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Deciphering the Pivotal Role of Nanoformulations of Vinca Alkaloids in Cancer: Preclinical, Clinical, and Patent Status

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Abstract: Cancer is the leading cause of disease-related mortality worldwide, characterized by the uncontrolled and rapid proliferation of abnormal cells. Vinca alkaloids (VAs) exert their anticancer effects by forming a tubulin-alkaloid complex by binding to microtubules. Vinblastine and vincristine are recognized as natural chemicals, whereas vindesine and vinorelbine are semi-synthetic derivatives. VAs have restricted therapeutic applicability due to several factors, including their poor bioavailability, extensive first-pass metabolism in the liver, significant side effects, and the development of multidrug resistance. Nanotechnology is a promising field that uses nanoparticles to diagnose diseases and develop drug-delivery systems to prevent and manage life-threatening conditions such as cancer. Nanoformulations of VAs, such as magnetic nanoparticles, polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, liposomes, niosomes, polymeric micelles, and inorganic nanoparticles, have been investigated for potential applications in cancer therapy. These studies have shown enhanced pharmacokinetics, targeted delivery to tumor cells, greater penetration, and improved chemotherapy outcomes. For example, the MTT assay revealed that TPGS emulsified vinorelbine solid lipid nanoparticles were 39.5-fold more effective compared to plain vinorelbine. This review encompasses preclinical and clinical investigations of nanoformulations of VAs in cancer therapies. Liposomal vincristine, used both as monotherapy and in combination, has demonstrated anticancer activity in refractory cancers, non-Hodgkin lymphoma, acute lymphoblastic leukemia, retinoblastoma, and malignant melanoma, according to clinical research. Apart from this, this review also analyses published patents pertaining to the anticancer properties of VAs nanoformulations.

Keywords: vinca alkaloids; nanoformulations; anticancer; vinblastine; vincristine; vindesine; vinorelbine.

1. Introduction

Cancer is the largest cause of disease-related mortality worldwide, marked by the fast and unregulated growth of aberrant cells [1–3]. The previous reports revealed that there were 18.1 million new cases of cancer and 9.6 million cancer deaths globally in 2018 [4]. Nearly 10 million people worldwide were affected by this medical condition in 2020 [5]. According to

data from Global Cancer Statistics, 20 million new cases of cancer were found in 2022, and 9.7 million people died due to cancer. Looking towards the current trend in the rise of cancer patients, it is anticipated that an estimated 35 million cases of cancer are expected by 2050 [6,7]. Chemotherapy is a widely available cancer treatment, but it adversely affects healthy cells due to the combination of pharmacological therapy and radiation therapy [8–11]. The first commercially available plant-based antimitotic medicines were vinca alkaloids (VAs), which were revealed as safe, effective, and essential components of the healthcare system [12-14]. Research has demonstrated their therapeutic applications in the management of non-small cell lung cancer, breast cancer, hematological and lymphatic neoplasms [15-17]. Vinblastine and vincristine have been the main VAs in the leaf extract of *Catharanthus roseus*, which showed potential anticancer effects to combat testicular germ cell cancer, non-Hodgkin lymphomas, Hodgkin lymphomas, and acute lymphoblastic leukemia [18-21]. In a meta-analysis, patients received either docetaxel or a vinca alkaloid as first-line treatment, and pemetrexed as second-line treatment for advanced NSCLC. The findings revealed that docetaxel and pemetrexed showed an insignificant difference in overall survival or response rate. However, findings revealed that docetaxel had an improved safety profile compared with vinca alkaloids, with a significant decrease in febrile neutropenia and grade ¾ serious adverse events [22-24].

