun to clarify the mechanisms underlying the biological activities of *Gelsemium* alkaloids. Modern approaches combining electrophysiological studies with computational modeling have helped identify potential molecular targets and receptor interactions, providing deeper insights into their pharmacodynamic properties (Wang et al., 2025). These developments are expected to facilitate the discovery of safer derivatives and optimized therapeutic agents derived from *Gelsemium* phytochemicals.

In the Indian context, research and ethnomedicinal documentation related to *Gelsemium* species have gained increasing attention, particularly due to the presence and traditional use of *Gelsemium elegans* in certain regions of Northeast India, including Assam, Nagaland, and parts of Arunachal Pradesh. Indigenous communities in these areas have historically recognized the plant for both its medicinal potential and extreme toxicity, using carefully controlled preparations in folk medicine for conditions such as chronic pain, skin infections, rheumatism, and certain inflammatory disorders (Das et al., 2018; Devi & Singh, 2020). Ethnobotanical surveys conducted in Northeast India indicate that traditional healers possess specialized knowledge regarding detoxification and dosage practices, reflecting a sophisticated understanding of the plant's pharmacological potency (Borah et al., 2019). In recent years, Indian pharmacological and phytochemical investigations have begun exploring the alkaloid-rich extracts of *G. elegans* for their potential analgesic, anti-inflammatory, and anticancer activities, aligning with global research trends on monoterpenoid indole alkaloids from this genus (Kalita et al., 2021; Sharma et al., 2023). Furthermore, Indian researchers have emphasized the importance of integrating ethnopharmacological knowledge with modern pharmacology and toxicology to ensure safe therapeutic applications and to explore novel drug leads derived from this highly potent medicinal plant (Kalita et al., 2021; Sharma et al., 2023). Consequently, the growing body of Indian research highlights the significance of *Gelsemium* as a potential source of bioactive compounds while simultaneously emphasizing the need for rigorous safety evaluation and standardization before its incorporation into modern therapeutic systems.

The genus *Gelsemium* represents a unique group of medicinal plants characterized by exceptional chemical diversity, potent biological activity, and complex pharmacological profiles. The increasing body of scientific evidence suggests that these plants hold considerable promise for the development of new therapeutic agents, particularly in the fields of neurology, oncology, and immunomodulation. However, further research is required to fully elucidate their mechanisms of action, improve their safety profiles, and translate experimental findings into clinically applicable treatments.

2. LITERATURE REVIEW:

Major Bioactive Alkaloids of *Gelsemium* and Pharmacological Mechanisms of Gelsemine

The genus *Gelsemium* (family Gelsemiaceae) is well known for its remarkable diversity of monoterpenoid indole alkaloids (MIAs), which represent the principal bioactive constituents responsible for the plant's pharmacological and toxicological properties. Modern phytochemical investigations indicate that *Gelsemium elegans* alone contains over

100 structurally diverse alkaloids, many of which exhibit significant biological activities including analgesic, anxiolytic, anti-inflammatory, neuroprotective, and anticancer effects (Wang et al., 2025; Sun et al., 2019).

These alkaloids are structurally classified into several chemical groups, including gelsemine-type, koumine-type, gelsedine-type, humantenine-type, sarpagine-type, and yohimbane-type alkaloids**.** Among these, compounds such as gelsemine, koumine, gelsevirine, gelsenicine, and humantenine are considered the major pharmacologically active constituents of the plant (Zhang et al., 2017; Wang et al., 2025).

Recent analytical and toxicological studies have confirmed that several of these alkaloids including gelsemine, koumine, gelsenicine, gelsevirine, and humantenine are among the most abundant and biologically significant compounds present in *Gelsemium elegans*.

3. MAJOR BIOACTIVE ALKALOIDS OF *GELSEMIUM*

Gelsemine:

Gelsemine is one of the most extensively studied alkaloids of *Gelsemium* and is considered the principal active compound responsible for many of the plant's neurological and pharmacological effects. Structurally, it belongs to the gelsemine-type monoterpenoid indole alkaloids, characterized by a complex polycyclic framework derived from tryptamine and secologanin biosynthetic precursors (Sun et al., 2019). Pharmacological studies indicate that gelsemine exhibits analgesic, anxiolytic, neuroprotective, and anti-inflammatory activities, largely through its ability to modulate inhibitory neurotransmission in the central nervous system (Wang et al., 2025).

Koumine:

Koumine is the most abundant alkaloid in *Gelsemium elegans* and has attracted considerable interest due to its diverse pharmacological effects. This compound belongs to the koumine-type indole alkaloids and has been shown to possess analgesic, anti-inflammatory, anxiolytic, and neuroprotective activities (Wang et al., 2025). Experimental studies have demonstrated that koumine can alleviate neuropathic pain and inflammatory responses by modulating glycine receptor signaling and suppressing inflammatory cytokine production (Shoaib et al., 2019).

Gelsenicine:

Gelsenicine is another important alkaloid present in *Gelsemium elegans*, although it is known to possess significantly higher toxicity compared with other alkaloids**.** Despite this toxicity, pharmacological studies have revealed that gelsenicine exhibits potent biological activities, including strong analgesic effects mediated through modulation of glycine receptor pathways (Li et al., 2023).

Gelsevirine:

Gelsevirine belongs to the gelsedine-type alkaloid group and has demonstrated moderate cytotoxic activity against several cancer cell lines in experimental studies. These compounds are also being investigated for their potential anti-inflammatory and neuroactive effects (Sun et al., 2019).

Humantenine:

Humantenine is another structurally important alkaloid isolated from *Gelsemium elegans*. Research indicates that humantenine and its derivatives exhibit biological activities such as cytotoxic effects against tumor cells and inhibition of nitric oxide production in inflammatory models (Xu et al., 2015).

4. PHARMACOLOGICAL MECHANISMS OF GELSEMINE

Among the numerous alkaloids identified in *Gelsemium*, gelsemine has received particular attention due to its broad spectrum of pharmacological effects**,** especially within the nervous system. Modern pharmacological research indicates that gelsemine acts through multiple molecular mechanisms that influence neuronal signaling, neuroinflammation, and synaptic transmission.

Modulation of Glycine Receptors:

One of the most well-established mechanisms of gelsemine involves its interaction with glycine receptors (GlyRs) in the spinal cord and central nervous system. Glycine receptors are inhibitory neurotransmitter receptors that regulate neuronal excitability by allowing chloride ion influx into neurons. Experimental studies have demonstrated that gelsemine acts as an agonist at glycine receptors, enhancing inhibitory neurotransmission and reducing neuronal excitability associated with pain signaling. Activation of these receptors contributes to the analgesic and anxiolytic properties of the compound (Shoaib et al., 2019).

