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Convallaria majalis (Lily of the Valley): A review of its cardiac glycosides, medicinal applications, and safety profile

Nvard Pahutyan[1], Hrachik Gasparyan[1], Sona Sargsyan[2], Gayane Melyan[3], Milena Shahinyan[1,4], Qristine Navoyan[1], Ivan Gabrielyan[5], Gohar Arajyan*[1,4,6,7]

[1]Scientific Technological Center of Organic and Pharmaceutical Chemistry NAS RA, 26 Azatutyan Ave., 0014, Yerevan, Armenia; [2]Yerevan State University, 1 Alek Manukyan St., 0025, Yerevan, Armenia; [3]Scientific Center of Agrobiotechnology, Branch of the Armenian National Agrarian University, 1 Isi le Mulino St., Ejmiatsin 1101, Armenia; [4]Eurasian International University RA; [5]Department of Palaeobotany, A.Takhtajan Institute of Botany of the NAS RA, 1 Acharyan, 0040, Yerevan, Armenia; [6]Armenian State Pedagogical University after KH. Abovyan, 17 Tigran Mets St., 0010, Yerevan, Armenia; [7]University of Traditional Medicine, 38a Marshal Babajanyan Str., Yerevan, Armenia.

***Corresponding author:** Gohar Arajyan, PhD., Associate professor, Pharmacology and Pathohistology laboratory; Scientific Technological Center of Organic and Pharmaceutical Chemistry NAS RA, 26 Azatutyan Ave, 0014, Yerevan, Armenia

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ABSTRACT

Convallaria majalis (Lily of the Valley) is a perennial flowering plant historically used in traditional medicine, especially for cardiovascular conditions such as heart weakness, tachycardia, and arrhythmias. Its therapeutic effects were primarily attributed to its high content of cardiac glycosides, particularly convallatoxin, which enhance cardiac contractility. However, the plant's narrow therapeutic index presents significant toxicity risks. All parts—especially the berries and roots—are poisonous, and ingestion can result in nausea, vomiting, diarrhea.

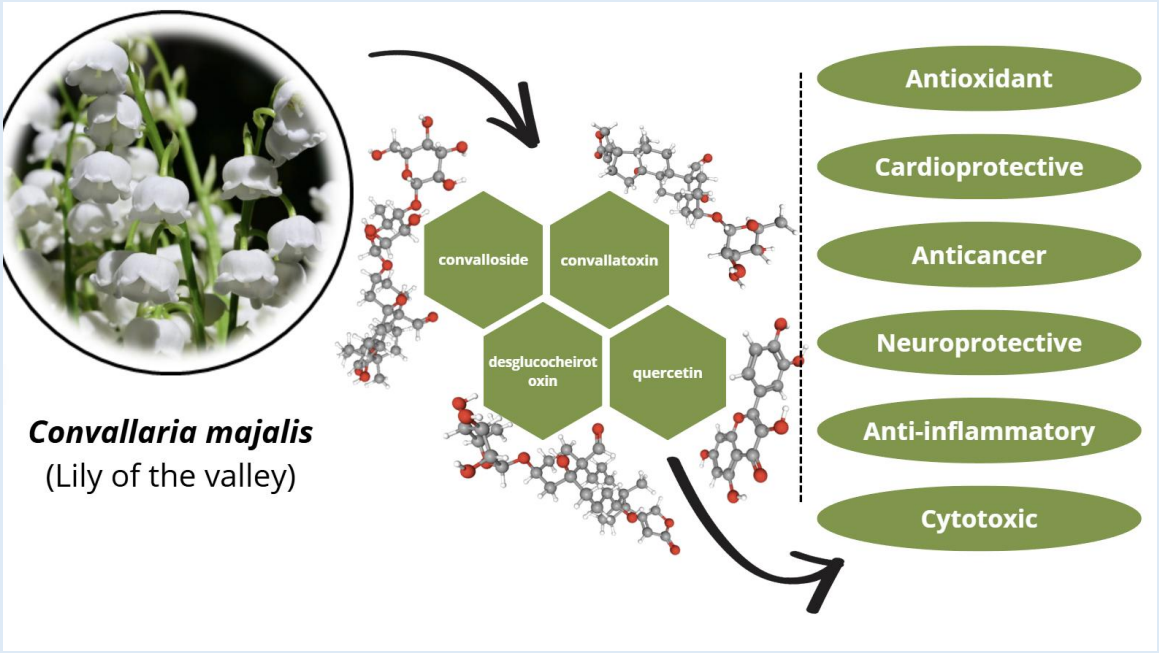
Despite its toxicity, modern research highlights the pharmacological potential of *C. majalis*. Convallatoxin has demonstrated anticancer effects, including inhibition of cell proliferation, induction of apoptosis, and suppression of angiogenesis in various cancers such as breast and colorectal, often independently of p53 status. Additionally, certain glycosides and flavonoids from the plant show neuroprotective and anticonvulsant properties, likely through modulation of GABAergic activity.

C. majalis also exhibits notable antioxidant, anti-inflammatory, and diuretic properties, suggesting possible roles in managing chronic inflammation, oxidative stress, and fluid retention. However, the plant's cytotoxic constituents, including specific saponins and steroidal glycosides, raise safety concerns that limit its clinical use.

