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Review Paper

Antitumor Potential of *Vinca herbacea* and Its Molecular Pathways in Inhibiting Cancer Cell Growth

Mohammad Kordkatouli[1, 2], Aryan Sateei[2, 3*], Tayyebeh Khoshbakht[4]

1. Department of Cell and Molecular Biology, Faculty of Sciences, Gorgan Branch, Islamic Azad University, Gorgan, Iran.
2. Institute of Medicinal Plants Research, Gorgan Branch, Islamic Azad University, Gorgan, Iran.
3. Department Biology, Faculty of Sciences, Gorgan Branch, Islamic Azad University, Gorgan, Iran.
4. Department of Clinical Medicine, Clinical Cardiovascular Research Group, UiT The Arctic University of Norway, Tromsø, Norway.

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ABSTRACT

Background: *Vinca herbacea*, a lesser-known member of the Apocynaceae family, has shown notable pharmacological effects, particularly in oncology. Its bioactive constituents—mainly vincristine, vinblastine, flavonoids, and phenolic acids—have demonstrated significant anticancer activity. These compounds primarily induce apoptosis, inhibit cell proliferation, and modulate key signaling pathways involved in cancer progression. Additionally, *V. herbacea* affects angiogenesis and metastasis, making it a promising candidate for integrative cancer therapy. Despite its potential, the plant remains underexplored in clinical settings.

Materials and Methods: A systematic literature review was conducted across PubMed, Scopus, Web of Science, and Google Scholar for studies published between 2000 and 2025. Keywords included "*Vinca herbacea*", "anticancer", "apoptosis", and "metastasis". Peer-reviewed articles reporting molecular mechanisms in vitro, in vivo, or in silico were selected. Data were extracted and synthesized to highlight bioactive compounds, pathways involved, and pharmacological effects.

Results: The collected data showed that *V. herbacea* exerts anticancer effects through mitochondrial apoptosis induction (via caspase activation, Bax/Bcl-2 modulation), microtubule disruption, and inhibition of mitosis. It downregulates VEGF and EMT-related genes, reducing angiogenesis and metastasis. It also modulates signaling pathways such as PI3K/AKT, MAPK, and NF-κB, enhancing its pro-apoptotic and anti-proliferative properties. Molecular docking analyses confirmed high binding affinities between plant-derived alkaloids and oncogenic targets.

Conclusion: *V. herbacea* exhibits strong antitumor potential through multi-targeted molecular mechanisms. Its ability to inhibit proliferation, angiogenesis, and metastasis, combined with apoptotic induction, makes it a promising natural agent in cancer treatment. However, further preclinical research and clinical trials are necessary to confirm its efficacy and safety before clinical application.

*** Corresponding Author:**
Aryan Sateei, PhD.
Address: *Department Biology, Faculty of Sciences, Gorgan Branch, Islamic Azad University, Gorgan, Iran.*
Phone: *+98 (911) 3754290*
E-mail: *saateyi@gmail.com*

Introduction

With millions of new cases and deaths each year, cancer remains a major global health concern [1, 2]. The disease remains challenging to treat due to its multifactorial nature and the emergence of resistance to traditional medicines, even with advancements in immunotherapy, radiation therapy, and chemotherapy [1-3]. The growing worldwide burden has fueled the search for innovative, efficient, and focused cancer treatments [2, 3]. In this context, chemicals originating from plants have emerged as attractive options due to their potential for selectivity and reduced toxicity [1]. The Apocynaceae family's Vinca genus is one such group that is particularly noteworthy. Species, such as *Vinca minor*, *Vinca major*, and *Vinca rosea* (*Catharanthus roseus*) have long been studied for their alkaloids, such as vincristine and vinblastine, which have demonstrated strong anticancer effects [4].

Vincristine and vinblastine inhibit microtubule polymerization during cell division, leading to mitotic arrest and apoptosis in cancer cells. These compounds have become the mainstay in treating hematologic malignancies, lymphomas, and certain solid tumors. However, there is growing interest in exploring other species within the Vinca genus that may possess anticancer properties similar to or superior to those of vincristine. *Vinca herbacea*, a lesser-known species, presents a promising but underexplored alternative [5, 6].