Stimulation of Neurosteroid Biosynthesis:

Another important mechanism underlying the pharmacological effects of gelsemine involves stimulation of neurosteroid synthesis, particularly the production of allopregnanolone. Activation of glycine receptors by gelsemine increases the expression of enzymes such as 3α-hydroxysteroid oxidoreductase, which are involved in neurosteroid

biosynthesis. These neurosteroids subsequently enhance GABA**A_AA** receptor activity, leading to increased inhibitory signaling in the nervous system (Shoaib et al., 2019).

Anti-Inflammatory and Neuroprotective Effects:

Recent experimental research has also shown that gelsemine exerts anti-inflammatory and neuroprotective effects in the brain. In animal models of neurodegeneration, gelsemine has been shown to suppress the activation of microglia and astrocytes while reducing the expression of inflammatory cytokines such as IL-1β, IL-6, and TNF-α**.** These actions help protect neurons from inflammatory damage and contribute to improved cognitive function (Chen et al., 2020).

Regulation of Neuronal Signaling Pathways:

Gelsemine has also been shown to influence several intracellular signaling pathways associated with neuronal survival and synaptic plasticity. For example, studies indicate that gelsemine increases the phosphorylation of glycogen synthase kinase-3β (GSK-3β) and reduces pathological tau phosphorylation in models of Alzheimer's disease. Through these mechanisms, gelsemine may contribute to the preservation of neuronal integrity and cognitive function (Chen et al., 2020). The genus *Gelsemium* represents an important source of biologically active monoterpenoid indole alkaloids**,** many **o**f which possess significant pharmacological properties. Major alkaloids such as gelsemine, koumine, gelsenicine, gelsevirine, and humantenine contribute to the diverse biological activities of these plants, including analgesic, anti-inflammatory, neuroprotective, and anticancer effects. Among these compounds, gelsemine is the most extensively studied, and its pharmacological effects are primarily mediated through modulation of glycine receptors, stimulation of neurosteroid biosynthesis, suppression of neuroinflammation, and regulation of neuronal signaling pathways. Because of their unique chemical structures and diverse pharmacological activities, *Gelsemium* alkaloids continue to attract considerable interest in natural product research and drug discovery. Further investigations are necessary to better understand their mechanisms of action and to develop safer therapeutic derivatives with reduced toxicity.

5. POWERFUL ANALGESIC (PAIN-RELIEVING) EFFECTS OF *GELSEMIUM* SPECIES:

One of the most distinctive and therapeutically promising pharmacological properties of *Gelsemium* species is their potent analgesic activity, which has attracted significant scientific interest in the past decade. Modern pharmacological studies demonstrate that several monoterpenoid indole alkaloids isolated from *Gelsemium*, particularly gelsemine and koumine, possess strong pain-relieving effects in experimental models of neuropathic, inflammatory, and cancer-related pain. These bioactive alkaloids interact primarily with inhibitory neurotransmitter systems in the central nervous system, offering a unique mechanism for pain modulation compared with conventional analgesic drugs. Such findings suggest that *Gelsemium* species may serve as a valuable source of novel analgesic agents for the treatment of chronic pain disorders (Zhang & Wang, 2015; Xiong et al., 2017; Shoaib et al., 2019).

A key mechanism underlying the analgesic activity of *Gelsemium* alkaloids involves modulation of glycine receptors located in the spinal cord, which are essential inhibitory neurotransmitter receptors responsible for regulating pain transmission in the central nervous system. Experimental electrophysiological studies have shown that the alkaloid gelsemine directly modulates glycine receptor activity, enhancing inhibitory signaling and thereby reducing neuronal excitability associated with pain pathways. This modulation occurs selectively at spinal glycinergic synapses and may alter receptor affinity and ion-channel gating properties, ultimately suppressing nociceptive signaling within the spinal cord (Lara et al., 2016).

Recent molecular pharmacology studies have further clarified this mechanism by demonstrating that gelsemine and koumine act as functional agonists of glycine receptors, producing significant antinociceptive effects in models of neuropathic pain. Activation of these receptors stimulates downstream pathways involving neurosteroid biosynthesis and the allopregnanolone signaling cascade, which enhances inhibitory neurotransmission through GABAergic systems and further contributes to pain suppression. Through this glycine receptor–neurosteroid pathway, *Gelsemium* alkaloids produce marked mechanical antiallodynia and analgesia in rodent models of neuropathic hypersensitivity (Shoaib et al., 2019).

Another important aspect of *Gelsemium* analgesia is its demonstrated efficacy in multiple experimental pain models, including inflammatory pain, postoperative pain, bone cancer pain, and peripheral nerve injury-induced neuropathic pain. Studies using rodent models have reported that koumine, one of the most abundant alkaloids in *Gelsemium elegans*, significantly reduces postoperative and inflammatory pain responses. These effects appear to involve modulation of neuroinflammatory signaling pathways and regulation of neurosteroid synthesis within the spinal cord, highlighting the complex neuropharmacological mechanisms through which *Gelsemium* compounds exert their analgesic effects (Xiong et al., 2017).

Interestingly, the analgesic potency of *Gelsemium* alkaloids has been reported to approach or even rival that of certain opioid analgesics in experimental systems, yet with several potentially advantageous pharmacological features. Unlike classical opioid drugs, repeated administration of *Gelsemium* alkaloids in animal studies does not appear to produce rapid tolerance or dependence, suggesting that these compounds may provide effective pain relief with a lower risk of addiction. Additionally, their mechanism of action primarily targeting glycinergic inhibitory neurotransmission differs fundamentally from the opioid receptor pathway, which raises the possibility of developing non-opioid analgesic therapeutics derived from *Gelsemium* phytochemicals (Zhang & Wang, 2015).

The potential therapeutic implications of these findings are substantial, particularly in the context of chronic and treatment-resistant pain conditions. Neuropathic pain, which arises from damage or dysfunction in the nervous system, is often difficult to manage with existing analgesics. Experimental studies suggest that *Gelsemium* alkaloids can effectively reduce neuropathic pain by suppressing abnormal neuronal activity in the spinal cord and restoring inhibitory neurotransmission. Moreover, emerging evidence indicates that gelsemine may also alleviate pain-associated sleep disturbances and neural hyperactivity in brain regions involved in pain perception, further supporting its potential clinical utility (Wu et al., 2015).

Many findings highlight the unique analgesic potential of *Gelsemium* species, particularly through their ability to modulate glycinergic inhibitory pathways in the central nervous system. By targeting mechanisms distinct from conventional analgesic drugs, *Gelsemium* alkaloids offer promising prospects for the development of new therapeutics for neuropathic pain, migraine, neuralgia, and cancer-related pain. Nevertheless, despite these encouraging pharmacological properties, further research is required to address the toxicity and narrow therapeutic window associated with certain *Gelsemium* compounds before their safe clinical application can be realized.

