VINCA ALKALOIDS IN BREAST CANCER: ANTIMITOTIC MECHANISMS AND THERAPEUTIC CHALLENGES

ALCALOIDES DE VINCA NO CÂNCER DE MAMA: MECANISMOS ANTIMITÓTICOS E DESAFIOS TERAPÊUTICOS

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ABSTRACT

Breast cancer represents one of the public health challenges worldwide, being responsible for morbidity and mortality rates among women. In view of the toxicity and limitations of conventional therapies, phytochemicals have emerged as potential agents, vinca alkaloids due to their antimitotic and cytotoxic activity. This review aimed to analyze the efficacy, mechanisms of action, and limitations of the vinca alkaloids in the treatment of breast cancer. A search was conducted in the PubMed and Virtual Health Library (VHL) databases using the MeSH descriptors “Breast Neoplasms,” “Vinca Alkaloids,” and “Phytochemicals.” A total of 12 articles published between 2015 and 2025 were selected based on criteria of relevance and originality. The data indicate that compounds vincristine, vinblastine, vindesine, vinflunine, and vinorelbine act by inhibiting microtubule dynamics, promoting mitotic arrest and apoptosis of cells. However, these agents are associated with adverse effects, including neurotoxicity and myelosuppression, and face therapeutic resistance, especially in triple-negative tumors. Recent advances, such as liposomal formulations and antibody–drug conjugates, have been investigated to improve efficacy and reduce toxicity. It is concluded that vinca alkaloids have promising potential in the management of breast cancer, but require pharmacological optimization and clinical studies to expand their applicability with therapeutic safety.

Keywords: Vinca Alkaloids, Phytochemical Compounds, Breast Neoplasms.

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RESUMO

O câncer de mama representa um dos desafios de saúde pública em todo o mundo, sendo responsável pelas taxas de morbidade e mortalidade entre as mulheres. Diante da toxicidade e limitações das terapias convencionais, fitoquímicos surgiram como potenciais agentes, alcaloides vinca, devido à sua atividade antimitótica e citotóxica. Esta revisão teve como objetivo analisar a eficácia, os mecanismos de ação e as limitações dos alcaloides da vinca no tratamento do câncer de mama. Foi realizada uma busca nos bancos de dados PubMed e Virtual Health Library (VHL) usando os descritores MeSH "Neoplasias da Mama", "Alcaloides de Vinca" e "Fitoquímicos". Um total de 12 artigos publicados entre 2015 e 2025 foram selecionados com base em critérios de relevância e originalidade. Os dados indicam que compostos vincristina, vinblastina, vindesina, vinflunina e vinorelbina atuam inibindo a dinâmica dos microtúbulos, promovendo a parada mitótica e a apoptose das células. No entanto, esses agentes estão associados a efeitos adversos, incluindo neurotoxicidade e mielosupressão, e enfrentam resistência terapêutica, especialmente em tumores triplo negativos. Avanços recentes, como formulações lipossmais e conjugados anticorpo–fármaco, foram investigados para melhorar a eficácia e reduzir a toxicidade. Conclui-se que os alcaloides da vinca têm potencial promissor no manejo do câncer de mama, mas requerem otimização farmacológica e estudos clínicos para ampliar sua aplicabilidade com segurança terapêutica.

Palavras-chave: Alcaloides de Vinca, Compostos Fitoquímicos, Neoplasias Mamárias.

INTRODUCTION

Breast cancer is one of the leading causes of mortality among women worldwide. It is estimated that more than two million cases are diagnosed annually, representing a serious challenge to global public health (Islam et al., 2019). In Brazil, in 2024 alone, there were about 61 thousand cases of malignant breast neoplasms, approximately 10% of the total of 625 thousand cases of neoplasms registered (Brasil, 2025). Several genetic, hormonal, and environmental factors influence its occurrence, as pointed out by Ataollahi et al. (2015). Its etiology involves a complex interaction between genetic and environmental factors, resulting in the uncontrolled multiplication of cells and the progressive invasion of healthy tissues. The disease is classified into three main forms: non-invasive, invasive, and metastatic. The non-invasive type remains restricted to the mammary ducts; the invasive reaches the adipose and connective tissues of the breast; metastatic cells, on the other hand, are characterized by the dissemination of malignant cells to distant organs, such as bones, lungs, and liver (Rampogu et al., 2022; Feng et al., 2018).