VAs are water-soluble compounds but have limited permeation potential, undergo extensive first-pass metabolism in the liver, and are excreted primarily in the bile. The clinical application of VAs has been constrained due to their severe side effects, poor absorption, and multidrug resistance [25]. Various studies have shown that nanoformulations of VAs can enhance permeation, improve pharmacokinetics, target tumor cells, and enhance cancer therapy [26-28]. An example of the application of nanoformulations for the transport of VAs was reported in a study in which Vinca rosea-capped ZnO nanoparticles produced via a green approach demonstrated strong antioxidant, antidiabetic, and anticancer activity [29]. This review provides a brief overview of the paradoxical role of apoptosis and inflammatory mediators in cancer. The VAs, such as vinblastine, vincristine, vindesine, and vinorelbine, are described in this review, including their anticancer mechanisms of action and potential challenges in clinical applications. This review comprehensively discussed preclinical/cell lines-based, clinical studies, and current updates about patents of VAs-based nanoformulations such as magnetic nanoparticles, polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, liposomes, niosomes, polymeric micelles, and inorganic nanoparticles. The inclusive literature search was undertaken on PubMed, Google Scholar, and ScienceDirect databases. A literature review was conducted using papers published in peer-reviewed journals between 2000 and 2025. The literature was searched using different combinations of several keywords which includes ‘vinca alkaloid’, ‘vincristine’, ‘vinblastine’, ‘vinorelbine’, ‘vindesine’, ‘nanoparticle’, ‘liposomes’, ‘niosomes’, ‘polymeric micelles’, ‘inorganic nanoparticles’, ‘solid lipid nanoparticles’, ‘magnetic nanoparticles’, and ‘nanostructured lipid carriers’, ‘cancer’ with specific inclusion and exclusion criteria. The scientific papers with certain characteristics were included, i.e., (i) English language papers, (ii) papers obtained from the aforementioned key search, (iii) papers containing sufficient information, and (iv) the papers that assessed nanoformulations of vinca alkaloids in cancer through in-vitro and/or in-vivo models. Papers written in any language other than English, letters to the editor, and editorials were excluded from the search strategy. The patent-related information from the World Intellectual Property Organization website about nanocarriers of VAs for anticancer activity has also been reviewed in this article [30].

2. Pharmacological Role of Apoptosis in Cancer

Apoptosis is a programmed process of cellular death that facilitates the removal of damaged or unwanted cells. Dysregulated apoptosis may lead to cancer genesis, advancement, and therapy resistance [31-33]. Apoptosis is characterized by morphological alterations, including shrinkage of cell membranes, loss of cytoplasmic organelle localization, and a reduction in heterochromatin core mass. Death receptors, often referred to as the extrinsic route, utilize caspases 8 and 10 to initiate apoptosis, while the intrinsic route acts via caspase 9 [34]. Comprehending the mechanisms that contribute to cancer development is crucial for formulating therapies for neoplastic disorders. The research evidence has shown that the antiproliferative pathway activated by VAs involves gene products such as p53, bcl-2, and bcl-x [35–37]. The classification of apoptotic proteins is mostly determined by their activity in apoptosis. Pro-apoptotic proteins are classified into two groups: caspases and the Bcl-2 family. Apoptosis is partially initiated by aspartate-specific cysteine proteases and caspases, which are frequently identified as inactive heterodimers, procaspases. Based on their structure and responsibilities, the 14 known caspase proteins are grouped. The Bcl-2 family affects cell activity by triggering programmed cell death [38]. Its principal function is to govern the release of cytochrome c from its position in the outer membrane of the mitochondria [39, 40].

3. Inflammatory Mediators in Cancer Progression

Chronic inflammation produces pro-inflammatory cytokines and immunomodulatory chemicals that tend to stimulate tumor proliferation and progression [41,42]. The inflammatory response can be actively triggered and modulated by a variety of substances from the bloodstream, injured tissue, and inflammation-related cells. Chemical mediators are released in response to inflammation in cancer, including cytokines, tumor necrosis factors, chemokines, growth factors, and inflammasomes [43–45].

3.1. Cytokines.

Cytokines are tiny, membrane-bound proteinaceous molecular messengers that facilitate intercellular communication regarding immune responses and promote migration of cells to areas of inflammation, infection, and injury [46, 47]. Interleukins are a type of cytokine that are released and bind to certain receptors [48]. Families of interleukins are identified according to receptor chains, sequences, and functional features. Certain subsets of CD4+ T helper cells can be recognized by their cytokine profile. Antigen-presenting cell types and T-cell activation influence the cytokine expression profile [49–53].