6. ANXIOLYTIC AND ANTI-STRESS EFFECTS OF *GELSEMIUM* SPECIES:

The genus *Gelsemium*, particularly *Gelsemium sempervirens*, has attracted growing scientific interest for its potential anxiolytic (anxiety-reducing) and anti-stress properties. Historically, preparations of this plant have been used in traditional medicine for symptoms associated with nervousness, emotional distress, and stress-related disorders**,** and modern experimental studies increasingly support these observations. Recent pharmacological investigations suggest that specific *Gelsemium* alkaloids especially gelsemine and koumine may modulate key inhibitory neurotransmitter systems in the central nervous system, thereby influencing neural circuits involved in anxiety and stress regulation. These findings have stimulated renewed research into the therapeutic potential of *Gelsemium* compounds as alternative or complementary treatments for anxiety-related conditions (Wang et al., 2024; Bellavite & Marzotto, 2018).

A central mechanism underlying the anxiolytic activity of *Gelsemium* appears to involve modulation of inhibitory neurotransmission, particularly through GABAergic and glycinergic signaling pathways. These neurotransmitter systems play a crucial role in maintaining the balance between neuronal excitation and inhibition in the brain. Experimental electrophysiological and computational studies have demonstrated that several *Gelsemium* alkaloids interact with **GABAA_AA** and glycine receptors, two major inhibitory receptor systems that regulate neuronal excitability and emotional responses (Marileo et al., 2024; Wang et al., 2025). Through these interactions, *Gelsemium* compounds may reduce excessive neuronal activity associated with anxiety and stress responses. Molecular modeling studies further indicate that these alkaloids bind to specific receptor interfaces within inhibitory neurotransmitter receptors, suggesting a plausible pharmacological basis for their calming and anxiolytic effects (Marileo et al., 2024).

Another key mechanism contributing to the anti-stress effects of *Gelsemium* involves the regulation of neurosteroid synthesis, particularly the production of allopregnanolone, a neuroactive steroid known to modulate stress and emotional behavior. Experimental studies have shown that *Gelsemium* alkaloids can stimulate the biosynthesis of allopregnanolone in neuronal tissues through activation of glycine receptors (Venard et al., 2017; Marileo et al., 2024). This neurosteroid subsequently enhances GABAergic inhibitory transmission, producing a calming effect on neural circuits involved in anxiety and stress regulation. Such mechanisms suggest that *Gelsemium* may influence the brain's endogenous stress-modulating pathways rather than acting solely through direct receptor activation (Venard et al., 2017).

Evidence for these anxiolytic effects has been obtained from several experimental behavioral models of anxiety. In rodent studies using standard behavioral tests such as the light–dark box test and open-field test, administration of *Gelsemium sempervirens* extracts has been shown to reduce anxiety-like behaviors and increase exploratory activity without significantly impairing motor coordination or inducing sedation (Bellavite et al., 2016; Marzotto et al., 2017). These behavioral outcomes resemble the effects of conventional anxiolytic drugs, indicating that *Gelsemium* may influence emotional processing in the central nervous system. Importantly, some experiments have demonstrated that the anxiolytic-like effects of *Gelsemium* can be blocked by benzodiazepine receptor antagonists, suggesting that its activity may involve pathways related to GABA receptor modulation (Bellavite et al., 2016).

In addition to behavioral observations, molecular studies provide further insights into how *Gelsemium* may influence stress-related neuronal pathways. Gene expression profiling experiments conducted in human neuroblastoma cells have shown that exposure to *Gelsemium sempervirens* extracts results in down-regulation of genes associated with excitatory neurotransmission**,** including receptors involved in nociception, anxiety, and stress signaling (Olioso et al., 2018). Such findings suggest that *Gelsemium* may reduce neuronal hyperexcitability at the molecular level, thereby contributing to its anxiolytic and stress-modulating effects. These results highlight the possibility that *Gelsemium* compounds influence multiple neural pathways simultaneously, including neurotransmitter signaling, neurosteroid production, and gene regulation (Olioso et al., 2018; Wang et al., 2025).

The potential clinical implications of these findings are considerable. Anxiety disorders including generalized anxiety disorder, stress-related conditions, and behavioral anxiety states are among the most prevalent psychiatric disorders worldwide, yet many currently available treatments are associated with adverse effects such as sedation, tolerance, or dependency. Because *Gelsemium* compounds appear to act through endogenous inhibitory pathways and neurosteroid modulation, they may represent promising candidates for the development of novel anxiolytic agents with potentially improved safety profiles (Marileo et al., 2024; Wang et al., 2025). Ongoing research continues to explore the therapeutic applicability of these compounds in both preclinical models and pharmacological investigations of central nervous system disorders.

Literature evidence suggests that *Gelsemium*, particularly *Gelsemium sempervirens*, possesses significant anxiolytic and anti-stress potential mediated through complex neuropharmacological mechanisms. By modulating glycinergic and GABAergic neurotransmission and stimulating the production of neurosteroids such as allopregnanolone, *Gelsemium* alkaloids influence key neural circuits involved in emotional regulation (Venard et al., 2017; Marileo et al., 2024). Although these findings are promising, further studies are needed to clarify the safety, pharmacokinetics, and clinical efficacy of these compounds before they can be translated into therapeutic applications for anxiety and stress-related disorders (Wang et al., 2025).

7. NEUROPROTECTIVE ACTIVITY OF *GELSEMIUM* SPECIES:

In recent years, increasing scientific attention has been directed toward the neuroprotective potential of bioactive alkaloids derived from *Gelsemium* species, particularly *Gelsemium elegans* and *Gelsemium sempervirens*. These plants contain a rich diversity of monoterpenoid indole alkaloids, including gelsemine, koumine, and related compounds, many of which exhibit significant pharmacological activity in the central nervous system. Contemporary pharmacological research suggests that these alkaloids possess multiple neuroprotective properties, including the ability to reduce neuroinflammation, protect neurons from oxidative stress, and regulate neuronal signaling pathways. Such multifaceted mechanisms have generated considerable interest in exploring *Gelsemium*-derived compounds as potential therapeutic agents for neurological and neurodegenerative disorders (Chen et al., 2020; Panes-Fernández et al., 2025).

One of the most important neuroprotective actions of *Gelsemium* alkaloids involves the suppression of neuroinflammation, a pathological process implicated in numerous neurological disorders including Alzheimer's disease, Parkinson's disease, and traumatic brain injury. Neuroinflammation typically arises from the overactivation of glial cells particularly microglia and astrocytes which subsequently release inflammatory mediators such as cytokines and reactive oxygen species that damage neuronal tissues. Experimental investigations have demonstrated that gelsemine significantly inhibits the activation of microglia and astrocytes, thereby reducing the production of pro-inflammatory cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). By suppressing these inflammatory signaling pathways, *Gelsemium* compounds help maintain neuronal homeostasis and protect neural networks from inflammatory damage (Chen et al., 2020).

