



Research article

Therapeutic Perspective of Natural Alkaloids in Cervical Cancer Management



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Cervical cancer is a major global public health concern that requires continuous advancements in screening methodologies and the management of associated challenges. This will make cervical cancer a preventable and treatable condition for women across the world. In this review, we explore the therapeutic potential of natural alkaloids in managing cervical cancer. These compounds are derived from diverse sources such as plants and marine organisms. They demonstrate multifaceted mechanisms, including anti-proliferative, anti-angiogenic, and immunomodulatory effects. Preclinical studies have shown their efficacy on cervical cancer cell lines, while clinical trials have showcased their potential inpatient interventions. To enhance their efficacy, synergistic approaches combining alkaloids with conventional treatments are being considered. Despite challenges such as bioavailability and toxicity, continued research is vital to unlocking the full potential of natural alkaloids. This will offer novel and complementary strategies in cervical cancer therapeutics.

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1. Introduction

Cervical cancer continues to be a significant health issue worldwide, affecting people from all parts of the world and different socioeconomic backgrounds. This type of cancer is mostly caused by persistent high-risk human papillomavirus (HPV) infections. It is a serious public health concern, particularly for women in developed and developing countries (CDC, 2012; Munoz et al., 2004; Woodman et al., 2001; Ho et al., 1998). The lower segment of the uterus, known as the cervix uteri, comprises two distinct compartments – the endocervix and the ectocervix. The ectocervix is lined with thin, flat squamous cells, while the inner endocervix is characterized by columnar glandular cells. At the junction of these two regions lies the transformation zone, a critical area prone to pre-cancerous lesions triggered by HPV infections. These initial infections are often categorized as low-grade squamous intraepithelial lesions (LSIL) or cervical intraepithelial neoplasia stage 1 (CIN1). Importantly, a significant proportion of these early-stage infections tend to resolve spontaneously, with up to 90% of cases showing self-resolution within a two-year period (Woodman et al., 2001; Ramachandran and Dörk 2021). An estimation revealed that approximately 500,000 women were diagnosed with cervical cancer, resulting in 274,000 attributed deaths, closely mirroring maternal mortality statistics as reported by the World Health

Organization (WHO) in 2010 (Ferlay et al., 2010; WHO, 2012). This devastating burden predominantly afflicts women in low-income countries, with an astounding 88% of cervical cancer deaths occurring in these regions. A sobering projection from Cervical Cancer Action in 2012 indicated that by 2030, cervical cancer could claim over 474,000 lives annually, with more than 95% of these fatalities concentrated in low- and middle-income countries, and the rates in sub-Saharan Africa expected to double (WHO, 2012). These numbers underscore the pressing need for global efforts to combat cervical cancer, addressing healthcare disparities to ensure all women have equal access to prevention and treatment, thereby tackling this critical public health issue and fulfilling a moral imperative for women's health and well-being worldwide (Stewart and Wild 2014).

Natural alkaloids are a diverse group of organic compounds found in various plants, fungi, and marine organisms. These bioactive molecules have complex chemical structures and possess a wide range of pharmacological properties. In the context of cancer treatment, natural alkaloids have gained attention due to their potential therapeutic effects. These include inhibiting tumor growth by inducing programmed cell death, anti-angiogenic properties that prevent the formation of new blood vessels, and immunomodulatory effects that help the body's immune system fight against cancer cells. The multifaceted nature of natural alkaloids makes them interesting candidates for new

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and targeted approaches in cancer treatment. This review focuses on describing the alkaloids of natural origin.