While topical or dermatological applications are occasionally proposed, the high toxicity of *C. majalis* warrants extreme caution. This review underscores the dual nature of *C. majalis*—a plant of considerable medicinal promise but also significant toxicological risk—highlighting the importance of further research to safely harness its bioactive compounds.

Novelty of the Study: This review uniquely integrates traditional medicinal uses of *Convallaria majalis* with recent pharmacological and molecular research, highlighting its cardiotonic glycosides not only in cardiovascular applications but also in emerging areas such as oncology and neuroprotection. It also discusses advancements in molecular identification techniques to prevent toxic misidentification, providing a comprehensive and modernized framework for the safe and therapeutic use of *C. majalis*.

Keywords: *Convallaria majalis*, cardiac glycosides, convallatoxins, neuroprotection, anticancer activity, traditional medicine, functional phytochemicals



Graphical abstract: Bioactive Constituents and Therapeutic Potentials of *Convallaria majalis*

INTRODUCTION

Convallaria majalis L. commonly known as Lily of the Valley, is a perennial plant from the Asparagaceae family which is from the angiosperm plants. The plant can grow up to 15-30 cm tall, blooms in early spring, and often seen forming significant clumps in deciduous and pine forests, as well as in mixed forests, on forest edges and clearings [1]. The stems grow to 15–30 cm tall, with one or

two leaves 10–25 cm long; flowering stems have two leaves and a raceme of five to fifteen flowers on the stem apex. The flowers are fused at the base of the plant to form a bell shape [2]. Lily of the Valley is native to the cool temperate Northern America, in Europe and Asia. It is widely grown around the world as an ornamental plant [3].

Historical and Traditional Uses in Medicine: The use of *Convallaria majalis* in herbal medicine dates to the 16th century. It has been traditionally considered a cardioprotective agent and is often included in herbal extracts marketed as heart tonics. Historically, herbalists have specifically employed the roots of *Convallaria* to address conditions such as a "weak heart," shortness of breath, tachycardia, and various arrhythmias [4].

In early allopathic medical practice, as observed in 1883, *Convallaria* was utilized as a heart tonic for a wide range of cardiovascular issues [4]. These include cases of deficient circulation stemming from organic cardiac disease, heart failure associated with pneumonia in elderly patients, and heart failure during typhoid fever. It was also applied to circulatory obstructions caused by pulmonary conditions like emphysema and bronchitis. The extensive historical and traditional use of *Convallaria majalis* for serious cardiac conditions, despite its well-documented toxicity, suggests that its perceived efficacy for life-threatening ailments, in the absence of modern pharmacological alternatives, was historically deemed significant enough to ignore the inherent dangers [5].

Despite its therapeutic potential, *C. majalis* carries a significant toxicity risk. All parts of the plant, especially the berries and roots, contain high concentrations of cardiac glycosides that can cause serious toxicity when ingested incorrectly. Symptoms of poisoning may include nausea, vomiting, diarrhea, and, in severe cases, cardiac arrhythmias, which can be fatal. The toxicological profile of *C. majalis* limits its use, but ongoing research continues to explore its pharmacological potential [6-7]. But recent studies have focused on its alternative uses, particularly its potential in adjunctive therapies for heart disease. The plant's compounds, especially convallatoxin, have also shown promising anticancer properties [8]. Early in vitro and animal studies suggest that convallatoxin can inhibit cancer cell proliferation, particularly in K562 cells, in a dose- and time-dependent manner [9]. These findings open the door for further investigation into the plant's role in cancer treatment.

Additionally, C. majalis is being investigated for its potential neuroprotective effects. Its antioxidant and anti-inflammatory properties make it an interesting candidate for the treatment of neurodegenerative diseases [10]. The plant's ability to influence cellular ion channels, reduce oxidative stress, and mitigate inflammation could offer novel therapeutic options for conditions like Alzheimer's disease and Parkinson's disease.

The properties of plants that are significant for human health have been studied in laboratory settings since 1926 [11].

RESEARCH METHODS

A comprehensive literature review was performed to collect and analyze relevant scientific data on the phytochemistry, pharmacological properties, toxicology, and therapeutic potential of *Convallaria majalis* (Lily of the Valley). The databases PubMed, FFHDJ.com, ScienceDirect, Web of Science, and Google Scholar were systematically searched for publications from 1935 to 2025. The following keywords and their combinations were used: "*Convallaria majalis*", "Lily of the Valley", "cardiac glycosides", "convallatoxin", "convalloside", "neuroprotective effects", "anticancer activity", "antioxidant", "Na^+/K^+-ATPase", "steroidal saponins", "phytochemistry", "toxicity", and "functional food potential".