Currently available therapeutic options include surgery, chemotherapy, radiation therapy, hormone therapy, and targeted agents. However, many of these treatments lack selectivity, also affecting healthy cells, which contributes to significant side effects such as nausea, gastrointestinal changes, cardiovascular toxicity, and immunosuppression (Garcia-Oliveira et al.,

2021). In addition, the possibility of tumor recurrence and therapeutic resistance limits long-term efficacy (Rampogu et al., 2022). In this context, there is a growing demand for safer therapies that combine antitumor efficacy with lower systemic toxicity (Krause et al., 2019).

Given these limitations, there is growing interest in new therapeutic approaches, especially phytochemicals, bioactive compounds found in fruits, grains, and vegetables. These natural agents demonstrate potential in chemoprevention and in the treatment of various pathologies, such as cancer, diabetes, cardiovascular diseases, and inflammation (Younas et al., 2018). Among the most relevant phytochemicals are vinca alkaloids, such as vincristine, vinblastine, vindesine, vinorelbine and vinflunine. These compounds exert a potent antimitotic action by binding to tubulin, inhibiting the polymerization of microtubules and causing mitotic arrest in metaphase, culminating in cell apoptosis (Feng et al., 2018; Garcia-Oliveira et al., 2021).

Vincristine is widely used in the treatment of several types of cancer, including breast cancer, due to its potent antimitotic activity. However, its clinical use is severely limited by its cumulative neurotoxicity, which can result in peripheral neuropathy even at relatively low doses. This toxicity is exacerbated by co-administration with azole antifungals, such as ketoconazole, which inhibit hepatic metabolism of the drug via cytochrome P450, raising its plasma concentrations and increasing the risk of serious adverse effects (Verma et al., 2022; Dhyani et al., 2022). Other vinca alkaloids, such as vinblastine and vindesine, have lower neurotoxicity but are more frequently associated with myelosuppression, which limits their application in patients with compromised hematological reserve (Feng et al., 2018; Garcia-Oliveira et al., 2021).

In addition to the adverse effects, resistance to vinca alkaloids represents a major obstacle to its clinical efficacy, especially in triple-negative tumors (TNBC), known for their aggressiveness and lack of specific molecular targets. Among the molecular mechanisms involved, the overexpression of the βIII isoform of tubulin (TUBB3) stands out, which compromises the binding of drugs to tubulin and preserves the functionality of the mitotic spindle. In vitro studies have shown that cell lines with high levels of TUBB3 are less sensitive to vincristine and vinblastine, exhibiting mitotic resistance and lower activation of cellular checkpoints (Kanakkanthara and Miller, 2021; Sharma et al., 2022). These findings underscore the need for new formulations, nanostructured vehicles, and targeted delivery strategies, which can overcome resistance mechanisms and reduce systemic toxicity associated with classical alkaloids (Verma et al., 2022; Kirchner and Pianowski, 2022).

Several recent studies have explored the potential of phytochemicals in the treatment of breast cancer by various mechanisms, including induction of apoptosis, blocking tumor progression, inhibition of metastasis, and modulation of microtubules (Younas et al., 2018; Kirchner and Pianowski, 2022). In addition, there is growing evidence that such compounds can reduce drug resistance, representing a relevant advancement in the context of precision oncology.

Despite their promising profile, alkaloids also face pharmacotechnical challenges, such as low solubility, difficult extraction, and potential toxicity, factors that require additional studies for formulation optimization (Dhyani et al., 2022; Garcia-Oliveira et al., 2021). Still, vinca alkaloids represent a class of phytochemicals with a wide range of biological activities, including anticancer, anti-inflammatory, antiviral, and neuroprotective effects (Rampogu et al., 2022).

Studies in tumor cells have demonstrated that these compounds inhibit proper mitotic spindle formation, interfere with microtubule dynamics, and activate spindle assembly checkpoint (SAC), leading to sustained mitotic arrest and cell death (Novais et al., 2021; Feng et al., 2018). This mechanism makes them

promising agents for the control of the disordered proliferation of tumor cells.