Native to the Mediterranean region, western Asia, and the Caucasus, *V. herbacea* has been traditionally used in folk medicine for various ailments [4, 5]. Although scientific studies on its anticancer potential are limited, preliminary research suggests that *V. herbacea* contains a unique array of bioactive compounds, such as alkaloids, flavonoids, and terpenoids, which may contribute to its pharmacological properties. These compounds are crucial in inhibiting cancer cell proliferation, inducing apoptosis, and modulating the molecular pathways involved in metastasis and angiogenesis [6-8].

V. herbacea is thought to have anticancer properties since it can target several crucial molecular pathways that control the survival and spread of cancer cells. Commonly dysregulated in malignancies, pathways, such as p53, nuclear factor kappa-B (NF-κB), phosphatidylinositol 3'–kinase/protein kinase B (PI3K/AKT), and mitogen-activated protein kinase (MAPK) is implicated in unchecked cell proliferation, evasion of apoptosis, and resistance to treatment. According to preliminary data, *V. herbacea* bioactive substances may interact with these pathways by directly impacting crucial proteins or regulating the gene expression that control immune responses, apoptosis, and the cell cycle. One crucial mechanism underlying *V. herbacea*'s anticancer effects has been suggested to be the activation of p53, a tumor suppressor gene essential for DNA repair and cell cycle arrest [9-13].

V. herbacea has not been extensively studied as other Vinca species, but its potential as a source of novel anticancer agents is clear. Its bioactive compounds offer a promising avenue for therapeutic development, especially in modulating key cancer-related molecular pathways. Further research is essential to fully understand its pharmacological profile and assess its clinical viability as a cancer treatment [9, 10].

Phytochemical and pharmacological properties

The pharmacological properties of medicinal plants are closely associated with their phytochemical composition, which influences their biological activity. *V. herbacea*, a species native to the Mediterranean, western Asia, and the Caucasus region, has gained attention for its potential therapeutic effects, particularly its anticancer activity. However, detailed investigations into its phytochemical profile and corresponding pharmacological actions remain limited compared to its more extensively studied relatives, such as *V. rosea*. Nonetheless, early studies suggest that *V. herbacea* harbors a diverse array of bioactive compounds, including alkaloids, flavonoids, terpenoids, and phenolic compounds, each of which may contribute significantly to its pharmacological effects [4, 14].

Phytochemical composition

Alkaloids: Alkaloids are among the most studied compounds in the Vinca genus, and *V. herbacea* is no exception. These nitrogen-containing compounds have been implicated in various biological activities, including anticancer, anti-inflammatory, and anti-microbial effects. Among the alkaloids identified in *V. herbacea*, indole-based compounds and terpenoid indole alkaloids, such as vincristine, vinblastine, and catharanthine are particularly interesting. Although vincristine and vinblastine are more commonly associated with *V. minor*, *V. major*, and *V. rosea*, their presence in *V. herbacea* suggests the potential for similar anticancer effects. These alkaloids exert their effects by disrupting microtubule dynamics, leading to mitotic arrest and apoptosis in rapidly proliferating cells [15].

Flavonoids: Flavonoids are polyphenolic compounds widely recognized for their antioxidant, anti-inflammatory, and anticancer activities. Flavonoids, such as quercetin and kaempferol, have been detected in *V. herbacea*. These compounds are believed to act by scavenging free radicals, thus reducing oxidative stress, a major contributor to cancer development and progression. Moreover, flavonoids modulate key cellular signaling pathways, including the NF-κB pathway, which is often upregulated in various cancers and is involved in tumorigenesis, metastasis, and chemotherapy resistance [16, 17].

Terpenoids: Terpenoids, a large and diverse group of naturally occurring organic chemicals, have been isolated from *V. herbacea*. These compounds, including diterpenoids and saponins, are known for their anti-inflammatory, anti-tumor, and immunomodulatory activities. Some terpenoids in *V. herbacea* may act by modulating the PI3K/AKT and MAPK signaling pathways, which are implicated in regulating cancer cell survival, apoptosis, and proliferation [16, 17].

Phenolic Compounds: Phenolic acids, including gallic and caffeic acid, contribute to the antioxidant potential of *V. herbacea*. These compounds neutralize reactive oxygen species (ROS), which can induce DNA damage and promote cancer cell proliferation. Moreover, phenolic compounds can modulate key enzymes in the cell cycle and apoptotic pathways, reinforcing their potential as anticancer agents [14-19].