Phytochemistry and Active Compounds: *Convallaria majalis* is a rich source of bioactive compounds, predominantly cardiac glycosides, with approximately 40

different types identified. Valuable herbal raw materials include leaves, fruits, seeds, and roots. The main glycosides in the dried aerial parts of the plant constitute between 0.1% and 0.5% of its cardiac glycoside content. Key cardiac glycosides include convallatoxin, which is the primary active glycoside, exhibiting structural similarity to digoxin. Its concentration in dried aerial parts can range from 4% to 40% [12], convalloside: A fundamental metabolic glycoside within the plant, it can transform into convallatoxin and other cardiac glycosides. It constitutes 4% to 24% of the cardiac glycosides, convallatoxol: Found in concentrations ranging from 10% to 20%, desglucocheirotoxin: Ranges from 3% to 15%, lokundjoside: Ranges from 1% to 25% [13].

Other cardiac glycosides mentioned in the literature include convallarin, convallasaponin, cholestane glycoside, strophanthidin, cannogenol, sarmentogenin, dipindogenin, and hydroxysarmentogenin.

Beyond cardiac glycosides, *Convallaria majalis* also contains other bioactive compounds. Saponins are present in the plant and are notably responsible for the digestive disorders associated with its ingestion. Additionally, convallamaroside, a steroidal saponin isolated from the plant, has been investigated for its anti-angiogenic, anticancer hemolytic, insecticidal, antiparasitic, antifungal, antibacterial, antiviral, anti-inflammatory, antihyperlipidemic, antidiabetic and antitumor properties, among others [14, 15].

Table 1 and on graphical abstract 1 provide a comprehensive summary of the principal pharmacological activities attributed to *Convallaria majalis*, along with the corresponding bioactive compounds, molecular targets, and experimental or clinical applications. The most prominent effects include cardioprotective, anticancer, neuroprotective, antioxidant, anti-inflammatory, and cytotoxic actions. These effects are primarily mediated by key constituents such as convallatoxin, convalloside, convallamaroside, flavonoids (e.g., quercetin, kaempferol derivatives), and steroidal saponins. [Table 1; graphical abstract 1].

Table 1. Therapeutic Activities and Supporting Evidence of Convallaria majalis

Pharmacological Activity	Supporting Compounds	Biological Targets / Effects	Applications / Models Studied
Cardioprotective	Convallatoxin, Convalloside	I cardiac output, regulation of rhythm, vasomotor stimulation, Na^+/K^+-ATPase inhibition	Heart failure, arrhythmia, hypotension
Anticancer	Convallatoxin, Convallamaroside	Inhibition of proliferation, angiogenesis, apoptosis induction	Colorectal & breast cancer, K562 cells, HCT116 cells
Neuroprotective	Glycosides, Flavonoids	GABA receptor modulation, reduced oxidative stress	Potential use in epilepsy, Alzheimer's, Parkinson's
Antioxidant	Quercetin, Kaempferol derivatives	ROS scavenging, redox modulation	Prevention of chronic diseases
Anti-inflammatory	Convallatoxin, Flavonoids	↓ TNF-α, IL-1β, NO; NF-kB inhibition	Arthritis, autoimmune, neurodegeneration
Cytotoxic	Convallasaponin A, steroidal saponins	Apoptosis in cancer cells, inhibition of proliferation	Submandibular carcinoma cells (HSG), general tumor models
Dermatological (limited)	Glycosides (with caution)	Possible circulation-boosting, anti-inflammatory, but risk of irritation or toxicity	Traditional wound healing (unproven); not recommended topically

Cardiovascular Activity: Cardiovascular diseases are the leading cause of death in the world. Scientists around the world continue to search for an herbal remedy that would be effective and have no adverse effects, either in

combination with or prior to standard pharmacological treatment.

Recent advances in functional food science highlights the importance of bioactive compounds such as flavonoids and terpenoids in developing safe, plant-based alternatives. According to Martirosyan and colleagues, such compounds are increasingly being incorporated into functional foods to support cardiovascular health and reduce dependence on conventional pharmaceuticals [16].

Such plant-based therapy may include *Convallaria majalis*. Owing to its numerous properties that contribute to the enhancement of overall health and the maintenance of physiological balance within the organism. Because of cardiac glycosides it is widely used as a cardioprotective agent for the prevention and reduction of the risk of cardiovascular diseases [17-18]. Its bioactive compounds, particularly cardiac glycosides, offer potential benefits either as complementary agents or alternatives to conventional therapies in managing heart failure and arrhythmias [19]. Their mechanisms of action at the organismal, cellular, and molecular levels, as well as their predominant target—Na^+-K^+-ATPase—underwent a thourough investigation, significantly expanding knowledge of their pharmacological activity and clinical potential [20].

Cardiac glycosides can inhibit the activity of the membrane ion-exchange pump complex of Na^+/K^+-ATPase, which is a key enzyme involved in maintaining the electrolyte balance and membrane potential of cardiac muscle cells and, consequently, leading to the strengthening of cardiac muscle contractions [21-23].