Recent years have witnessed important advances in the understanding of the therapeutic application of vinca alkaloids in breast cancer. Although their pharmacological properties and clinical use have been previously reviewed, emerging evidence regarding resistance mechanisms, βIII-tubulin overexpression, nanotechnology-based drug delivery systems, antibody–drug conjugates, and other targeted strategies has substantially expanded current knowledge. These developments justify an updated synthesis of the available evidence, emphasizing recent therapeutic advances, remaining challenges, and future perspectives for the clinical application of vinca alkaloids in breast cancer.

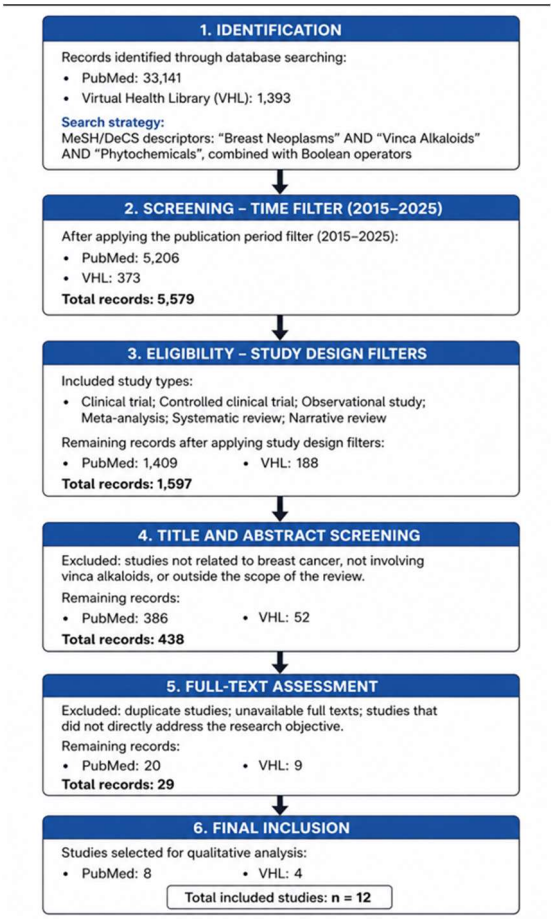
Thus, this review aims to evaluate the efficacy of vinca alkaloids in the treatment of breast cancer, highlighting their mechanisms of action, therapeutic limitations, and possible innovative approaches, with the aim of contributing to safer, more effective, and individualized therapies in the oncological context.

MATERIALS AND METHODS

This study is an integrative literature review conducted in the PubMed and Virtual Health Library (VHL) databases. The search strategy was based on the MeSH and DeCS descriptors “Breast Neoplasms”, “Vinca Alkaloids”, and “Phytochemicals”, combined with Boolean operators and adapted according to the indexing system of each database, considering studies published between 2015 and 2025. Eligible study designs included clinical trials, controlled clinical trials, observational studies, meta-analyses, systematic reviews, and narrative reviews. Whenever necessary, full-text articles were retrieved through institutional library access.

The study selection process followed five sequential stages. Initially, 34,534 records were identified across the consulted databases, including 33,141 from PubMed and 1,393 from the VHL. After applying the publication period filter (2015–2025), the number of records was reduced to 5,579 articles. Subsequently, study design filters were applied, resulting in 1,597 eligible records, of which 1,409 were from PubMed and 188 from the VHL.

In the third stage, title screening was performed to exclude studies outside the thematic scope, including articles not specifically related to breast cancer or not addressing vinca alkaloids. In the fourth stage, full-text assessment was conducted, excluding duplicate studies, unavailable publications, and articles tangential to the research objective. Finally, 12 studies met the eligibility criteria and were included in the qualitative analysis. The selection process followed a structured screening strategy, reported according to PRISMA recommendations to ensure transparency in study identification, screening, eligibility, and inclusion.



MeSH: Medical Subject Headings; DeCS: Descritores em Ciências da Saúde; VHL: Virtual Health Library.

RESULTS AND DISCUSSION

The present integrative review analyzed twelve studies investigating the role of vinca alkaloids in breast cancer, focusing on cytotoxic activity, molecular mechanisms, resistance pathways, and emerging therapeutic strategies. These studies were selected according to previously established criteria and included in vitro and in vivo assays, as well as systematic reviews. The main findings are summarized in Chart 1.