3.2. Tumor necrosis factors.

Tumor necrosis factors (TNFs) comprise a collection of pro-inflammatory cytokines primarily secreted by activated macrophages, T-lymphocytes, natural killer cells, and tumor cells. TNF is a homotrimer whose biological activity is primarily modulated by soluble TNFα-binding receptors. They participate in a diverse array of signaling pathways related to inflammation, viral replication, apoptosis, cancer, angiogenesis, cell proliferation, and differentiation [54,55]. TNFs are primarily produced by macrophages and monocytes [56]. Both mTNF and sTNF bind to two receptors: TNFR1, which is expressed in every human tissue, and TNFR2, which is predominantly expressed in neurons, immune cells, and

endothelial cells [57,58]. TNFs are vital to the body's physiological and pathological functioning. It induces two forms of tumor cell death: necrosis, characterized by cell swelling, organelle damage, and eventual rupture; and apoptosis, defined by cell shrinkage, condensation of cellular components, and DNA breakage [59].

3.3. Chemokines.

Chemokines are tiny proteins that belong to a class of small cytokines released by cells. These are referred to as chemotactic cytokines because of their capacity to elicit directed chemotaxis in adjacent responder cells [60, 61]. The arrangement of crucial cysteine residues and the amino acid sequence of chemokines characterize them. The chemokine monomer, which comprises a short, flexible N-terminus that is important for receptor activation, a C-terminal α-helix, and a core three-stranded β-sheet, is maintained by disulfide bonds created by cysteines [62,63]. Chemokines regulate stem-like properties of cancer cells, proliferation, and invasiveness; they also affect neoangiogenesis, neurogenesis, and fibrogenesis in stromal cells. Chemokines control immune cell interactions and localization within lymphoid organs and the tumor microenvironment, thereby greatly influencing immune cell phenotype and function. Chemokines control activation, recruitment, phenotypic, and activity of immune cells during the development of cancer [64]. Chemokines are a small assortment of secreted cytokines with a similar structural makeup that are essential for immunity and inflammation [65, 66].

3.4. Growth factors.

Cancer cells produce growth factors to enhance proliferation through autocrine signaling, establishing a positive feedback loop that facilitates replication regardless of external signals [67]. Growth factors can bind to specific cell-surface receptors, which, in turn, can alter gene expression by signaling to other intracellular components. The comprehensive process of supplying a cell with an external chemical signal to initiate a biological response is known as signal transduction [68, 69]. It is commonly recognized that VEGF makes it simpler for blood vessels associated with tumors to leak proteins. VEGF receptors are crucial factors that regulate angiogenesis and vasculogenesis [70,71].

3.5. Inflammasomes.

Inflammasomes are cytosolic multiprotein complexes primarily composed of proinflammatory caspase-1 and sensor protein. These complexes are present within the innate immune system that control caspase-1 activation and trigger inflammation in response to infection and host-derived substances [72, 73]. Inflammasomes can produce pro-IL-1β and pro-IL-18, thereby promoting a rapid, highly stimulable and modulatable proinflammatory response. These cytokines are processed to their active forms by active caspase-1, leading to pyroptosis, a form of inflammatory cell death [74, 75].

4. Vinca Alkaloids in Cancer Therapy

VAs are the first family of plant alkaloids to be exploited in cancer treatment for over 30 years due to evidence of their clinical benefit [76]. VAs are regarded as a class of substances with established applications in cancer chemotherapy, as they contain the naturally occurring

molecules vinblastine (VBL) and vincristine (VNC), along with the semi-synthetic derivatives vindesine and vinorelbine (Figure 1) [77-79].