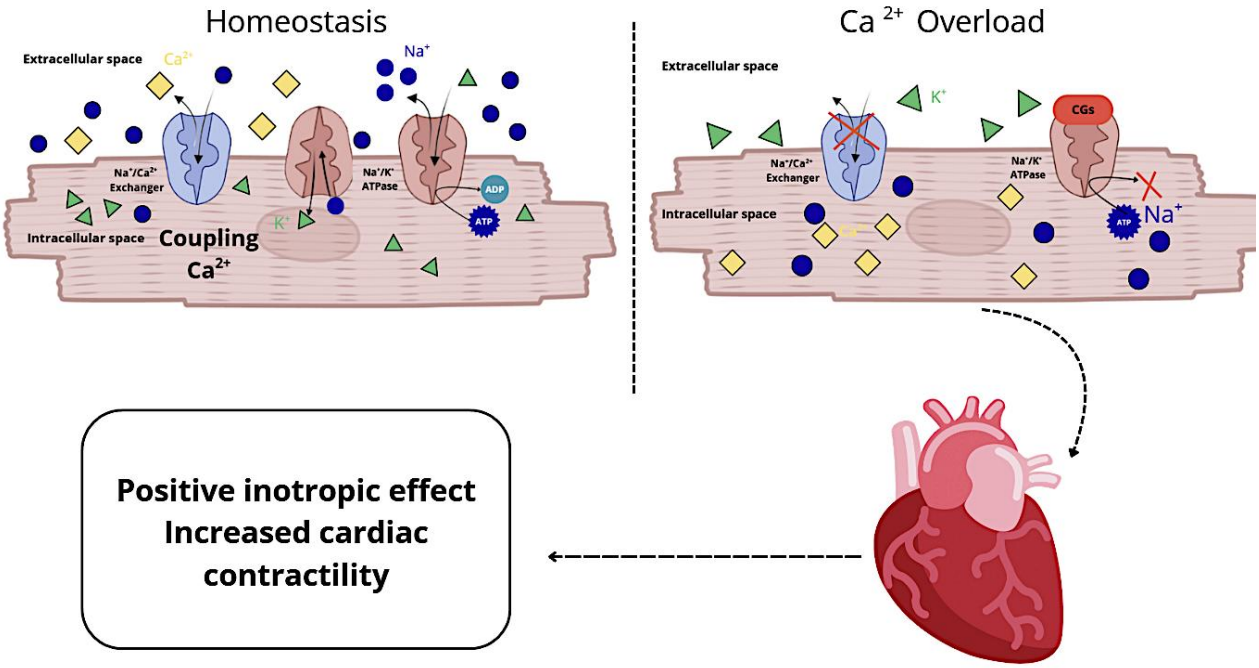


Figure 1. Mechanistic Pathway of Cardiac Glycoside-Induced Enhancement of Myocardial Contractility

The primary positive inotropic effect of cardiac glycosides is mediated through the inhibition of the Na^+/K^+-ATPase in cardiomyocytes. Under normal conditions, this pump maintains intracellular Na^+ at low concentrations, enabling the Na^+/Ca^{2+} exchanger to extrude Ca^{2+} during relaxation. Inhibition of Na^+/K^+-ATPase disrupts this balance, elevating intracellular Na^+ and reduces the driving force for Na^+/Ca^{2+} exchange. Consequently, intracellular Ca^{2+} accumulates, leading to enhanced calcium-induced calcium release from the sarcoplasmic reticulum. This increased cytosolic Ca^{2+} concentration augments myocardial contractility,

producing the hallmark positive inotropic effect of cardiac glycosides [Figure 1].

This mechanism contributes to an increase in cardiac output in patients suffering from heart failure and arrhythmias [24-26]. Unlike synthetic analogs, the glycosides extracted from C. majalis represent a natural alternative with potentially more favorable toxicity profile when administered at optimal dosages. Furthermore, convallatoxin not only demonstrates the capacity to enhance cardiac function but also is characterized by a rapid onset of clinical effectiveness, which can be particularly significant in acute cardiac conditions. Contemporary clinical and preclinical studies indicate the feasibility of standardizing these compounds for subsequent integration into comprehensive therapeutic protocols aimed at treating chronic cardiovascular diseases, considering their potential as adjuvant agents [27].

As highlighted in Martirosyan and Baghdasaryan's (2024) review on the economic implications of functional foods, implementing bioactive agents such as convallatoxin requires robust regulatory frameworks—like Japan's FOSHU system—and a strong emphasis on post-market evaluation [28].

Recent findings reveal that olfactory receptors, previously known only for their role in smell, are also present in the kidneys and heart, where they respond to short-chain fatty acids from the diet. In the kidney, they regulate renin release, influencing blood pressure. Mice lacking these receptors exhibit chronically low blood pressure, suggesting a novel mechanism of cardiovascular control. While Convallaria majalis glycosides act via Na^+/K^+-ATPase inhibition, these sensory pathways may represent complementary targets for antihypertensive strategies [29].

C. majalis has been observed to slow the heart rate, often contributing to the restoration of a normal rhythm, while simultaneously augmenting the energy of systole and increasing overall blood pressure. Its effects on cardiac contractions can involve an initial retardation, followed by a pronounced acceleration, both associated with increased blood pressure. However, at higher or toxic doses, it can lead to an arrest of the heartbeat accompanied by a diminution of blood pressure. Early observations indicated that small doses could primarily accelerate the pulse [30].