Analysis Table of Articles on Vinca Alkaloids

Authors / Year	Study Type/Method	Objective	Main Results and Conclusions
Gourmelon et al. (2016)	Review/Toxicology	To investigate neurological toxicity of vinca alkaloids.	It confirms significant neurotoxicity, especially of vincristine, and discusses mitigation strategies.
Younas et al. (2018)	Review/ Literature	Discuss phytochemicals in cancer treatment.	Vinca alkaloids are recognized for their antimitotic efficacy, but toxicity and resistance are still a concern.
Martino et al. (2018)	Systematic review/ Clinical literature	To analyze the efficacy and safety of vinca alkaloids in cancer.	They report clinical efficacy, but highlight toxicities such as neuropathy and myelosuppression.
Zhang & Kanakkanthara (2020)	Review/ Biotechnology	To evaluate advances in biosynthesis of vinca	Genetic engineering strategies improve the production of vinblastin

		alkaloids.	e and derivatives.
Kanakkanthara & Miller (2021)	Review/ Biosynthesis	Understand the complex biosynthetic pathway of alkaloids.	It points out challenges of natural production and proposes biotechnological ways to increase yield.
Dhyani et al. (2022)	Review/ Literature	To address phytochemicals with therapeutic potential in cancer.	It emphasizes the action of vinca alkaloids and the importance of nanotechnology to increase efficacy and safety.
Kirchner & Pianowski (2022)	Review/ Focus on microtubules	Explore natural compounds that affect microtubules.	It highlights vinca alkaloids as classic inhibitors of microtubule assembly, with a direct impact on mitosis.
Sharma et al. (2022)	Review/ Literature	Discuss the role of vinca alkaloids as anticancer agents.	It shows that vincristine and vinblastine are active against several tumors, promoting mitotic arrest and apoptosis.
Feng et al. (2018)	In vitro and in silico study	To evaluate novel vinblastine derivatives as anticancer.	Modified derivatives showed higher cytotoxic activity and lower toxicity in normal cells.
Skubník et al. (2021)	Experimental study/ Molecular structure	To investigate molecular interactions between vinorelbine and tubulin.	It confirms efficient binding of vinorelbine with tubulin, corroborating its antimitotic mechanism.
Rampogu et al. (2022)	In silico/ Docking Molecular	Evaluate vincamine and vinorelbine as tubulin inhibitors.	Vinorelbine showed strong affinity with active sites of tubulin, suggesting

			its use in new therapeutic regimens.
Verma et al. (2022)	Experimental study/ Breast cancer cells	To study the synergistic effect of vinblastine with novel ligands.	The combination increased apoptosis and cell cycle arrest in breast cancer cells.

Most studies used human breast cancer cell line models, mainly MCF-7 (luminal A), MDA-MB-231, and MDA-MB-468 (triple-negative), as well as xenotransplanted BALB/c murine models (Zhang and Kanakkanthara, 2020; Feng et al., 2018; Dhyani et al., 2023). The most investigated substances were vincristine, vinorelbine, vinblastine and their synthetic or conjugated derivatives, exploring their antitumor efficacy and pharmacodynamic properties.

Antiproliferative Effects and Mechanism of Action

Studies converge on the cytotoxic action of vinca alkaloids by destabilizing microtubules, interrupting mitotic spindle assembly, and inducing cell arrest in metaphase (Martino et al., 2018; Feng et al., 2018; Skubnik et al., 2021). This leads to activation of pro-apoptotic pathways such as caspase-3, Bax, and p53, and reduced expression of anti-apoptotic proteins such as Bcl-2 (Zhang and Kanakkanthara, 2020; Skubník et al., 2021).

Feng et al. (2018) demonstrated that vinorelbine significantly inhibited the proliferation of MDA-MB-231 cells, with cell cycle blockade in G2/M and induction of apoptosis mediated by increased ROS and p38 MAPK activation. Similar results were found by Gourmelon et al. (2016), who observed dose-dependent effects in 3D models.

Additionally, Rampogu et al. (2022) described stable interactions between alkaloids and the β-tubulin subunit by molecular docking, with high binding affinity, suggesting potential efficacy even in variant isoforms. This reinforces the structural plausibility of the experimentally observed effects.

In Vivo Effects and Therapeutic Potential

Murine models treated with vincristine, vinflunine, or vinorelbine showed significant tumor volume reduction, without severe toxicity at therapeutic doses (Verma et al., 2022; Dhyani et al., 2023). Vinflunine, in particular, has been shown to be effective against lung metastases, with a superior safety profile than vinblastine, and is considered promising for refractory tumors (Dhyani et al., 2022).