2. Women's health: Global concern

Cervical cancer screening includes various techniques for different contexts. The Pap smear is commonly used in high-resource settings, but it can be resource-intensive. Visual inspection techniques are a good alternative. Later-stage precancers can be treated with cryotherapy freezing or LEEP. HPV testing is highly sensitive and can be conducted through self-sampling techniques. The low global coverage of screening methods highlights the need to bridge the gap between effective screening methods and their practical implementation, particularly in underserved regions. Remarkably, young women can clear HPV infections (Ferreccio et al., 2011). In the first year of infection, clearance rates can reach as high as 70%. And within two to five years, clearance rates can go up to 70% to 100%. These statistics are interesting because cervical cancer is very rare in this age group, with only 0.1 cases per 100,000 (Sagadevan and Oh 2023). High-grade cervical intraepithelial neoplasia (CIN2) also regresses 60% of the time within the first three years in adolescents. This indicates that self-resolution is likely, as well as for other infectious diseases (Kurya et al., 2022; Yusuf et al. 2023a; Yusuf et al. 2023b; Almehmadi et al., 2022). Therefore, cervical cancer screening for adolescents is a double-edged sword. It not only fails to offer significant benefits, but it also increases the potential for unnecessary evaluations and treatments. As a result, the current consensus supports initiating cervical cancer screening at the age of 21, regardless of risk factors. It's important to note that not all HPV strains are equal in terms of persistence. Low-risk HPV strains tend to clear more rapidly than high-risk strains. Among the high-risk types, HPV 16 is the primary cause of persistent infections. This has led to a paradigm shift in cervical cancer screening. High-risk HPV DNA testing is now gaining prominence as a more effective and nuanced approach. These advancements in understanding HPV's dynamics and the distinct risks associated with various strains are propelling the field towards more precise and tailored screening strategies for cervical cancer prevention (Loke et al., 2022; Torres 2020). The International Federation of Gynecology and Obstetrics (FIGO) has established a staging system for cervical cancer to categorize the extent of disease progression. The stages are as follows (Mohamud et al., 2022):

- Stage 0 (Carcinoma in situ): At this early stage, abnormal cells are present only in the innermost lining of the cervix, without invading deeper tissues.
- Stage I (Early invasive cancer): Divided into two sub-stages:
 - IA: Cancer is confined to the cervix and is not visible without a microscope.
 - IB: The tumor is still confined to the cervix, but it is visible without a microscope.
- Stage II (Locally invasive cancer): Further divided into two sub-stages:
 - IIA: The cancer has spread beyond the cervix but has not reached the walls of the pelvis or the lower part of the vagina.
 - IIB: The tumor has spread to the walls of the pelvis or involves the lower third of the vagina.

- Stage III (Advanced local spread): Further divided into two sub-stages:
 - IIIA: Cancer has spread to the lower part of the vagina but not to the walls of the pelvis.
 - IIIB: The tumor has extended to the pelvic walls or has caused kidney problems.
- Stage IV (Advanced spread): Further divided into two sub-stages:
 - IVA: The cancer has spread to nearby organs such as the bladder or rectum.
 - IVB: Distant metastasis has occurred, involving organs beyond the pelvic area.

Understanding the FIGO stages (detailed various stages are defined in Figure 1) is crucial for determining appropriate treatment strategies and predicting the prognosis for individuals with cervical cancer. Regular screenings and early detection play a significant role in improving outcomes for patients at various stages of the disease. Cervical cancer is a significant burden on underserved populations with limited access to quality healthcare services. Cervical cancer is a global health issue that affects women, particularly in underserved regions. More than half a million new cases are diagnosed each year, with 90% occurring in the least developed economies (Mahantshetty et al., 2021). Cervical cancer screening programs are crucial in detecting precancerous lesions, but their translation into effective and widespread screening programs remains a challenge (WHO, 2012; Ferlay et al., 2010). The prevalence of cervical cancer is exacerbated by limited access to healthcare, a lack of awareness, and insufficient screening programs.

Disparities in healthcare access intensify the impact of this disease, particularly in underserved communities. Insufficient awareness often leads to delayed diagnoses and missed opportunities for preventive care. Additionally, the absence or inadequacy of screening initiatives further compounds the challenges in identifying and addressing cervical cancer at early stages.