Convallaria significantly increases arterial tension, with a concurrent increase in heart rate. Interestingly, the heart rate may begin to decrease before the arterial tension. The reduction in cardiac frequency is attributed to a direct action on the heart's muscular structure rather than an exaltation of cardiac inhibitory mechanisms. The observed rise in arterial tension is primarily mediated by the stimulation of the vaso-motor apparatus, as opposed to direct action on central vaso-motor centers [31]. Convallatoxin, specifically, exhibits a dual effect on vasculature, possessing both vasoconstrictor and vasodilator properties. This suggests a complex, potentially dose-dependent or context-dependent vascular response that could contribute to its variable effects on blood pressure [31].

According to Martirosyan et al. (2023), the development of functional foods from potent natural compounds like convallatoxin requires a structured regulatory pathway that includes biomarker validation, safety assessment, and post-market monitoring [32].

Anticancer activity: Convallamaroside, a steroid saponin isolated from *Convallaria majalis*, demonstrates potential in the field of oncology due to its ability to inhibit angiogenesis processes. Specifically, this compound can suppress the formation of new blood vessels, which is critically important for the growth and metastasis of tumor tissues [33-34].

Additionally, steroidal saponins possess the potential to enhance the therapeutic efficacy of chemotherapeutic agents and reduce their toxicity, which underscores their promise as key components in

the development of innovative combined treatment strategies [35].

Chemical studies of higher plants, especially their steroidal glycosides, represent a promising approach for the development of anticancer agents derived from natural products [36-37]. Cardiotonic glycosides, a class of steroidal glycosides with significant physiological activity, have been thoroughly studied also in the context of oncology. Plants are particularly rich sources of bioactive steroidal glycosides, such as OSW-1 and galtonioside A, which exhibit cytotoxic activity against cancer cells [9, 34]. Cardiac glycosides are structurally similar with their secondary metabolites with diverse pharmacological activities, including cytotoxic, antiviral, and anti-inflammatory effects. Found in various plant families, they are notably abundant in *Convallaria majalis*. Despite their therapeutic potential, their clinical use is limited by toxicity, highlighting the need for further research into safer, bioactive derivatives [38].

Current scientific data demonstrate that this class of compounds can selectively inhibit the proliferation of various human tumor cells [39]. Specifically, convallatoxin, a natural compound found in the *Convallaria majalis*, belongs to the group of cardiotonic glycosides and numerous studies have confirmed the presence of significant antitumor potential of it. Notably, this glycoside exhibits substantial pro-apoptotic, anti-proliferative, and anti-angiogenic effects, especially against colorectal cancer cells, indicating its possible application as an anticancer agent [38]. Additionally, experimental data show that convallatoxin exerts dose- and time-dependent cytotoxic effects on breast cancer cells, further emphasizing its therapeutic potential [40].

Convallatoxin could induce a cytotoxic effect on colorectal cancer cells *in vitro*, suggesting its potential as an anticancer agent [35].

To test this hypothesis, a comprehensive experimental study was conducted, which confirmed that convallatoxin indeed demonstrates significant antitumor activity against colorectal cancer cells cultured in vitro. The research revealed that this effect is mediated through inhibition of cellular proliferation and activation of apoptotic pathways in HCT116 cell line cultures, indicating the potential application of convallatoxin as a therapeutic anticancer agent. Importantly, analysis showed that the efficacy of convallatoxin's action is independent of the p53 gene status, a key regulator of the cell cycle and apoptosis. This suggests that its mechanism of antitumor activity does not rely on p53 pathway functionality, thereby broadening the scope of its potential applications, including cases where p53 is inactivated or mutated in cancer cells. Thus, the obtained results highlight the promising prospects for further research into convallatoxin as a potential therapeutic agent for colorectal cancers, especially those characterized by disrupted p53 signaling pathways [41].

However, despite the compelling preliminary evidence, the mechanisms by which convallatoxin acts on osteosarcoma cells remain insufficiently studied. Currently, there is a lack of comprehensive understanding of the molecular pathways through which this glycoside exhibits its antitumor activity, highlighting the need for further research to elucidate its role and potential in the treatment of various malignancies.

Neurological activity: In recent decades, there has been an increased interest from pharmacological and neurobiological studies in the bioactive components of *C. majalis*, driven by the plant's chemical composition potential to exhibit neuroprotective, anticonvulsant, and sedative effects. Focus is placed on studying flavonoids and specific glycosides present in the plant as possible molecular targets for developing new drugs with neuroprotective properties [42].

In the context of traditional European herbal medicine, *Convallaria majalis* has repeatedly been mentioned as a potential remedy for neurological disorders, particularly epilepsy. Folk practices included the use of diluted tinctures and extracts of the plant with

the aim of achieving a sedative effect and reducing the frequency and severity of seizures. These therapeutic approaches were likely based on the observed properties of the plant, such as its calming effects [43]. Recent studies in the fields of phytotherapy and neuroscience have demonstrated that certain flavonoids exhibit a broad spectrum of therapeutic properties, which may positively influence the clinical course of epilepsy. It is also noted that these compounds do not induce the adverse effects commonly associated with traditional pharmacological treatments, highlighting their potential as safe alternative agents in the comprehensive management of this neurological disorder [44]. Some neurotransmitters, performing inhibitory and excitatory functions, play a key role in the pathogenesis of epileptic seizures, and their regulation through alternative therapeutic strategies represents a promising direction in clinical practice [45]. However, for a long time, such methods remained outside the scope of rigorous scientific research and lacked sufficient clinical validation, which limited their application in modern medicine.