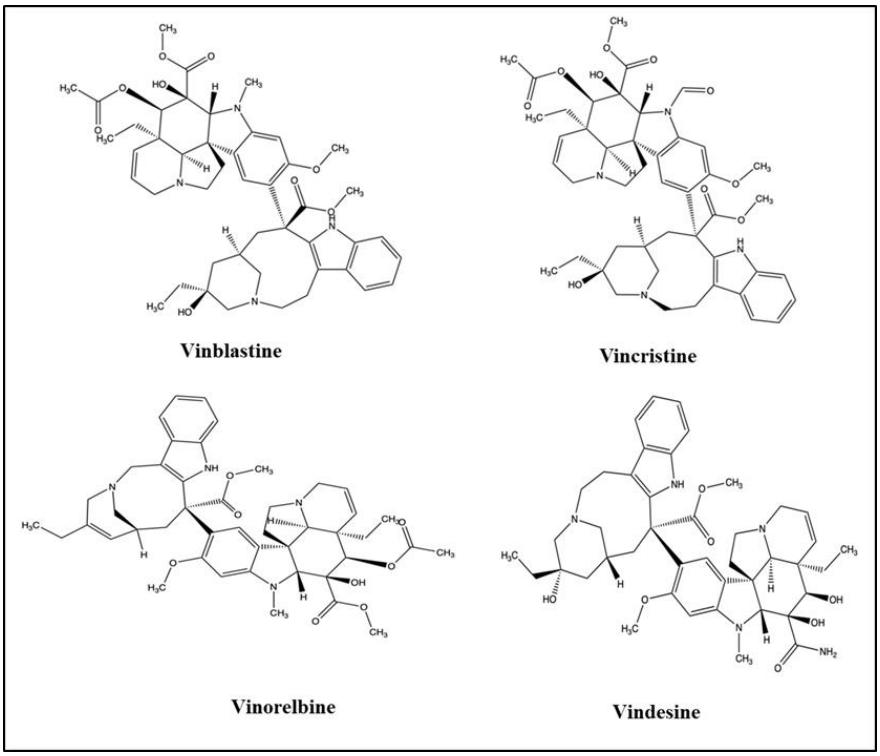

Figure 1. Chemical structures of vinca alkaloids.

VAs exert anticancer activity through multiple mechanisms, including tubulin binding, microtubule destabilization, mitotic spindle arrest, cell cycle arrest, and apoptosis. The anticancer activity of VAs is attributed to compromised microtubule function, which underlies mitotic spindle formation and causes metaphase arrest. VAs bind to spindle fiber tubulins and inhibit their production, preventing the cell from entering metaphase. The cell cycle stops at metaphase, leading to mitotic failure and programmed cell death (apoptosis), which kills the cancer cells. VAs also exert anticancer effects by depolymerizing microtubules and destabilizing mitotic spindles, leading to cell death (Figure 2) [80-85].

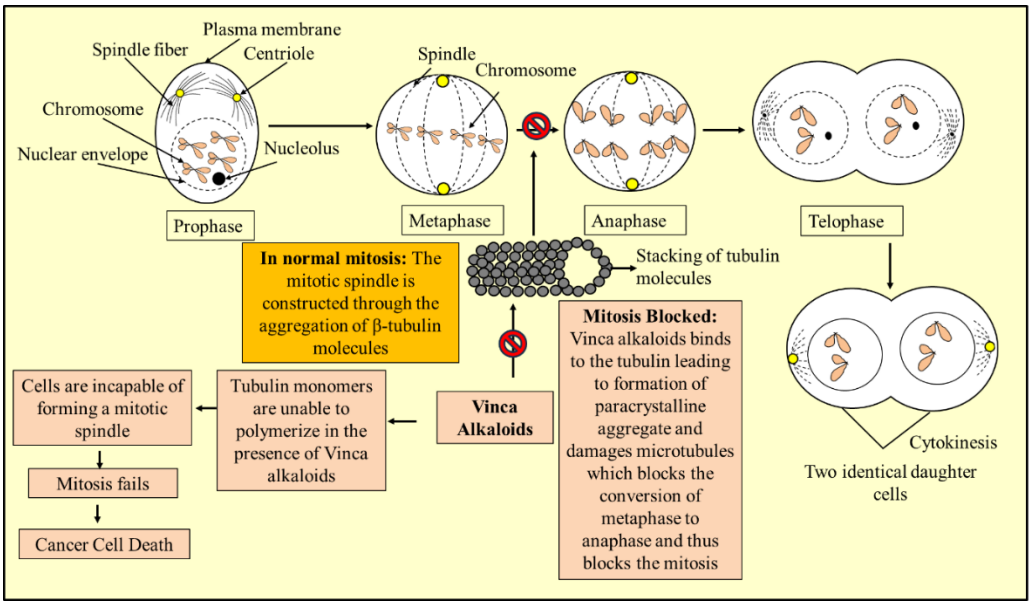

Figure 2. The schematic representation of the mechanism of action of the anticancer activity of vinca alkaloids.