Pharmacological effects

Anticancer Activity: The prominent pharmacological effect of *V. herbacea* is its anticancer potential, driven by the various bioactive compounds it contains. Alkaloids, especially vincristine and vinblastine derivatives, inhibit microtubule assembly during mitosis, preventing cancer cell division and causing cell death. The compounds in *V. herbacea* have shown promise in inducing apoptosis by activating intrinsic pathways involving the mitochondria, caspases, and B-cell lymphoma 2 (Bcl-2) family proteins. Additionally, flavonoids and terpenoids may enhance the activity of these alkaloids by modulating signaling pathways such as p53, NF-κB, and PI3K/AKT, which play crucial roles in cell cycle regulation, survival, and resistance to chemotherapy [14-18].

Anti-inflammatory and Antioxidant Activity: Chronic inflammation and oxidative stress are stablished cancer etiologies. *Vincaherbacea* contains phenolic acids and flavonoids with strong antioxidant activity in the form of reactive oxygen species (ROS) scavenging, which protects DNA from damage and prevents tumorigenesis. These compounds exhibit anti-inflammatory activities by inhibiting pro-inflammatory cytokines and enzymes, such as cyclooxygenase-2 (COX-2) and lipoxygenase. This bidirectional activity of fighting oxidative stress and inflammation provides a beneficial mechanism for reducing cancer risk and progression [14, 17, 20-23].

Angiogenesis Inhibition: Angiogenesis, the formation of new blood vessels, is a critical process in cancer progression, enabling tumors to grow and metastasize. Some bioactive compounds in *V. herbacea*, particularly alkaloids and flavonoids, may inhibit angiogenesis by downregulating vascular endothelial growth factor (VEGF) and other angiogenic factors. Inhibition of angiogenesis prevents tumor from establishing their blood supply, which is essential for tumor growth and spread [4, 10, 14, 17].

Metastasis Inhibition: Metastasis, the spread of cancer cells from the primary site to distant organs, is the leading cause of cancer-related deaths. Terpenoids and flavonoids in *V. herbacea* may hinder metastasis by modulating the epithelial-mesenchymal transition (EMT) process, essential for tumor cells to acquire migratory and invasive properties. Inhibition of this process may prevent tumor cells from disseminating through the bloodstream and colonizing other tissues [23-27].

Immunomodulatory Effects: Several compounds in *V. herbacea* exhibit immunomodulatory properties. These bioactive molecules may enhance the immune system's ability to recognize and eliminate cancer cells by activating various immune cells, including T-cells, macrophages, and dendritic cells. By modulating immune responses, *V. herbacea* can potentially increase the efficacy of existing cancer immunotherapies and reduce the immunosuppressive environment that tumors often create [4, 14, 17, 25-27].

Alexandra Ciorîță et al. in Romania studied the phytochemical properties of *V. minor*, *V. herbacea*, *V. major*, and *V. major var. variegata* leaf extract. They observed species-specific differences in antioxidant, antibacterial, and cytotoxic activities, with vincamine found in multiple species. *V. herbacea* exhibited the highest phenolic content and antioxidant capacity, while *V. major var. variegata* had the most flavonoids. *V. minor* was the most effective against *S. aureus* and *E. coli*, while *V. herbacea* showed significant antibacterial activity against *S. aureus*. The extracts also exhibited dose-dependent effects on cancer cells, suggesting their potential for use in bacterial treatments and cancer therapy [4].

Therapeutic applications of *V. herbacea* and molecular mechanisms in cancer treatment

V. herbacea, a species from the Vinca genus within the Apocynaceae family, holds considerable promise as a potential source for novel anticancer therapies. Despite its relative under-exploration compared to *V. rosea* (*C. roseus*), *V. herbacea* is a promising candidate due to its distinctive phytochemical composition, which includes alkaloids, flavonoids, terpenoids, and phenolic compounds. These bioactive molecules have been implicated in various molecular pathways crucial for inhibiting cancer cell growth, metastasis, and survival [4, 14, 17, 20, 21].