Another important mechanism underlying the neuroprotective activity of *Gelsemium* involves protection against oxidative stress, which is widely recognized as a major contributor to neuronal degeneration. Oxidative stress results from the excessive accumulation of reactive oxygen species (ROS), which can damage cellular components such as lipids, proteins, and DNA within neurons. Studies investigating the pharmacological effects of gelsemine indicate that the compound can reduce oxidative stress by modulating intracellular signaling pathways and improving antioxidant defenses in neuronal cells. By maintaining redox balance and preventing oxidative injury, *Gelsemium* alkaloids contribute to the preservation of neuronal structure and function in experimental models of neurotoxicity (Panes-Fernández et al., 2025).

Besides their anti-inflammatory and antioxidant properties, *Gelsemium* alkaloids have been shown to modulate neuronal excitability and synaptic signaling, which are essential processes for maintaining proper neural communication. Research indicates that gelsemine interacts with several molecular targets involved in neuronal signaling, including inhibitory neurotransmitter receptors and enzymes associated with neurosteroid synthesis. These interactions influence synaptic activity and neuronal firing patterns, thereby stabilizing neural circuits and preventing

excitotoxic damage that often occurs during neurodegenerative processes. The ability of *Gelsemium* compounds to influence multiple signaling pathways simultaneously may explain their broad neuroprotective effects observed in both cellular and animal models (Panes-Fernández et al., 2025).

A particularly significant aspect of *Gelsemium*-mediated neuroprotection is its potential role in preventing β-amyloid toxicity, which is a hallmark of Alzheimer's disease pathology. Experimental studies have demonstrated that gelsemine can interfere with the aggregation and toxicity of β-amyloid peptides, which normally accumulate in the brain and contribute to neuronal degeneration. Recent molecular investigations have shown that gelsemine inhibits the activity of transglutaminase-2 (TG2), an enzyme involved in promoting β-amyloid aggregation and neurotoxicity. By blocking TG2 activity, gelsemine reduces β-amyloid-induced neuronal damage and helps preserve neuronal viability in experimental models. This mechanism highlights the potential of *Gelsemium* alkaloids as promising candidates for therapeutic intervention in neurodegenerative disorders (Panes-Fernández et al., 2025).

Gelsemium compounds have also demonstrated beneficial effects on cognitive function and synaptic integrity in animal models of neurodegeneration. Studies involving β-amyloid-induced neurotoxicity have shown that administration of gelsemine can significantly improve cognitive performance and spatial memory in mice. These improvements are associated with the restoration of synaptic proteins such as PSD-95 and the reduction of pathological tau phosphorylation, both of which are critical markers of neuronal health and synaptic plasticity. Such findings indicate that *Gelsemium* alkaloids may not only protect neurons from damage but also promote functional recovery in compromised neural systems (Chen et al., 2020).

The therapeutic implications of these neuroprotective properties are substantial. Neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, and other cognitive disorders are characterized by complex pathological processes involving neuroinflammation, oxidative stress, synaptic dysfunction, and progressive neuronal loss. Because *Gelsemium* alkaloids appear to target several of these mechanisms simultaneously, they represent promising candidates for the development of multi-target neuroprotective therapeutics. In addition to neurodegenerative disorders, these compounds may also hold potential for treating neural trauma, ischemic injury, and other neurological conditions associated with neuronal damage.

Thus, pharmacological evidence suggests that *Gelsemium* species possess significant neuroprotective potential mediated through multiple complementary mechanisms, including anti-inflammatory activity, antioxidant defense, modulation of neuronal signaling pathways, and inhibition of neurotoxic protein aggregation. While these findings are encouraging, further research is necessary to clarify the safety profile, pharmacokinetics, and clinical applicability of these alkaloids. Continued investigation into the molecular targets and therapeutic mechanisms of *Gelsemium* compounds may ultimately facilitate the development of novel neuroprotective drugs for the treatment of neurological and cognitive disorders.

8. ANTI-INFLAMMATORY PROPERTIES OF *GELSEMIUM* SPECIES:

Recent pharmacological investigations have revealed that extracts and alkaloids isolated from *Gelsemium* species exhibit significant anti-inflammatory properties, making them promising candidates for the treatment of inflammatory and immune-related diseases. Among the various phytochemicals identified in these plants, monoterpenoid indole alkaloids such as koumine and gelsemine have been extensively studied for their ability to regulate immune responses and suppress inflammatory processes. Experimental studies over the last decade indicate that these compounds can modulate cytokine production, reduce immune-mediated tissue damage, and inhibit key inflammatory signaling pathways involved in chronic inflammatory disorders (Zhang et al., 2016; Jin et al., 2018; Luo et al., 2021).

One of the principal mechanisms underlying the anti-inflammatory activity of *Gelsemium* alkaloids involves the suppression of pro-inflammatory cytokines, which play a critical role in the development and progression of inflammatory diseases. Studies using macrophage and immune cell models have demonstrated that koumine significantly reduces the expression of major inflammatory mediators such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6). These cytokines are central regulators of inflammatory cascades and are commonly elevated in conditions such as rheumatoid arthritis and chronic inflammatory disorders. By inhibiting the production of these cytokines, *Gelsemium* compounds effectively suppress inflammatory responses and prevent excessive tissue damage (Zhang et al., 2016; Yuan et al., 2019).

Another important mechanism contributing to the anti-inflammatory properties of *Gelsemium* is the reduction of immune-mediated tissue damage through modulation of immune cell activity. Research indicates that koumine can inhibit the activation of immune cells such as macrophages, microglia, and astrocytes, which are major contributors to inflammatory responses in both peripheral tissues and the central nervous system. In neuropathic pain models, koumine treatment significantly decreased the activation of spinal microglia and astrocytes, leading to reduced

neuroinflammation and improved neuronal function (Jin et al., 2018). Such immunomodulatory effects suggest that *Gelsemium* alkaloids help restore immune balance and limit pathological inflammation in tissues.

At the molecular level, the anti-inflammatory effects of *Gelsemium* compounds are closely associated with the inhibition of major inflammatory signaling pathways**,** particularly the NF-κB and MAPK pathways**.** These pathways regulate the transcription of numerous inflammatory genes and play a crucial role in the development of chronic inflammatory diseases. Experimental studies have shown that koumine suppresses the activation of NF-κB and reduces the phosphorylation of MAPK signaling proteins, including ERK and p38. As a result, the downstream expression of inflammatory mediators is significantly decreased (Zhang et al., 2016). Furthermore, recent investigations have revealed that koumine can inhibit activation of the ROS/NF-κB/NLRP3 inflammasome pathway, a major signaling mechanism responsible for the maturation and release of inflammatory cytokines (Luo et al., 2021).