3. Alkaloids derived from plants to treat cervical cancer.

3.1 Vinblastine and Vincristine from *Catharanthus roseus*

Catharanthus roseus, commonly known as the Madagascar periwinkle or rosy periwinkle, is a medicinal plant celebrated for its rich reservoir of phytoconstituents. Native to Madagascar, this flowering plant has garnered significant attention in traditional medicine and pharmaceutical research due to its diverse array of bioactive compounds (Yusuf et al., 2023a; Yusuf 2023, Alam et al. 2017) including vinblastine (Fig. 3A) and vincristine (Fig. 3B), are potent and have demonstrated remarkable anti-cancer properties (Kumar et al., 2022). Vinblastine and vincristine, derived from the leaves and stems of the plant, have been extensively studied for their efficacy in treating various forms of cancer, including leukaemia and lymphoma. These alkaloids interfere with microtubule formation during cell division, inducing cell cycle arrest and apoptosis in cancer cells.

Vincristine and Vinblastine have garnered substantial attention for their potent anti-cancer properties. These alkaloids, primarily derived from the leaves of the plant, have been

instrumental in the treatment of various malignancies. Vincristine interferes with microtubule formation during cell division, a crucial process for the growth and division of cancer cells. By disrupting this dynamic process, Vincristine effectively halts cancer cell proliferation. This alkaloid has found extensive use in the treatment of leukemia, lymphoma, and certain solid tumours (Ke et al., 2019). These alkaloids are derived from the Madagascar periwinkle plant. They work by disrupting microtubule formation, which prevents the proper segregation of chromosomes during cell division. This disruption causes cell cycle arrest and apoptosis in cervical cancer cells (Ravi et al., 2023). Notably, Vincristine is part of combination chemotherapy regimens and has demonstrated efficacy in improving patient outcomes. Similarly, Vinblastine, another alkaloid derived from *Catharanthus roseus*, operates through the inhibition of microtubule formation. By targeting this essential cellular mechanism, Vinblastine arrests the growth and division of cancer cells, making it effective against various malignancies, including testicular and breast cancers. Vinblastine is often used in combination with other chemotherapeutic agents, contributing to its role in the treatment of a range of cancers. The therapeutic significance of Vincristine and Vinblastine underscores the importance of *Catharanthus roseus* in cancer research and treatment. These alkaloids, with their specific mechanisms of action, exemplify the plant's potential in providing crucial compounds for the development of anti-cancer drugs, showcasing the intricate and valuable pharmacological profile of this tropical medicinal plant.

Catharanthus roseus is a plant that contains various secondary metabolites, including alkaloids, terpenoids, flavonoids, and tannins. These compounds contribute to the plant's overall medicinal properties, exhibiting antioxidant, anti-inflammatory, and antimicrobial activities. The diverse range of phytoconstituents present in *Catharanthus roseus* makes it an excellent source for drug discovery and the development of novel pharmaceuticals. Additionally, apart from its medicinal benefits, this plant is also cultivated for its ornamental value, due to its attractive flowers and ability to grow in different climates.

3.2 *Camptothecin from Camptotheca acuminata*

Camptothecin (Fig. 3C), a potent monoterpene indole alkaloid, stands as a beacon of hope in the realm of cervical cancer treatment, deriving its significance from the bark and wood of the Chinese Happy tree, *Camptotheca acuminata*. This deciduous tree, native to China and various parts of Asia, harbors a remarkable phytoconstituent profile, with camptothecin serving as the principal alkaloid of interest (Fan et al., 2022). Characterized by a distinctive chemical structure featuring a pentacyclic ring system with an indole moiety, camptothecin holds the key to its pharmacological prowess. The intricate lactone ring and alpha-hydroxylactone ring are pivotal elements that enable its interaction with DNA topoisomerase I, presenting a mechanism of action that sets it apart in the realm of anticancer agents. In the fight against cervical cancer, camptothecin operates as a potent inhibitor of DNA topoisomerase I. By forming a complex with the enzyme and DNA, it disrupts the vital re-ligation step of DNA replication. This disruption culminates in the accumulation of single-strand DNA breaks, instigating a

cascade of events that ultimately lead to apoptosis in cancer cells, offering a targeted and effective therapeutic strategy.