The mechanisms of action of these compounds are believed to involve their ability to modulate GABA activity through interactions with specific receptor systems, thereby stabilizing neuronal functions and slowing the progression of neurological conditions [45].

Traditional herbal remedies are characterized by the preservation of the natural and biological properties of their active components, which ensures minimal toxicity and side effects [41]. Moreover, animals typically do not develop drug resistance to such compounds, and their use generally does not leave pharmacological residues, reducing the potential health and environmental risks.

Antioxidant and anti-inflammatory activities: In addition to its well-known cardiotonic properties, *Convallaria majalis* exhibits a pronounced anti-inflammatory effect, which expand its potential applications in clinical practice. Studies have shown that the plant's glycosides, such as convallotoxin, can significantly influence the inflammatory processes by regulating the production of pro-inflammatory cytokines and mediators. Specifically, these compounds have been found to reduce the synthesis of key inflammatory molecules such as TNF-α, IL-1β, and NO [20]. The mechanism underlying these effects is largely associated with the suppression of NFκB pathway activation, which plays a central role in transducing inflammatory signals and regulating the expression of genes responsible for the inflammatory response. This mechanism provides a basis for the potential use of *Convallaria majalis* in the treatment of chronic inflammatory diseases such as arthritis, autoimmune disorders, and other inflammatory conditions.

Further enhancement of its anti-inflammatory properties is attributed to the presence of various antioxidant compounds in the plant, such as flavonoids and phenolic constituents. These substances can reduce oxidative stress, which often accompanies and exacerbates inflammatory processes, thereby aiding in the restoration of tissue homeostasis and reducing damage caused by free radicals. Thus, the synergistic action of glycosides and antioxidant compounds within *Convallaria majalis* underscores its potential in comprehensive therapy of inflammatory diseases, warranting further research to determine optimal dosages and formulations [46].

Among the numerous flavonoids identified in the composition of *Convallaria majalis*, the derivatives of quercetin and kaempferol hold particular significance. These compounds belong to the class of polyphenolic anthocyanins, characterized by pronounced antioxidant properties, which are attributed to their ability to effectively neutralize free radicals and reactive oxygen species [14, 47].

One of the mechanisms by which the presence of antioxidant flavonoids and phenolic compounds

contributes to the enhancement of anti-inflammatory effects is their involvement in modulating redox processes, leading to a reduction in oxidative stress - a factor often associated with the development and progression of chronic inflammatory conditions [14,44].

The presence of antioxidants in *Convallaria majalis* and their activity are significantly associated with a reduced likelihood of developing chronic diseases, also such as ischemic heart disease, oncological pathologies, neurodegenerative diseases, diabetes, obesity, aging, and various chronic inflammatory conditions [48-49]. Polyphenolic compounds present in *Convallaria majalis* exhibit pronounced antioxidant activity, primarily due to their ability to effectively neutralize free radicals - highly reactive species generated within biological systems under the influence of endogenous and exogenous factors [49].

Cytotoxic Activity: *Convallaria majalis*, as we mention before, widely known for its cardiac glycosides such as convallatoxin and convalloside, also exhibits cytotoxic and pro-apoptotic activities that may be relevant to cancer therapy. These compounds can interfere with cell proliferation and induce apoptosis—mechanisms vital for cancer suppression [50-51].

Natural products have long been explored for antiviral drug development, including potential therapies targeting the HIV life cycle. *Convallaria majalis* is among several traditional medicinal plants noted for anti-HIV activity, likely due to its glycosides and flavonoids, which may interfere with the viral entry and replication of HIV. While promising, further evidence is needed to validate these effects and explore their clinical applicability [52].

Despite their visual appeal, some plants contain highly cytotoxic compounds that pose serious health hazards. Notably, species from the *Lilium* genera are extremely toxic to cats and dogs. In felines, even small amounts can cause rapid and often fatal kidney failure. This toxicity targets the renal tubular epithelial cells, likely due to unidentified, water-soluble compounds that are quickly absorbed. Common clinical symptoms include vomiting, lethargy, and loss of appetite, which can escalate to anuric renal failure without prompt intervention, often resulting in a poor prognosis—even with dialysis. Diagnosis typically depends on clinical signs, patient history, and markers of acute kidney injury. This underscores the potential lethality of natural plant compounds in specific biological systems and highlights the importance of interdisciplinary research involving toxicology, phytochemistry, and cellular biology to unravel the underlying cytotoxic mechanisms of such plants [53].

Research on *Convallaria majalis* steroidal glycosides showed that adding polar substituents reduced cytotoxicity [10]. These compounds, characterized by three or more hydroxyl groups on the aglycone skeleton, exhibit potent cytotoxic, anti-inflammatory, antimicrobial, and cAMP phosphodiesterase inhibitory effects. A total of 407 such saponins have been identified across 11 plant families and 36 genera—especially within Asparagaceae, the family of C. majalis. Given their structural similarity and taxonomic proximity, further exploration of steroidal saponins in C. majalis is warranted to evaluate their therapeutic relevance [10, 33].