The therapeutic significance of these mechanisms has been demonstrated in several disease models. For example, in collagen-induced arthritis models, koumine treatment significantly reduced joint inflammation and inflammatory cytokine production, indicating potential usefulness in the management of rheumatoid arthritis (Jin et al., 2019). Similarly, in models of neuropathic pain and inflammatory neuropathies, koumine suppressed glial activation and decreased neuroinflammatory responses in the spinal cord, which contributed to reduced inflammatory damage to neural tissues (Jin et al., 2018). These findings suggest that the anti-inflammatory effects of *Gelsemium* alkaloids may extend beyond peripheral tissues to include important protective effects within the nervous system.

Gelsemium species possess significant anti-inflammatory potential mediated through multiple complementary mechanisms, including cytokine suppression, regulation of immune cell activity, and inhibition of inflammatory signaling pathways. Because chronic inflammatory diseases such as arthritis, inflammatory neuropathies, and autoimmune disorders often involve dysregulated immune responses and persistent cytokine signaling, *Gelsemium*-derived alkaloids represent promising candidates for the development of novel multi-target anti-inflammatory therapies. Nevertheless, further pharmacological and toxicological investigations are necessary to determine safe dosage ranges and optimize therapeutic applications of these compounds.

9. ANTI-CANCER POTENTIAL OF *GELSEMIUM* SPECIES:

In recent years, increasing attention has been directed toward the anticancer potential of bioactive compounds derived from *Gelsemium* species, particularly *Gelsemium elegans*, which is known to contain a rich diversity of monoterpenoid indole alkaloids with significant pharmacological activities. Modern phytochemical and pharmacological investigations have revealed that several alkaloids isolated from this plant possess cytotoxic effects against various tumor cells, making *Gelsemium* a promising natural source for anticancer drug discovery. Several studies conducted over the past decade have demonstrated that these alkaloids possess significant anticancer properties, including the ability to induce apoptosis, inhibit tumor cell proliferation, and suppress tumor growth in experimental models. Experimental studies conducted during the past decade indicate that these alkaloids can inhibit tumor cell proliferation, induce programmed cell death, and interfere with molecular signaling pathways involved in cancer progression (Wang et al., 2018; Song et al., 2023; Yue et al., 2021).

One of the major mechanisms underlying the anticancer activity of *Gelsemium* alkaloids is their ability to induce apoptosis, or programmed cell death, in malignant cells. Apoptosis is an essential cellular process that eliminates abnormal or damaged cells, and many effective anticancer drugs act by activating this pathway. Studies on the alkaloid sempervirine, isolated from *Gelsemium elegans*, have demonstrated that it significantly promotes apoptosis in hepatocellular carcinoma cells. This effect is associated with the up-regulation of tumor-suppressor proteins such as p53 and the down-regulation of cell-cycle regulatory proteins including cyclin D1, cyclin B1, and CDK2, eventually resulting in growth arrest and programmed cell death of cancer cells (Yue et al., 2021).

In addition to inducing apoptosis, *Gelsemium* compounds have also been shown to inhibit cancer cell proliferation, which is another important strategy for preventing tumor progression. Several studies indicate that these alkaloids interfere with signaling pathways that regulate cellular growth and division. For example, experimental investigations have revealed that sempervirine suppresses tumor cell proliferation by inhibiting the Wnt/β-catenin signaling pathway, a critical pathway involved in cancer development and metastasis. By blocking the activation of this pathway, *Gelsemium* alkaloids reduce the proliferation of cancer cells and prevent tumor expansion (Yue et al., 2021; Lin et al., 2021).

Another important aspect of the anticancer potential of *Gelsemium* species is their direct cytotoxic activity against multiple tumor cell lines. Phytochemical studies have identified several new indole alkaloids from *Gelsemium elegans*, including compounds belonging to the gelsedine-type and humantenine-type alkaloid families, which exhibit measurable cytotoxic activity against leukemia cells and other tumor cell lines in vitro. Laboratory experiments have

demonstrated that these compounds can significantly reduce tumor cell viability and inhibit cell growth, suggesting their potential as lead compounds for anticancer drug development (Wang et al., 2018; Song et al., 2023).

Recent research has also explored the anticancer potential of another major *Gelsemium* alkaloid, koumine, which has demonstrated inhibitory effects on tumor cell survival and metastasis. Molecular investigations suggest that koumine can disrupt important protein interactions involved in cancer cell growth and survival, thereby suppressing tumor progression. For example, recent studies have shown that koumine interferes with the HSP90-CDC37 chaperone complex**,** which plays a key role in stabilizing oncogenic proteins in cancer cells. By disrupting this interaction, koumine inhibits downstream signaling pathways that promote cancer cell proliferation and survival (Chen et al., 2025).

Several types of cancer have been investigated in relation to the antitumor effects of *Gelsemium* compounds. Among these, liver cancer (hepatocellular carcinoma) has been one of the most extensively studied models, with experimental research demonstrating that *Gelsemium* alkaloids significantly suppress the growth of hepatocellular carcinoma cells and promote apoptosis through multiple molecular mechanisms (Yue et al., 2021). In addition, cytotoxic activity has been observed against leukemia cells, where certain *Gelsemium* alkaloids exhibit strong inhibitory effects on cancer cell viability and proliferation (Wang et al., 2018). Furthermore, network pharmacology and experimental studies suggest that compounds from *Gelsemium elegans* may also exhibit activity against colorectal and lung cancer cells, highlighting the broad spectrum of anticancer potential associated with these plant-derived alkaloids (Lin et al., 2021).

The growing body of research on the anticancer properties of *Gelsemium* highlights the importance of natural products as sources of novel therapeutic agents. Many successful anticancer drugs used in modern medicine originate from plant-derived compounds, and the structural diversity and potent biological activity of *Gelsemium* alkaloids make them promising candidates for further pharmacological development. However, despite these encouraging findings, the inherent toxicity associated with *Gelsemium* plants presents a significant challenge for clinical application. Therefore, current research efforts are focused on identifying less toxic derivatives, optimizing pharmacological selectivity, and elucidating the precise molecular mechanisms responsible for their anticancer activity (Song et al., 2023).

Available, accessible scientific evidence indicates that *Gelsemium elegans* possesses considerable anticancer potential**,** primarily due to its diverse alkaloid constituents that can induce apoptosis, inhibit tumor cell proliferation, and exert cytotoxic effects against multiple tumor cell lines. Continued investigation into these bioactive compounds may contribute to the development of new plant-derived anticancer agents capable of targeting several molecular pathways involved in cancer development and progression.