The phytoconstituent profile of *Camptotheca acuminata* extends beyond camptothecin itself, encompassing analogues and derivatives. These additional constituents contribute to the overall therapeutic potential and may influence the compound's pharmacological properties (Lorence and Nessler 2004). Extraction of camptothecin from the plant involves meticulous processes such as solvent extraction or supercritical fluid extraction, aiming to obtain a concentrated and pure form of this valuable alkaloid. While camptothecin holds immense promise in treating cervical cancer, challenges such as its relatively low yield in the plant necessitate ongoing research into optimizing extraction methods and exploring biotechnological approaches.

3.3 *Paclitaxel from Taxus brevifolia*

Paclitaxel (Fig. 3D), a remarkable phytoconstituent derived from the bark of the Pacific yew tree, *Taxus brevifolia*, stands as a beacon in the fight against cervical cancer (Lee et al., 2012). This compound, known for its complex and unique chemical structure, serves as a powerful antineoplastic agent with profound implications for cancer therapy. The chemical backbone of paclitaxel features a taxane ring system, a structural marvel that underlies its potent pharmacological effects. This intricate structure plays a pivotal role in paclitaxel's mechanism of action against cervical cancer. By binding to microtubules within the cancer cells, paclitaxel disrupts normal microtubule dynamics essential for cell division (Ullah et al., 2014). This interference results in the arrest of the cell cycle, preventing the cancer cells from proliferating and inducing apoptosis, or programmed cell death. *Taxus brevifolia*, often referred to as the Pacific yew or Western yew contains paclitaxel as its primary phytoconstituent. However, the phytoconstituent profile of this tree extends beyond paclitaxel alone. The plant may contain related taxanes and secondary metabolites that contribute to its overall medicinal properties and potential synergistic effects in treating cervical cancer.

The extraction of paclitaxel from *Taxus brevifolia* is a meticulous process, typically involving advanced extraction techniques to ensure a high yield of this valuable compound. The significance of paclitaxel in cervical cancer treatment lies not only in its potent anticancer properties but also in its ability to enhance the efficacy of conventional therapeutic approaches. The integration of curcumin into cancer therapy represents a pioneering strategy, offering a novel and synergistic adjunct to conventional treatment modalities. This review explores the promising potential of curcumin as a therapeutic ally in combination chemotherapy, particularly when paired with paclitaxel. Beyond its traditional role as a spice and natural pigment, curcumin has emerged as a bioactive compound with multifaceted anti-cancer properties, making it an intriguing candidate for enhancing the efficacy of existing chemotherapeutic agents. The synergy between curcumin and paclitaxel is a focal point of investigation, aiming to capitalize on the complementary mechanisms of action exhibited by these compounds. While paclitaxel disrupts microtubule dynamics to impede cancer cell division, curcumin's diverse pharmacological effects, including anti-inflammatory and antioxidant properties, offer a multi-dimensional approach to cancer treatment. This combination not

only seeks to augment the cytotoxic effects on cancer cells but also endeavours to mitigate the adverse effects associated with paclitaxel (Ashrafizadeh et al., 2020). As we unravel the multifaceted nature of paclitaxel and its phytoconstituent companions, we uncover not just a botanical compound but a pivotal player in the ongoing quest for innovative and effective treatments for cervical cancer.

4. Alkaloids from Marine Organisms to treat cervical cancer.

The exploration of alkaloids derived from marine organisms presents a captivating avenue for the development of novel treatments for cervical cancer (Sharifi et al. 2020). These marine-derived alkaloids come from various organisms such as sponges and bryozoans and exhibit unique chemical structures and pharmacological activities that make them promising candidates in the fight against this malignancy. One notable alkaloid is Discodermolide (Fig. 3E) sourced from marine sponges. This compound displays potent antiproliferative activity by stabilizing microtubules within cancer cells. Its distinct mechanism of action disrupts the dynamic equilibrium of microtubules, resulting in cell cycle arrest and apoptosis in cervical cancer cells. This unique property positions Discodermolide as a valuable player in the pursuit of effective and targeted therapies.