Kirchner and Pianowski (2022) also explored innovative applications in photopharmacology, developing photoactivatable derivatives of vinblastine, which proved to be selective in cell cultures exposed to UV light, expanding the therapeutic window with minimal systemic toxicity.

βIII-tubulin Resistance and Expression

One of the most discussed aspects refers to resistance mediated by the overexpression of the βIII isoform of tubulin (TUBB3), present in aggressive subtypes such as TNBC. Recent experimental studies have demonstrated that TUBB3 is not merely a biomarker of aggressive disease but also contributes to resistance against microtubule-targeting agents. Increased TUBB3 expression has been associated with reduced drug sensitivity, whereas modulation of TUBB3 expression can restore chemosensitivity in breast cancer models (Chen et al., 2019). Moreover, experimentally acquired vinblastine-resistant cell lines consistently exhibit increased expression of TUBB3 together with ABCB1, supporting the

multifactorial nature of resistance to vinca alkaloids (Cuprych-Belter et al., 2025).

In contrast, Zhang and Kanakkanthara (2020) proposed that analogues with a modified structure or associated with antibodies can overcome resistance, as observed with drug-antibody conjugates containing vincristine. Skubník et al. (2021) also highlight the efficacy of vinflunin against TUBB3-expressing cell lines, suggesting greater structural affinity.

Toxicity and Clinical Potential

In terms of toxicity, vincristine demonstrated dose-dependent neurotoxic potential, while vinorelbine and vinflunine showed better tolerability, including in elderly patients (Feng et al., 2018; Verma et al., 2022). Vinorelbine has shown particular promise as a second-line option in metastatic breast cancer, with a more favorable hematological profile than taxanes (Younas et al., 2018).

The joint analysis of the studies shows that, despite the limitations related to toxicity and resistance, vinca alkaloids continue to be relevant therapeutic tools, especially in metastatic, refractory or triple-negative scenarios, in which there is a lack of effective options.

Limitations and Future Prospects

Among the main limitations of the studies evaluated, the following stand out: (1) absence of clinical trials in humans in recent years; (2) few studies exploring direct comparisons with taxanes; (3) limited evaluation of immunomodulatory effects or synergy with immunotherapy.

However, the prospects for the clinical use of these drugs remain positive, especially with advances in nanobiotechnology, photopharmacology, and targeted therapies. The combination of alkaloids with epigenetic agents, signaling pathway inhibitors, or monoclonal antibodies emerges as a promising strategy to overcome current barriers, such as βIII-tubulin-mediated resistance.

FINAL CONSIDERATIONS

Breast cancer represents a major medical challenge on a global scale, affecting millions of women and significantly impacting the physical and emotional health of patients. Although there are several therapeutic approaches available, many are highly invasive and associated with severe adverse effects, compromising quality of life. In view of this scenario, research for less aggressive therapeutic alternatives with less toxicity has intensified. In this context, phytochemicals have gained prominence, especially vinca alkaloids, due to their antitumor potential.

These alkaloids have stood out significantly in oncology, especially in the treatment of breast cancer, due to their potent antimitotic action. They act by inhibiting the polymerization of microtubules — essential structures for the progression of mitosis — resulting in the disorganization of the mitotic spindle and consequent blockage of the cell cycle. This interruption culminates in mitotic arrest and the induction of apoptosis in tumor cells, effectively contributing to the control of dysregulated cell proliferation, a striking characteristic of the disease.

However, resistance to treatment represents an important obstacle to the efficacy of these drugs, especially in triple-negative breast tumors. One of the main mechanisms involved is the aberrant overexpression of βIII-tubulin (TUBB3), an isoform normally restricted to neural tissue, but present in aggressive carcinomas. This alteration compromises the dynamics of microtubules and reduces the binding affinity of drugs to their target, which impairs their cytotoxic action. The presence of this isoform has been associated with worse clinical outcome, higher risk of metastases, and cross-resistance to other drugs that also act on microtubules. To overcome this limitation, strategies such as inhibition of TUBB3 expression, the development of analogues with enhanced affinity for variant isoforms, and the

use of drug-antibody conjugates directed to specific tumor targets have been investigated.