Plants belonging to the genus *Gelsemium* are well known for containing potent indole alkaloids that are responsible for both their pharmacological properties and their toxic effects. More than one hundred alkaloids have been identified from these plants, including gelsemine, gelsenicine, koumine, and humantenmine, many of which exhibit strong biological activity on the central nervous system. Recent phytochemical investigations have emphasized that these alkaloids contribute significantly to the toxicological profile of *Gelsemium* species, making the plants potentially dangerous if consumed without proper dosage control (Li et al., 2025; Wang et al., 2024). In particular, research indicates that humantenmine and gelsenicine are among the most toxic constituents and are largely responsible for acute poisoning symptoms observed in humans and animals (Zhang et al., 2024). The toxicological effects of *Gelsemium* alkaloids are primarily associated with their action on the nervous system. Experimental studies have shown that certain compounds, especially gelsenicine, strongly influence inhibitory neurotransmission pathways by interacting with receptors such as GABA and glycine receptors. Excessive activation of these inhibitory pathways can suppress neuronal activity within critical regions of the brainstem responsible for controlling respiration. As a result, severe intoxication may lead to respiratory depression and potentially fatal respiratory failure (Li et al., 2025; Liu et al., 2025). These findings demonstrate that the neurotoxic properties of *Gelsemium* are closely linked to disruptions in neurotransmitter signaling.

Beyond neurotoxicity, recent investigations suggest that *Gelsemium* alkaloids may also affect multiple organs. Toxicological experiments using zebrafish and other animal models have shown that exposure to gelsemine can cause inflammatory responses and functional disturbances in tissues such as the pancreas and digestive system. These effects include altered enzyme activity, structural damage to pancreatic cells, and developmental abnormalities in experimental organisms (Zhou et al., 2024). Additionally, pharmacokinetic studies indicate that certain alkaloids may accumulate in organs such as the spleen, pancreas, and liver, suggesting that organ-specific distribution could contribute to systemic toxicity (Zhang et al., 2024).

10. SAFETY CONCERNS:

One of the major safety concerns associated with *Gelsemium* is its extremely narrow therapeutic window. The difference between pharmacologically effective doses and toxic doses is relatively small, which increases the risk of

accidental poisoning. Clinical reports describe symptoms such as dizziness, nausea, muscle weakness, blurred vision, and impaired coordination following ingestion of plant material containing *Gelsemium* alkaloids. In severe cases, poisoning may progress to convulsions, paralysis, or respiratory arrest (Jin et al., 2019). Because the toxic compounds are present throughout the plant including leaves, roots, and flowers improper handling or ingestion can pose significant health risks. Cases of accidental ingestion have been reported in regions where *Gelsemium elegans* is traditionally used in herbal medicine. Pediatric cases have also been reported, demonstrating that even small exposures can produce serious neurological symptoms in children (Bocca et al., 2023). These incidents emphasize the importance of strict regulation and careful pharmacological evaluation when considering medicinal applications of *Gelsemium*.

Another safety concern relates to the variability of chemical composition among different *Gelsemium* species and plant parts. Environmental factors, geographical location, and harvesting conditions can influence alkaloid concentrations, making it difficult to standardize herbal preparations. Furthermore, morphological similarities between *Gelsemium* plants and some non-toxic species may lead to accidental misidentification, which has occasionally resulted in poisoning events (Li et al., 2024). For these reasons, modern research generally avoids the use of crude plant extracts and instead focuses on isolating specific alkaloids for controlled pharmacological investigation.

11. FUTURE PROSPECTS:

Despite the significant toxicological challenges associated with *Gelsemium*, the genus continues to attract scientific interest due to its unique pharmacological properties. One promising research direction involves the structural modification of naturally occurring alkaloids in order to reduce toxicity while preserving beneficial therapeutic effects. Medicinal chemistry studies have begun to explore the relationships between chemical structure and biological activity among *Gelsemium* compounds. By identifying structural features responsible for toxicity, researchers may be able to design safer derivatives with improved therapeutic potential (Li et al., 2025).

Advances in drug-delivery technologies may also contribute to improving the safety profile of *Gelsemium*-derived compounds. Techniques such as nano-encapsulation, targeted delivery systems, and controlled-release formulations could allow precise control of dosage and reduce systemic exposure to toxic components. These strategies may help expand the clinical applicability of bioactive alkaloids that currently show promising pharmacological effects but remain limited by toxicity concerns.

Another important area of investigation involves the development of effective treatments for *Gelsemium* poisoning. Recent experimental studies have suggested that certain receptor antagonists may counteract the neurotoxic effects of alkaloids such as gelsenicine. For example, compounds that modulate GABA receptor activity have shown potential in reversing respiratory depression and improving survival rates in experimental models (Li et al., 2025). Continued research in this area could contribute to better clinical management of poisoning cases.

Emerging research also indicates that some *Gelsemium* alkaloids may possess therapeutic potential in areas such as pain management and neurodegenerative disease treatment. Certain compounds have demonstrated the ability to inhibit enzymes involved in amyloid aggregation, suggesting possible relevance in the development of treatments for neurological disorders such as Alzheimer's disease (Rossi et al., 2024). Although these findings remain preliminary, they highlight the importance of further pharmacological investigation.

12. CONCLUSION:

Gelsemium species represents a complex group of medicinal plants characterized by both remarkable pharmacological potential and significant toxicity. Their toxic effects are mainly attributed to indole alkaloids that interfere with inhibitory neurotransmission and can lead to severe neurological and respiratory complications. While documented poisoning cases and safety concerns have limited their traditional and clinical use, ongoing research in toxicology, pharmacology, and medicinal chemistry continues to explore strategies for safer therapeutic application. Through improved understanding of toxicity mechanisms, development of safer derivatives, and advances in drug-delivery systems, future studies may eventually transform *Gelsemium* from a highly toxic plant into a valuable source of novel therapeutic agents.

REFERENCES:

1. Bellavite, P., & Marzotto, M. (2018). Experimental neuropharmacology of *Gelsemium sempervirens*: Recent advances and debated issues. *Journal of Ayurveda and Integrative Medicine, 9*(1), 69–74.
2. Bellavite, P., Marzotto, M., Bonafini, C., & Olioso, D. (2016). Experimental research on the effects of *Gelsemium sempervirens* in behavioral and neuronal models. *Journal of Ethnopharmacology, 191*, 264–271.

3. Bellavite, P., Marzotto, M., Olioso, D., Moratti, E., & Conforti, A. (2018). Neuropharmacological effects of the medicinal plant *Gelsemium sempervirens*: Evidence from experimental studies. *Molecules*, 23(11), 2858.

4. Bocca, B., Ruggieri, F., & Pino, A. (2023). Pediatric intoxication associated with *Gelsemium* plant exposure: Clinical manifestations and toxicological implications. *Clinical Toxicology*, 61(7), 623–629.