Another noteworthy alkaloid is Bryostatin (Fig. 3F) derived from marine bryozoans and has potential applications in cervical cancer treatment. Its mode of action involves the modulation of protein kinase C (PKC) and the induction of apoptosis pathways. These activities contribute to its anticancer effects, making Bryostatin an intriguing candidate for therapeutic exploration.

Halichondrin B (Fig. 3G), sourced from certain marine sponges, is characterized by its ability to disrupt microtubule dynamics. The unique mechanism by which Halichondrin B interferes with cell division processes marks it as a compound of interest in the search for effective cervical cancer treatments (Gupta et al., 2015). The extraction and isolation of these marine-derived alkaloids involve sophisticated techniques to ensure purity and efficacy. The challenges associated with their low availability of natural sources have led to investigations into sustainable harvesting practices and alternative synthetic

methods. Although the field of marine-derived alkaloids for cervical cancer treatment is still in its early stages, the diverse mechanisms of action and unique chemical structures hold promise for the development of innovative therapies. Continued research into these compounds, along with advancements in extraction methods and sustainable sourcing, may unlock new frontiers in the quest for effective and targeted treatments for cervical cancer. The rich biodiversity of the marine environment offers a wealth of compounds that may revolutionize cancer therapeutics, providing hope for improved outcomes and quality of life for patients facing cervical cancer.

5. Future Directions

Valuable insights can be drawn from the analyses of cervical cancer to help advance prevention and treatment on a global level. Cervical cancer and public health advocates need to understand that shaping policy agendas requires more than just presenting evidence of health burden or distribution. Research and developments in cervical cancer screening are focusing on advanced technologies such as next-generation sequencing and point-of-care tests to improve accuracy and accessibility. It was navigated toward the horizon of advancements, several promising directions emerge, offering avenues for enhanced efficacy and precision in cervical cancer therapeutics. Firstly, the identification and isolation of novel alkaloids from diverse natural sources hold significant potential. Exploring untapped botanical and marine resources may unearth compounds with unique structures and mechanisms, providing a broader arsenal for targeted interventions. The integration of advanced technologies, such as metabolomics and bioinformatics, could streamline the discovery process, facilitating the identification of promising candidates for further study (Burmeister et al., 2022). Secondly, the transition from preclinical to clinical studies marks a critical juncture in translating the therapeutic potential of natural alkaloids into real-world applications. Future research should focus on designing well-controlled clinical trials to assess the safety, efficacy, and optimal dosage of these alkaloids in cervical cancer patients. Investigating potential synergies with existing treatments and exploring combination therapies may further enhance therapeutic outcomes. Additionally, the development of targeted drug

Various FIGO Stages	Description
IA	Invasive carcinoma diagnosed only by microscopy, with maximum depth of invasion <5 mm.
IA1	Measured stromal invasion <3 mm in depth.
IA2	Measured stromal invasion ≥3 mm and <5 mm in depth.
IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than IA2.
IB1	Invasive carcinoma ≥5 mm depth of stromal invasion, and <2 cm in greatest dimension.
IB2	Invasive carcinoma ≥2 cm and <4 cm in greatest dimension.
IB3	Invasive carcinoma ≥4 cm in greatest dimension.
II	Cervical carcinoma invades beyond uterus but not to pelvic wall or to lower third of vagina.
IIA	Tumour without parametrial invasion or involvement of the lower one-third of the vagina.
IIA1	Clinically visible lesion <4 cm in greatest dimension with involvement of less than the upper two-thirds of the vagina.
IIA2	Clinically visible lesion >4 cm in greatest dimension with involvement of less than the upper two-thirds of the vagina.
IIB	Tumour with parametrial invasion but not up to the pelvic wall.
III	Tumour extends to pelvic wall and/or involves lower third of vagina, and/or causes hydronephrosis or nonfunctioning kidney, and/or involves pelvic and/or para-aortic lymph nodes.
IIIA	Tumour involves lower third of vagina, no extension to pelvic wall.
IIIB	Tumour extends to pelvic wall and/or causes hydronephrosis or nonfunctioning kidney.
IIIC	Tumour involves pelvic and/or para-aortic lymph nodes, irrespective of tumour size and extent.
IV	Tumour invades mucosa of bladder or rectum (biopsy proven), and/or extends beyond true pelvis.
IVA	Tumour has spread to adjacent pelvic organs.
IVB	Tumour has spread to distant organs.