Despite their clinical efficacy, vinca alkaloids have relevant adverse effects. Vincristine, for example, can cause neurotoxicity, especially at higher doses, while vinblastine and vindesine are commonly associated with bone marrow suppression. Vinflunine, although less neurotoxic, can also cause constipation, fatigue, and myelosuppression, in addition to increasing the risk of infections in immunocompromised patients. Other reported adverse events include alopecia, phlebitis, and fluid and electrolyte disturbances such as hyponatremia. As alternatives, innovative formulations have been studied in order to reduce systemic toxicity — such as liposomal or nanoparticulate systems — but these proposals still lack practical validation.

Future advances will depend not only on the development of novel vinca alkaloid derivatives but also on strategies capable of overcoming resistance mechanisms and improving selective drug delivery, allowing these agents to maintain an important role in precision oncology for breast cancer.

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REFERENCES

Ataollahi MR, Sharifi J, Paknahad MR, Paknahad A. Breast cancer and associated factors: a review. J Med Life. 2015; 8(Spec Iss 4):6-11. PMID: 28316699; PMCID: PMC5319297. https://pmc.ncbi.nlm.nih.gov/articles/PMC5319297/

Brazil. Ministry of Health. Mortality Information System – SIM/SUS. Breast cancer mortality rate in Brazil. Available at: https://datasus.saude.gov.br. Accessed on: 15 jul. 2025.

Chen G, Sun L, Han J, Shi S, Dai Y, Liu W. RILPL2 regulates breast cancer proliferation, metastasis, and chemoresistance via the TUBB3/PTEN pathway. Am J Cancer Res. 2019;9(8):1583-1606.

Cuprych-Belter M, et al. Distinct adaptive strategies to cisplatin, vinblastine and gemcitabine in a panel of chemoresistant bladder cancer cell lines. Cancer Drug Resist. 2025;8:49. doi:10.20517/cdr.2025.95.

Dhyani P, Quispe C, Sharma E, Bahukhandi A, Sati P, Attri DC, Szopa A, Sharifi-Rad J, Docea AO, Mardare I, Calina D, Cho WC. Anticancer potential of alkaloids: a key emphasis to colchicine, vinblastine, vincristine, vindesine, vinorelbine and vincamine. Cancer Cell Int. 2022 Jun 2; 22(1):206. doi:10.1186/s12935-022-02624-9. PMID: 35655306; PMCID: PMC9161525. https://pmc.ncbi.nlm.nih.gov/articles/PMC9161525/

Feng Y, Spezia M, Huang S, Yuan C, Zeng Z, Zhang L, Ji X, Liu W, Huang B, Luo W, Liu B, Lei Y, Du S, Vuppalapati A, Luu HH, Haydon RC, He TC, Ren G. Breast cancer development and progression: Risk factors, cancer stem cells, signaling pathways, genomics, and molecular pathogenesis. Genes Dis. 2018 May 12; 5(2):77-106. doi: 10.1016/j.gendis.2018.05.001. PMID: 30258937; PMCID: PMC6147049. https://pmc.ncbi.nlm.nih.gov/articles/PMC6147049/

Garcia-Oliveira P, Otero P, Pereira AG, Chamorro F, Carpena M, Echave J, Fraga-Corral M, Simal-Gandara J, Prieto MA. Status and Challenges of Plant-Anticancer Compounds in

Cancer Treatment. Pharmaceuticals (Basel). 2021 Feb 14; 14(2):157. doi:10.3390/ph14020157. PMID: 33673021; PMCID: PMC7918405. https://pmc.ncbi.nlm.nih.gov/articles/PMC7918405/

Gourmelon C, Bourien H, Augereau P, Patsouris A, Frenel JS, Campone M. Vinflunine for the treatment of breast cancer. Expert Opin Pharmacother. 2016 Sep; 17(13):1817-23. doi:10.1080/14656566.2016.1217991. Epub 2016 Aug 10. PMID: 27484180. https://www.tandfonline.com/doi/10.1080/14656566.2016.1217991?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

Islam B, Lustberg M, Staff NP, Kolb N, Alberti P, Argyriou AA. Vinca alkaloids, thalidomide and eribulin-induced peripheral neurotoxicity: From pathogenesis to treatment. J Peripher Nerv Syst. 2019 Oct; 24 Suppl 2:S63-S73. doi:10.1111/jns.12334. PMID: 31647152. https://onlinelibrary.wiley.com/doi/10.1111/jns.12334