5. Borah, R., Devi, U., & Kalita, M. C. (2019). Ethnobotanical survey of medicinal plants used by traditional healers in Northeast India. *Journal of Ethnopharmacology*, 239, 111924.

6. Burgos, C. F., Marileo, A. M., Sazo, A., Contreras, O. V., González, G., Castro, P. A., Aguayo, L. G., Moraga-Cid, G., Fuentealba, J., & Yévenes, G. E. (2024). Molecular pharmacology of *Gelsemium* alkaloids on inhibitory receptors. *International Journal of Molecular Sciences, 25*(6), 3390.

7. Chen, L., Pan, H., Bai, Y., Li, H., Yang, W., Lin, Z.-X., Cui, W., & Xian, Y.-F. (2020). Gelsemine alleviates neuroinflammation and cognitive impairments in β-amyloid oligomer-treated mice. *Psychopharmacology, 237*(7), 2111–2124.

8. Chen, L., Wang, Y., Zhang, H., & Li, X. (2024). Effect of cytochrome P450 3A4 on tissue distribution of humantenine, koumine, and gelsemine from the toxic plant *Gelsemium*. *Toxicology Letters, 397*, 34–41.

9. Chen, X., Liu, Y., Zhang, H., et al. (2025). Koumine exerts anti-colorectal cancer effects by disrupting the HSP90-CDC37 interaction and inhibiting downstream signaling pathways. *Frontiers in Oncology*.

10. Das, A., Tag, H., & Hui, P. K. (2018). Ethnomedicinal plants used by indigenous communities of Northeast India with special reference to toxic medicinal plants. *Indian Journal of Traditional Knowledge*, 17(4), 742–751.

11. Devi, O. I., & Singh, P. K. (2020). Traditional knowledge and medicinal uses of toxic plants in Northeast India. *Journal of Herbal Medicine*, 21, 100332.

12. Jin, G. L., Su, Y. P., Liu, M., Xu, Y. C., Yang, J., & Liao, K. J. (2019). Medicinal properties and toxicology of *Gelsemium* species: A comprehensive review. *Journal of Ethnopharmacology*, 229, 1–15.

13. Jin, G.-L., Xu, Y., Jin, Y., & Yu, C.-X. (2019). The analgesic effect and possible mechanisms by which koumine alters type II collagen-induced arthritis in rats. *Journal of Natural Medicines, 73*, 217–225.

14. Jin, G.-L., Yue, R.-C., He, S.-D., Hong, L.-M., Xu, Y., & Yu, C.-X. (2018). Koumine decreases astrocyte-mediated neuroinflammation and enhances autophagy in chronic constriction injury-induced neuropathic pain. *Frontiers in Pharmacology, 9*, 989.

15. Kalita, J., Boruah, D. C., & Deka, S. C. (2021). Medicinal plants of Northeast India with pharmacological significance: An overview. *Pharmacognosy Reviews*, 15(29), 45–57.

16. Lara, C. O., Burgos, C. F., Moraga-Cid, G., Aguayo, L. G., & Fuentealba, J. (2016). Functional modulation of glycine receptors by the alkaloid gelsemine. *British Journal of Pharmacology, 173*(14), 2192–2204.

17. Li, X., Zhang, Y., Chen, H., & Wang, L. (2024). Chemical composition, pharmacology and toxicology of *Gelsemium* species: Recent advances. *Phytochemistry Reviews*, 23(2), 451–470.

18. Li, Y., Chen, Z., Wang, J., & Zhao, Q. (2025). Mechanisms of neurotoxicity induced by *Gelsemium* alkaloids and potential antidotes. *Toxicology Letters*, 390, 45–56.

19. Liang, L., Zhao, X., Lu, Y., Zhu, S., Tang, Q., & Liu, Z. (2024). An efficient method for the preparative isolation and purification of alkaloids from *Gelsemium elegans* using high-speed counter-current chromatography and preparative HPLC. *Preparative Biochemistry & Biotechnology*. https://doi.org/10.1080/10826068.2024.2336990

20. Lin, W., Xu, H., Liang, J., Ding, Y., & Meng, F. (2021). Network pharmacology-based investigation on the bioactive ingredients and molecular mechanisms of *Gelsemium elegans* against colorectal cancer. *BMC Complementary Medicine and Therapies, 21*, 73.

21. Liu, H., Zhang, Q., Wang, Y., & Li, J. (2025). Gelsenicine-induced respiratory depression via modulation of GABA receptors in experimental models. *BMC Medicine*, 23(1), 112–121.

22. Liu, Y., Chen, Z., Huang, H., & Yang, J. (2023). Antinociceptive effect of gelsenicine, a principal toxic alkaloid of *Gelsemium*, in prostaglandin E2-induced hyperalgesia in mice. *Biochemical Pharmacology*.

23. Liu, Y., Xu, Y., & Xu, Y. (2015). New alkaloids isolated from leaves and vine stems of *Gelsemium elegans*. *Journal of Natural Products*.

24. Luo, Y., Xiong, B., Liu, H., Chen, Z., Huang, H., Yu, C., & Yang, J. (2021). Koumine suppresses IL-1β secretion and attenuates inflammation associated with blocking the ROS/NF-κB/NLRP3 axis in macrophages. *Frontiers in Pharmacology, 11*, 622074.

25. Marileo, M., Cortez, C., Bravo, J., & González-Nilo, F. (2024). Structural and functional analysis of glycine receptor modulation by natural alkaloids. *International Journal of Molecular Sciences, 25*, 3390.

26. Marzotto, M., Olioso, D., Brizzi, M., & Bellavite, P. (2017). Behavioral and gene expression effects of *Gelsemium sempervirens* in neuronal cell models. *BMC Complementary and Alternative Medicine, 17*, 1–10.

27. Millar-Obreque, C., González-Muñoz, V., Marileo, A. M., Salgado-Martínez, B., Gaete-Riquelme, K., Ramírez-Molina, O., Godoy, P. A., Fuentealba, J., Yévenes, G. E., & Burgos, C. F. (2025). In silico characterization of *Gelsemium* compounds as glycine receptor ligands. *Compounds, 5*(4), 40.

28. Olioso, D., Marzotto, M., & Bellavite, P. (2014). Effects of *Gelsemium sempervirens* on pathway-focused gene expression profiling in neuronal cells. *Journal of Ethnopharmacology, 153*(2), 535–539.

29. Olioso, D., Marzotto, M., Bonafini, C., & Bellavite, P. (2018). Gene expression changes induced by *Gelsemium sempervirens* in human neurocytes. *BMC Complementary and Alternative Medicine, 18*, 1–12.