5. Challenges in Therapeutic Applications of Vinca Alkaloids

The clinical utility of VAs is limited by their dose-dependent neurotoxicity. Intrathecal administration of vincristine may result in lethal myeloencephalopathy. Vincristine is linked to a substantial incidence of peripheral neuropathy (30–40%), which may be because of microtubule obstruction of axonal transport [86,87]. Vincristine administration in children frequently causes vinca-induced peripheral neuropathy. Numbness, tingling, and neuropathic pain in upper and lower extremities are prevalent manifestations of sensory neuropathy. Vinca-induced peripheral neuropathy commonly progresses from distal to proximal regions; symptoms generally begin in the toes and feet, and as the condition progresses, clinical abnormalities manifest in the foot, ankle, and leg, eventually affecting the fingers and hands [88]. To address these constraints, scientists have developed Vinca alkaloid derivatives with enhanced physicochemical properties and reduced toxicity. The derivatives, such as vindesine, vinorelbine, and vinflunine, demonstrate greater tolerance and efficacy [89]. The other challenges that limit their therapeutic use include poor permeability and absorption, extensive liver metabolism, and the development of drug resistance [25].

6. Preclinical Status of Nanoformulations of Vinca Alkaloids

The various nanoparticles have been utilized previously for the drug delivery of VAs. These include solid lipid nanoparticles, magnetic nanoparticles, polymer-based nanoparticles, liposomes, nanostructured lipid carriers, polymeric micelles, and inorganic nanoparticles [90–93]. Polymeric nanoparticles are produced from natural or synthetic polymers and serve as drug carriers for delivering drugs to intended targets [94,95]. Albumin nanoparticles are an emerging approach to address the limited bioavailability of pharmaceuticals, which have several biological benefits but are offset by short biological half-life [96]. PLGA-based nanoparticles are biodegradable and biocompatible nanocarriers for controlled drug release applications [97]. Although PLGA nanoparticles are effective carriers for both hydrophilic and hydrophobic drugs, they have certain limitations, including protein opsonization and rapid clearance by the reticuloendothelial system [98]. Vincristine nanoparticles comprised of PLGA-PEG modified with folic acid and R-7 peptide act in conjunction with nanocarriers to overcome mechanisms that promote drug resistance [99]. Dextran sulfate-PLGA hybrid nanoparticles with VNC self-assembly have been developed as a useful tool to circumvent resistance systems, enhancing oral bioavailability and augmenting the drug absorption in MCF-7 cell lines [100]. PLGA nanoparticles pose major challenges, such as initial burst release of the drug, and may exhibit low drug loading efficiency.

Solid lipid nanoparticles (SLNs) are colloidal carriers with distinctive characteristics but limited drug loading; therefore, the development of nanostructured lipid carriers (NLCs) was initiated to address the challenges associated with SLNs [101,102]. SLNs of other anticancer drugs have also shown potential efficacy in reducing tumor volume and improving survival, for example, docetaxel [103], paclitaxel and doxorubicin [104], 5-fluorouracil [105], and talazoparib [106]. The preclinical study of resveratrol-SLN showed superior inhibitory effects on the proliferation, invasion, and migration of breast cancer cells compared with the free drug [107]. However, key formulation challenges for SLNs include low drug loading, heat sensitivity, solvent and surfactant toxicity, poor hydrophilic drug encapsulation, particle aggregation, high cost, and aggregation risks [107,108].