Mechanistic insights into the anticancer activity of *V. herbacea*

Interference With Microtubule Dynamics: *V. herbacea*'s anticancer activity primarily comes from interference with microtubule dynamics, a trait most Vinca genus anticancer drug share. Similar to *V. rosea* and *V. major*, *V. herbacea* alkaloids bind to the protein subunit tubulin and inhibit its polymerization, preventing the formation of the mitotic spindle. This leads to mitosis inhibition and subsequent apoptosis induction in proliferating cancer cells. *V. herbacea* alkaloids, including vincristine-like alkaloids, can interfere with the cell cycle of normal cells, leading to cell arrest at the metaphase-anaphase transition and inhibiting chromosome segregation. The microtubule-disrupting effect of *V. herbacea* is most pronounced in rapidly growing cancers, including hematologic malignancies, solid tumors, and lymphomas [14, 20, 12, 24].

Induction of Apoptosis Through Multiple Pathways: Apoptosis, or programmed cell death, is an essential mechanism for cancer cell elimination. *V. herbacea* activates intrinsic and extrinsic apoptotic pathways through its alkaloid and flavonoid content. Alkaloids, such as vincristine derivatives, can induce mitochondrial dysfunction by releasing cytochrome c into the cytoplasm, activating caspases and initiating apoptosis. In addition, flavonoids and phenolic acids of *V. herbacea*, including quercetin and kaempferol, modulate the expression of key apoptotic regulators like Bcl-2, Bax, and p53. Activation of p53, a tumor suppressor protein, results in cell cycle arrest, DNA repair, and apoptosis in response to DNA damage. Flavonoids also increase caspase cascades activation, amplifying the apoptotic response and suppressing the cancer cell viability [14, 20-22].

Inhibition of Angiogenesis and Tumor Vasculature Formation: Angiogenesis, the process of new blood vessel formation, is crucial for the survival and growth of solid tumors. *V. herbacea* inhibits angiogenesis by targeting various angiogenic factors, including VEGF and fibroblast growth factor (FGF), which are overexpressed in the cancerous tissue. Flavonoids found in *V. herbacea*, such as luteolin and apigenin, are potent inhibitors of VEGF and fibroblast growth factor (FGF) signaling and suppressing endothelial cell proliferation, migration, and new vessel formation in tumors. Angiogenesis inhibition deprives tumors of oxygen and nutrients, limiting their growth and metastasis. Additionally, terpenoids of *V. herbacea* were shown to down-regulate the expression of pro-angiogenic enzymes such as matrix metalloproteinases involved in the degradation of extracellular matrix components and blood vessel formation [12, 24].

Dehghanipour et al. conducted a study to evaluate the anti-tumor effects of *V. herbacea* extract on human ovarian cancer (SKOV3) cells. The results demonstrated that the extract had significant cytotoxic effects, inducing apoptosis through caspase-3 activation and an increased Bax/Bcl-2 ratio. Additionally, *V. herbacea* inhibits angiogenesis by reducing the expression of angiogenesis-related genes (VEGF, VEGFR-1, and VEGFR-2), effectively reducing cancer cell adhesion and invasion [15].

Modulation of Inflammatory and Immune Responses: Chronic inflammation is crucial in tumor initiation and promotion. *V. herbacea* contains several compounds with anti-inflammatory properties, such as flavonoids and alkaloids, which exert their effects by modulating the production of inflammatory cytokines and the activity of enzymes like COX-2 and lipoxygenase (LOX). These enzymes are overexpressed in cancer and contribute to the pro-inflammatory tumor microenvironment. The flavonoids kaempferol and quercetin in *V. herbacea* inhibit COX-2 and lipoxygenase (LOX), thereby reducing the production of pro-inflammatory mediators, such as prostaglandins and leukotrienes. By modulating inflammatory pathways, *V. herbacea* decreases the inflammatory microenvironment that leads to cancer formation and enhances immune surveillance, allowing the immune system to recognize and kill cancer cells [23-26].

Suppression of Metastasis: Metastasis is the primary cause of cancer-related death since it allows cancer cells to spread to distant organs. *V. herbacea* has been found to suppress metastasis by suppressing EMT, which enables cancer cells to acquire migratory and invasive capabilities. By modulating key signaling pathways, including NF-κB, PI3K/AKT, and MAPK, *V. herbacea* suppresses

the activation of transcription factors that induce EMT. Particularly, *V. herbacea* flavonoids inhibit NF-κB signaling, downregulating mesenchymal marker expression and matrix remodeling enzymes, preventing cancer cells from detaching from the parent tumor, migrating through the extracellular matrix, and invading distant tissues [25-29].