Advanced analytical techniques were used to investigate cytotoxic properties of plant-derived compounds. A methanol extract of *Convallaria majalis* yielded 15 distinct steroidal glycosides after extensive chromatography.

Dermatological Benefits: *Convallaria majalis* presents both potential skin-related therapeutic effects and notable dangers, particularly concerning its application in dermatology. Some of its biologically active compounds, especially glycosides, are believed to possess anti-inflammatory properties that may help soothe skin redness or irritation. However, the scientific support for these effects remains scarce, with most studies centered

on more extensively studied anti-inflammatory agents [54].

In folk medicine, *C. majalis* has occasionally been included in topical treatments purported to enhance peripheral circulation, theoretically aiding wound recovery. Nonetheless, substantiated evidence for such claims is minimal, highlighting the necessity for more rigorous investigation to confirm these traditional applications [55].

Conversely, the plant harbors toxic elements—primarily cardiac glycosides such as convallatoxin—that can pose significant risks upon contact with the skin. These substances are known to cause localized inflammation or discomfort, particularly in individuals with sensitive or damaged skin or during prolonged exposure. While the most severe toxic effects occur through ingestion—leading to symptoms like nausea, vomiting, and potentially fatal cardiac arrhythmias—topical use still demands caution. Due to its poisonous nature, the application of *C. majalis* in skin care or dermatological preparations should be undertaken with prudence and only under professional supervision. Its use without expert oversight is inadvisable, as the balance between its possible therapeutic advantages and substantial health hazards remains precarious [55].

Convallaria majalis as a Functional Food: In recent years, there has been a growing convergence between floriculture and horticulture—two historically separate disciplines. While floriculture traditionally fulfills ornamental and aesthetic roles, and horticulture addresses nutritional needs, a new agro-food paradigm is emerging. In this context, flowers are increasingly viewed as a novel class of "vegetables," offering both sensory appeal and health-promoting compounds. This innovation reflects a broader trend toward food diversification and nutraceutical development [56].

Edible flowers, characterized by vibrant pigmentation due to high concentrations of flavonoids and carotenoids, are being recognized for their strong antioxidant potential and ability to counteract oxidative stress-related diseases. Scientific interest has grown in evaluating their phytochemical content, sensory properties, cultivation practices, and limitations—including toxicity and shelf life. These developments frame the importance of assessing specific ornamental species, such as *Convallaria majalis*, not only for their traditional uses but also for their bioactive potential in functional food systems.

Although *C. majalis* is not currently edible due to its toxicity, it contains phytochemicals—particularly cardiac glycosides, flavonoids, and phenolic acids—that exhibit significant antioxidant, anti-inflammatory, and antimicrobial activities. With targeted purification and proper safety protocols, its non-toxic compounds may contribute to future functional food applications, including specialized nutraceuticals and health-supportive formulations.

As we mention before, *Convallaria majalis*, commonly known as Lily of the Valley, is a medicinal plant historically valued for its content of cardiac glycosides—bioactive compounds with potent cardiotonic effects, particularly in supporting heart health. In addition to these, the plant contains a variety of phytochemicals with reported antioxidant, anti-inflammatory, and antimicrobial properties. However, its application as a functional food remains severely restricted due to its well-documented toxicity.

Edible flowers have long been incorporated into traditional culinary and medicinal practices across diverse cultures. Beyond their aesthetic and flavor-enhancing qualities, they are increasingly appreciated as functional foods, rich in bioactive constituents such as flavonoids, polyphenols, and essential vitamins. These compounds are known to offer health-promoting effects, including anti-inflammatory and antioxidant actions. With proper cultivation practices and safety protocols, edible flowers have the potential to serve not only as ornamental additions but also as natural dietary

supplements, contributing to the development of health-oriented food products [57].

Although C. majalis is currently excluded from this category due to the high toxicity of its cardiac glycosides (notably convallatoxin), it nevertheless harbors a diverse array of bioactive compounds—such as flavonoids, phenolic acids, and steroidal saponins—with therapeutic potential. These constituents have demonstrated various pharmacological effects, including antioxidant, anti-inflammatory, cardioprotective, and antimicrobial activities.

Looking forward, advances in phytochemical extraction, selective purification, and formulation technologies may enable the isolation of non-toxic components from C. majalis. Such progress could allow for their safe incorporation into nutraceuticals, pharmaceuticals, or specialized health products. With rigorous safety assessments, standardization protocols, and regulatory oversight, C. majalis could potentially be repositioned as a source of valuable functional ingredients.

Scientific Innovation and Practical Implications: This review presents a scientifically innovative synthesis by bridging the ethnopharmacological legacy of *Convallaria majalis* with recent advancements in phytochemistry, molecular biology, and therapeutic sciences. It is one of the few comprehensive reviews to explore *C. majalis* not only as a cardiotonic plant but also as a potential source of anticancer and neuroprotective agents, supported by contemporary studies on its steroidal glycosides such as convallatoxin and convallamaroside.