Figure 1. Various FIGO stages with description

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delivery systems for natural alkaloids is an avenue that holds promise in mitigating issues related to bioavailability. Furthermore, investigations into the molecular mechanisms underlying alkaloid-induced cytotoxicity could uncover potential biomarkers for patient stratification. Personalized medicine approaches, tailored to individual patient profiles, may enhance treatment precision and therapeutic outcomes, ushering in an era

of more effective and patient-centric cervical cancer care. To improve the therapeutic landscape, researchers, clinicians, and pharmaceutical developers need to work together. By collaborating, the scientific community can bridge the gap between laboratory discoveries and clinical applications, which can help natural alkaloids become viable therapeutic options for cervical cancer patients worldwide.

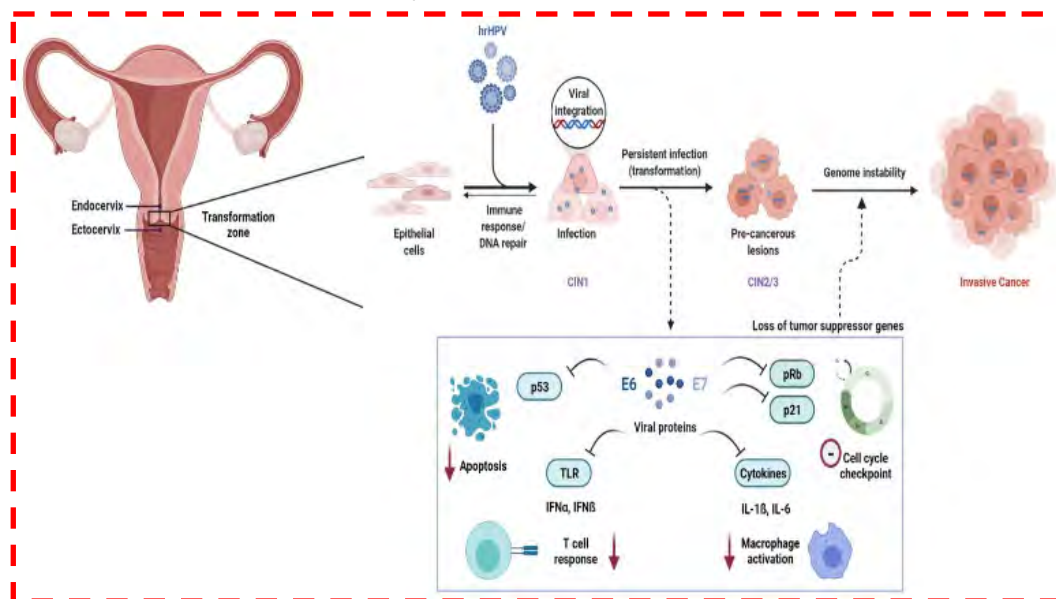


Figure 2. Comprehensive Illustration of the Pathogenesis of Cervical Cancer (Reproduced from Ramachandran And Dörk under CC-BY License, MDPI 2021).