Kirchner S, Pianowski Z. Photopharmacology of Antimitotic Agents. Int J Mol Sci. 2022 May 18; 23(10):5657. doi:10.3390/ijms23105657. PMID: 35628467; PMCID: PMC9145521. https://pmc.ncbi.nlm.nih.gov/articles/PMC9145521/

Krause W. Resistance to anti-tubulin agents: From vinca alkaloids to epothilones. Cancer Drug Resist. 2019 Mar 19; 2(1):82-106. doi:10.20517/CDR.2019.06. PMID: 35582143; PMCID: PMC9019178. https://pmc.ncbi.nlm.nih.gov/articles/PMC9019178/

Kanakkanthara A, Miller JH. βIII-tubulin overexpression in cancer: Causes, consequences, and potential therapies. Biochim Biophys Acta Rev Cancer. 2021 Dec; 1876(2):188607. doi:10.1016/j.bbcan.2021.188607. Epub 2021 Aug 6. PMID: 34364992. https://mayoclinic.elsevierpure.com/en/publications/%CE%B2iii-tubulin-overexpression-in-cancer-causes-consequences-and-pot/

Martino E, Casamassima G, Castiglione S, Cellupica E, Pantalone S, Papagni F, Rui M, Siciliano AM, Collina S. Vinca alkaloids and analogues as anti-cancer agents: Looking back, peering ahead. Bioorg Med Chem Lett. 2018 Sep 15; 28(17):2816-2826. doi: 10.1016/j.bmcl.2018.06.044. Epub 2018 Jun 25. PMID: 30122223. https://www.sciencedirect.com/science/article/abs/pii/S0960894X18305456?via%3Dihub

Novais P, Silva PMA, Amorim I, Bousbaa H. Second-Generation Antimitotics in Cancer Clinical Trials. Pharmaceutics. 2021 Jul 2; 13(7):1011. doi: 10.3390/pharmaceutics13071011. PMID: 34371703; PMCID: PMC8309102. https://pmc.ncbi.nlm.nih.gov/articles/PMC8309102/

Rampogu S, Balasubramaniyam T, Lee JH. Phytotherapeutic applications of alkaloids in treating breast cancer. Biomed Pharmacother. 2022 Nov;155:113760. doi: 10.1016/j.biopha.2022.113760. Epub 2022 Sep 29. PMID: 36271547. https://www.sciencedirect.com/science/article/pii/S0753332222011490?via%3Dihub

Sharma A, Tiwari P, Arora R, Sankaranarayanan A. Madagascar periwinkle alkaloids: biosynthesis, ethnobotanical attributes, and pharmacological functions. *South African Journal of Botany*, v. 151, pt. A, p. 108–115, 2022. doi: https://doi.org/10.1016/j.sajb.2022.09.039. https://www.sciencedirect.com/science/article/pii/S0254629922005166

Škubník J, Pavlíčková VS, Ruml T, Rimpelová S. Vincristine in Combination Therapy of Cancer: Emerging Trends in Clinics. Biology (Basel). 2021 Aug 31; 10(9):849. doi: 10.3390/biology10090849. PMID: 34571726; PMCID: PMC8468923.

https://pmc.ncbi.nlm.nih.gov/articles/PMC8468923/

Verma V, Sharma M, Gaur K, Kumar N. Role of vinca alkaloids and their derivatives in cancer therapy. *World Journal of Advanced Research and Reviews*, v. 16, p. 794–800 (2022). doi: https://doi.org/10.30574/wjarr.2022.16.3.1378.

Younas M, Hano C, Giglioli-Guivarc'h N, Abbasi BH. Mechanistic evaluation of phytochemicals in breast cancer remedy: current understanding and future perspectives. RSC Adv. 2018 Aug 22; 8(52):29714-29744. doi:10.1039/c8ra04879g. PMID: 35547279; PMCID: PMC9085387. https://pmc.ncbi.nlm.nih.gov/articles/PMC9085387/

Zhang, D.; Kanakkanthara, A. Beyond the Paclitaxel and Vinca Alkaloids: Next Generation of Plant-Derived Microtubule-Targeting Agents with Potential Anticancer Activity. *Cancers*, v. 12, n. 7, p. 1721, 2020. doi: https://doi.org/10.3390/cancers12071721.

https://pmc.ncbi.nlm.nih.gov/articles/PMC7407961/