This review uniquely bridges the traditional ethnomedicinal use of *Convallaria majalis*—historically valued for its cardiotonic effects—with modern pharmacological insights that reveal its potential in oncology and neuroprotection. While folk medicine primarily employed the plant for heart-related ailments, recent studies have demonstrated that its cardiac glycosides exert anticancer effects through pro-apoptotic, anti-proliferative, and anti-angiogenic mechanisms in various cancer models. Simultaneously, emerging data suggest that compounds such as convallatoxin may also modulate neuroinflammatory pathways and oxidative stress, indicating neuroprotective properties. By aligning ancestral knowledge with molecular pharmacodynamics and translational research, this review highlights *C. majalis* as a promising candidate for multi-target therapeutic strategies in chronic diseases beyond cardiovascular health.

Furthermore, the manuscript highlights practical tools—such as qPCR-based molecular diagnostics—for accurately distinguishing *C. majalis* from morphologically similar edible species, thus contributing to food safety and toxicological awareness. These insights are crucial for guiding the development of *C. majalis*-derived products as functional foods, adjuncts to chemotherapy, or neuroprotective agents, while simultaneously addressing concerns related to toxicity, standardization, and quality control.

By integrating traditional knowledge with modern pharmacological data and safety considerations, this review provides a forward-looking perspective on the therapeutic positioning of *C. majalis* within the framework of functional food science and phytotherapeutics.

CONCLUSION

Convallaria majalis represents a fascinating subject in ethnopharmacology and modern phytomedicine, characterized by its long history of traditional use for cardiac ailments alongside its well-documented inherent toxicity. As this review consolidates, the plant's rich phytochemistry, dominated by a diverse array of cardiac glycosides and other bioactive compounds, underpins a broad spectrum of reported pharmacological activities. Beyond its historical cardiovascular applications, contemporary research highlighted herein points to its compelling potential in oncology, neuroprotection, and

as an anti-inflammatory and antioxidant agent, among others.

Recent investigations into the seed lipid profile of *Convallaria majalis* reveal high unsaturation and the presence of biologically active lipid compounds, including β-sitosterol and essential fatty acids, supporting its potential for non-food industrial applications such as cosmetics and pharmaceuticals

In addition to its known cardiotonic effects, highlighted an additional mechanism underlying the procoagulant toxicity of *Convallaria majalis*. Convallatoxin, a primary cardiac glycoside derived from the plant, was shown to induce a hypercoagulable state by promoting thrombin generation and increasing tissue factor expression in monocytes. Using rotational thromboelastometry and ELISA-based thrombin–antithrombin complex assays, CNT was observed to shorten clotting time and elevate extracellular vesicle-associated TF (EV-TF) activity. These effects were further validated in THP-1 monocytic cells, where CNT increased TF mRNA expression and EV-TF release—effects that were reversed by a MAPK pathway inhibitor (PD98059), suggesting the involvement of MAPK signaling in CNT-induced coagulopathy. These findings provide important mechanistic insight into the cardiotoxic and prothrombotic risks associated with convallatoxin exposure, underscoring the need for cautious application and further investigation into its safety profile [59]. However, the persistent challenge of its narrow therapeutic index and the critical concerns regarding cardiotoxicity underscore the urgent need for stringent research. Future endeavors must focus on precise compound isolation, mechanistic elucidation, and the development of safer derivatives or formulations that can maximize therapeutic benefits while mitigating adverse effects. This review emphasizes that while *C. majalis* holds significant promise as a source of novel bioactive molecules, the translation of its traditional uses into safe and effective modern clinical applications will require continued, rigorous scientific investigation and a deep understanding of its complex pharmacology

Future applications of *C. majalis* may benefit from innovative delivery systems such as aptamer-functionalized nanoplatforms, which have shown promise in enhancing targeting specificity and reducing systemic toxicity of potent natural compounds. Such approaches could pave the way for the safe clinical integration of glycosides like convallatoxin

Abbreviations: National Academy of Sciences of the Republic of Armenia - NAS RA; Gamma-aminobutyric acid – GABA; the sodium-potassium adenosine triphosphatease - Na+-K+-ATPase; Osteoporosis Screening in Older Women - OSW-1; Foods for Specified Health Uses – FOSHU; a human colorectal carcinoma cell line - HCT116; Tumor necrosis factor-alpha - TNF-α; Interleukin-1 beta - IL-1β; Nitric oxide – NO; Nuclear Factor kappa B – NFκB. Human Immunodeficiency Virus – HIV; quantitative Polymerase Chain Reaction – qPCR; Enzyme-Linked Immunosorbent Assay – ELISA; Extracellular Vesicle–Tissue Factor - EV-TF; Mitogen-Activated Protein Kinase – MAPK; Carbon Nanotube - CNT NP –supervision, critical revision of the manuscript, writing–review and editing; HG – literature search, data analysis, writing – review and editing; SS – literature review, data organization, writing – original draft preparation, GM – literature search, writing – review and editing; MS – validation, writing – review and editing; QN – literature review, data organization; IG – plant taxonomy and botanical background, writing – review and editing; GA - conceptualization, supervision, critical revision of the manuscript, writing–review and editing.

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