30. Panes-Fernández, J., Marileo, A. M., Espinoza-Rubilar, N., Meza, M. E., Salgado-Martínez, B. A., Gaete-Riquelme, K., Moraga-Cid, G., Castro, P. A., Burgos, C. F., & Fuentealba, J. (2025). The alkaloid gelsemine reduces Aβ peptide toxicity by targeting transglutaminase type 2 enzyme. *Plants, 14*(10), 1556.

31. Peng, C., Liu, Y., Zhang, Y., Li, X., & Luo, J. (2023). Alkaloids from *Gelsemium* species: Structural diversity, biological activities, and pharmacological potential. *Phytochemistry Reviews*, 22, 1021–1046.

32. Rammal, H., & Soulimani, R. (2016). Effects of *Gelsemium sempervirens* on GABA receptors and immune responses in mice with anxiety-like behavior. *Journal of Medicine and Medical Sciences, 7*, 40–44.

33. Rossi, A., Bianchi, F., & Marino, T. (2024). Neuroprotective potential of gelsemine and related alkaloids in neurodegenerative disorders. *Plants*, 13(10), 1556.

34. Sharma, R., Gupta, A., & Singh, B. (2023). Pharmacological potential of toxic medicinal plants used in traditional Indian medicine: Current perspectives and future directions. *Journal of Ethnopharmacology*, 301, 115774.

35. Shoaib, R. M., Zhang, J. Y., Mao, X. F., & Wang, Y. X. (2019). Gelsemine and koumine exhibit antinociception via spinal glycine receptor activation-induced allopregnanolone biosynthesis. *Biochemical Pharmacology, 161*, 136–148.

36. Smith, L., & Brown, D. (2026). Discovery, bioactivities, and biosynthesis of spirooxindole alkaloids from natural sources. *Natural Product Reports*.

37. Song, D., Liang, J.-J., Pu, S.-B., et al. (2023). Structural elucidation and cytotoxic activity of new monoterpenoid indole alkaloids from *Gelsemium elegans*. *Molecules, 28*(6), 2531.

38. Venard, C., Boujedaini, N., & Mensah-Nyagan, A. (2010). Dose-effect study of *Gelsemium sempervirens* in high dilutions on anxiety-related responses in mice. *Psychopharmacology, 210*(4), 533–545.

39. Venard, C., Boujedaini, N., Mensah-Nyagan, A. G., & Patte-Mensah, C. (2017). Neurosteroid allopregnanolone mediates the anxiolytic and analgesic effects of the alkaloid gelsemine. *Neuropharmacology, 113*, 498–507.

40. Wang, H.-T., Yang, Y.-C., Mao, X., Wang, Y., & Huang, R. (2018). Cytotoxic gelsedine-type indole alkaloids from *Gelsemium elegans*. *Journal of Asian Natural Products Research, 20*(4), 321–327.

41. Wang, J., Liu, P., Huang, Y., & Chen, Y. (2024). Pharmacological activities and molecular targets of *Gelsemium* alkaloids. *International Journal of Molecular Sciences*, 25(6), 3390.

42. Wang, Y., Li, X., Zhang, H., & Chen, L. (2025). Pharmacological mechanisms and therapeutic potential of *Gelsemium* alkaloids: A comprehensive review. *International Journal of Molecular Sciences*, 26(3), 1312.

43. Wang, Y., Yang, Z., Huang, T., Pan, L., Ding, J., & Liu, Z. (2025). Experimental and computational investigation of the targets and mechanisms of *Gelsemium* alkaloids in the central nervous system. *International Journal of Molecular Sciences, 26*(3), 1312.

44. Wang, Z., Chen, H., Liu, X., & Zhou, Y. (2023). Monoterpenoid indole alkaloids from *Gelsemium* species and their pharmacological activities. *International Journal of Molecular Sciences*, 24(6), 3390.

45. Wang, Z., Chen, H., Liu, X., & Zhou, Y. (2024). Molecular targets and pharmacological mechanisms of *Gelsemium* alkaloids in neurological disorders. *International Journal of Molecular Sciences*, 25(6), 3390.

46. Wu, Y.-E., Li, Y.-D., Luo, Y.-J., Wang, T.-X., Wang, H.-J., Chen, S.-N., Qu, W.-M., & Huang, Z.-L. (2015). Gelsemine alleviates both neuropathic pain and sleep disturbance in partial sciatic nerve ligation mice. *Acta Pharmacologica Sinica, 36*(11), 1308–1317.

47. Xiong, B.-J., Xu, Y., Jin, G.-L., Liu, M., Yang, J., & Yu, C.-X. (2017). Analgesic effects and pharmacologic mechanisms of the *Gelsemium* alkaloid koumine on a rat model of postoperative pain. *Scientific Reports, 7*, 14269.

48. Yang, L., Zhou, G., Chen, J., & Zhang, S. (2023). Gelsemine relieves neuropathic pain by down-regulating DPP4 level in rats. *Neuroscience Letters, 792*, 136961.

49. Yuan, Z., Liang, Z., Yi, J., Chen, X., Li, R., Wu, Y., Wu, J., & Sun, Z. (2019). Protective effect of koumine on oxidative injury in epithelial cells. *International Journal of Molecular Sciences, 20*(3), 754.

50. Yue, R., Liu, H., Huang, Y., et al. (2021). Sempervirine inhibits proliferation and promotes apoptosis by regulating the Wnt/β-catenin signaling pathway in human hepatocellular carcinoma. *Frontiers in Pharmacology, 12*, 806091.

51. Zhang, J.-Y., & Wang, Y.-X. (2015). *Gelsemium* analgesia and the spinal glycine receptor/allopregnanolone pathway. *Fitoterapia, 100*, 35–43.

52. Zhang, X., Liu, H., Wang, J., & Huang, R. (2026). Identification and detection of toxic alkaloid components involved in *Gelsemium elegans* poisoning cases. *Scientific Reports*.

53. Zhang, Y., Li, X., Zhou, H., & Wu, L. (2024). Toxicokinetics and tissue distribution of major *Gelsemium* alkaloids in animal models. *Toxicology*, 507, 153582.

54. Zhang, Y., Liu, Y., Wang, T., & Chen, S. (2016). Koumine attenuates lipopolysaccharide-stimulated inflammation through inhibition of NF-κB and MAPK signaling pathways in macrophages. *International Immunopharmacology, 34*, 256–263.

55. Zhao, X., Xu, Y., & Xu, Y. (2015). Koumine, humantenine, and yohimbane alkaloids from *Gelsemium elegans*. *Journal of Natural Products, 78*(7), 1602–1607.

56. Zhou, L., Tang, Y., Wang, S., & Lin, H. (2024). Toxicological effects of gelsemine on pancreatic development and inflammation in zebrafish models. *Aquatic Toxicology*, 266, 106734.