Comparison with *V. rosea* and other alkaloid-based anticancer agents

Phytochemical profile: *V. herbacea*'s pharmacological activity is substantiated by a distinctive combination of alkaloids, flavonoids, terpenoids, and phenolic acids. Although *V. rosea* has been renowned for its alkaloids vincristine and vinblastine used in large-scale chemotherapy, *V. herbacea* contains different flavonoid and terpenoid compounds with synergistic mechanisms of action. These molecules not only enhance the anticancer effect by targeting different biological pathways but also have the potential to reduce the toxicity of alkaloid-based therapies. For example, the antioxidant and anti-inflammatory potential of flavonoids in *V. herbacea* can modulate the side effects of chemotherapy, such as oxidative stress and inflammation, which are omnipresent in conventional cancer therapies [29-33].

Anticancer activity and toxicity: While *V. rosea* is a prolific source of vincristine and vinblastine, which have been found useful in treating leukemias, lymphomas, and solid tumors, the alkaloids are marred by dose-limiting toxicities, such as neurotoxicity and myelosuppression. Other bioactive compounds in *V. herbacea* can potentially offer a broader therapeutic window and reduce the intensity of side effects. Additionally, *V. herbacea* has proven effective in treating primary tumors and in metastasis inhibition and angiogenesis, a phenomenon that is often difficult to suppress using conventional chemotherapy [29-35].

Synergistic potential: The pleotropic variety of bioactive molecules in *V. herbacea* suggests that it can synergize with other therapeutic approaches, including targeted therapies, immune checkpoint inhibitors, and radiation therapy. For instance, the anti-angiogenic properties of *V. herbacea* can enhance the activity of vascular-targeted therapies, while its anti-inflammatory and immune-modulating properties can enhance the efficacy of immunotherapy. Furthermore, its microtubule-disrupting activity can complement the actions of other chemotherapeutic agents, leading to enhanced tumor cell killing [31-37].

Challenges

The investigation and application of *V. herbacea* in cancer therapy are hindered by various concerns, including limited studies on its phytochemical constituents, with most bioactive compounds still poorly characterized and understood. Clinical trials in humans to validate its safety and efficacy have not been well established. Although some alkaloids, such as vincristine, exhibit inherent anticancer activity, their toxicity remains a concern, especially at elevated levels. Moreover, the variability of chemical composition with environmental factors makes standardization an issue, and it is not easy to ensure consistent quality for therapeutic formulations. Furthermore, *V. herbacea* interactions with conventional cancer chemotherapeutic agents are unknown, and regulatory issues exist for clinical registration. Issues related to extraction methods and bioavailability of active compounds also hinder its effectiveness, whereas overharvesting results in sustainability issues, necessitating the implementation of sustainable cultivation practices [37-43].

Conclusion

V. herbacea is a candidate anticancer agent due to its diverse pharmacological activities. The bioactive metabolites of the plant, such as alkaloids, flavonoids, and phenolic acids, are credited with its active anticancer activities. These compounds have been found to exert their effects by inducing apoptosis by activating intrinsic pathways involving caspases and influencing the Bax/Bcl-2 ratio. In addition, *V. herbacea* inhibits cancer cell growth and invasion by modulating key signaling pathways, such as PI3K/AKT, NF-κB, and MAPK, which are central to cell survival, apoptosis, and metastasis. Furthermore, the anti-angiogenic activity of the plant, through the inhibition of VEGF and its receptors, also inhibits tumor growth and metastasis. Despite these mechanistic considerations, *V. herbacea* provides a promising therapeutic strategy for cancer treatment, the efficacy of which will be proven by additional preclinical and clinical trials and maximized by further clinical development.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

Conceptualization, methodology, software, formal analysis, investigation, resources, data curation and writing the original draft: Mohammad Kordkatouli, Aryan Sateei; Validation, Mohammad Kordkatouli, Aryan Sateei, Tayyebeh Khoshbakht; Review, editing, visualization, supervision and project Administration: Mohammad Kordkatouli, Aryan Sateei, Tayyebeh Khoshbakht; Funding acquisition: Mohammad Kordkatouli.

Conflicts of interest

The authors declared no conflict of interest.

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