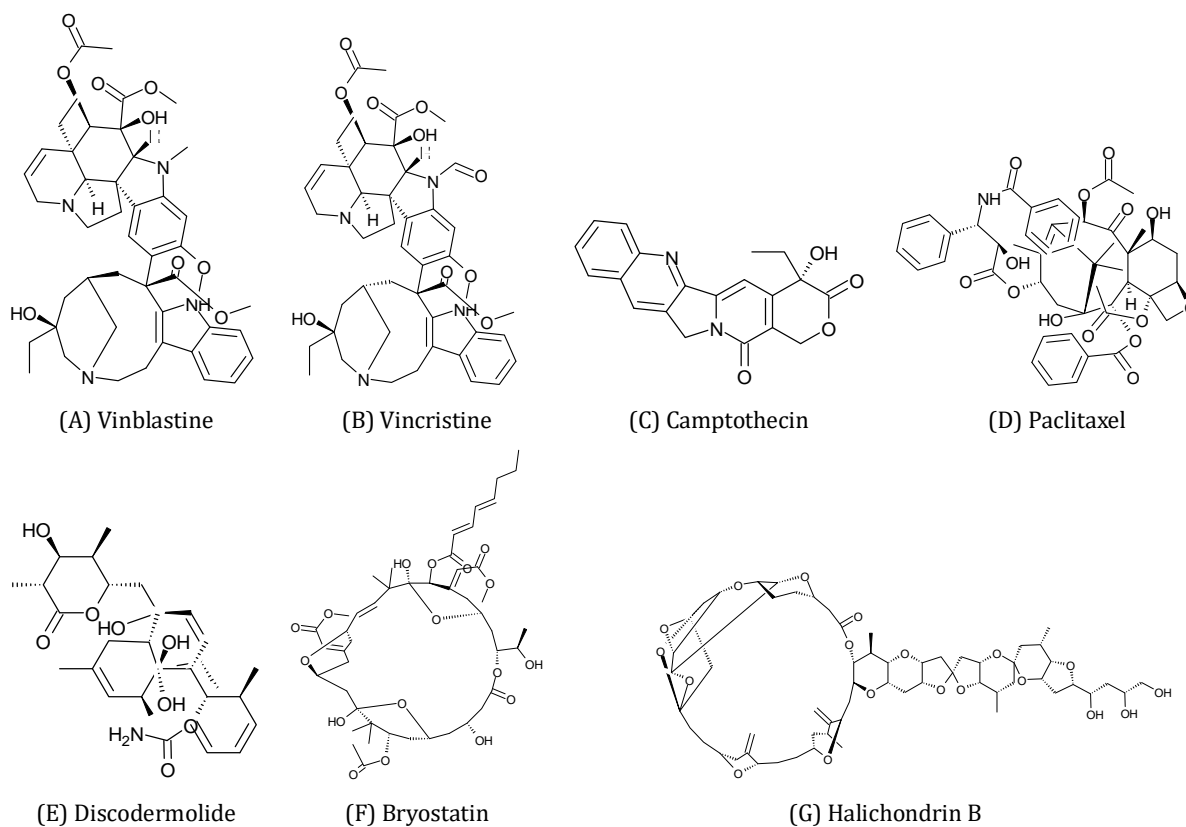


Figure 3. Chemical structures of some potential natural alkaloids for the management of cervical cancer.

6. Conclusion

In conclusion, the exploration of natural alkaloids as a therapeutic avenue in cervical cancer management presents a promising and intriguing prospect. The comprehensive review underscores the potential of these compounds in targeting various cellular pathways involved in cancer progression, offering a multifaceted approach to treatment. The documented anti-cancer properties of natural alkaloids, coupled with their relatively low toxicity compared to conventional treatments, highlight their potential as valuable additions to the existing therapeutic arsenal. However, it is essential to acknowledge the need for further research, clinical trials, and a deeper understanding of the specific mechanisms through which these alkaloids exert their effects. Through collaborative efforts, the scientific community can connect the dots between laboratory breakthroughs and real-world clinical applications. This synergy holds the key to transforming natural alkaloids from promising compounds into practical and effective therapeutic options for cervical cancer patients on a global scale.

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Conflict of Interest

Authors declared no conflict of interests.

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