Liposomes are phospholipid lipid bilayer vesicles with diameters ranging from 50 to 1000 nm. These vesicular systems have various benefits, which include enhancement of solubility, bioavailability, and stability of medicinal products [109–112]. In a clinical study, it was observed that temperature-sensitive vinorelbine liposomes are highly effective in comparison to free vinorelbine in preventing the onset and growth of cancer [113]. It was observed that liposome-based carriers of vinblastine successfully targeted the tumor vasculature and enhanced antiproliferative effects when applied in conjunction with an external magnetic field [114]. A clinical study revealed that VNC sulfate liposomes showed improved antitumor activity and faster, significantly enhanced cellular absorption. Liposomes are highly efficient carrier systems but may cause drug leakage in some cases and pose a challenge to low encapsulation efficiency [115]. Lipid emulsions and microspheres for vinorelbine have been launched in the pharmaceutical market to minimize phlebitis and venous irritation caused by the standard intravenous formulation [116]. Inorganic nanoparticles offer greater stability, inherent physicochemical properties, superior drug-loading capacity, and variable degradation rates compared to organic nanoparticles [117,118]. Figure 3 provides a pictorial representation of the nanotechnology-based carriers previously explored for the delivery of VAs. These include liposomes, niosomes, polymeric micelles, inorganic nanoparticles, solid lipid nanoparticles, magnetic nanoparticles, and nanostructured lipid carriers. Table 1 elucidates the research outcomes of *in vitro* assays, preclinical and cell line studies of nanoformulations of VAs for anticancer activity.

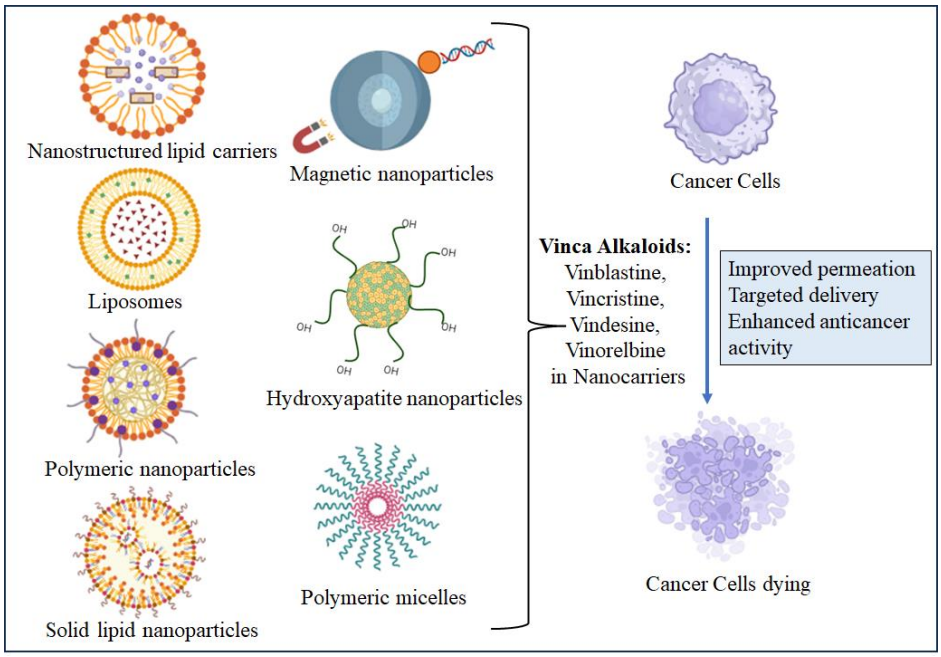

Figure 3. Illustration of nanocarriers explored for the delivery of Vinca Alkaloids in cancer treatment.

Table 1. Recent advances in in-vitro assays, cell line studies, and preclinical studies of nano-formulations of vinca alkaloids for anticancer activity.

Nanocarrier (technique) [cancer type]	Excipients	Preclinical/cell line study/in-vitro assay	Research outcomes	Ref.
Vinblastine				
Niosomes	Span 60, tween 60, PEG 600, Cholesterol	TC-1 cells	Demonstrated the cytotoxicity of pegylated niosomes carrying vinblastine on murine lung cancer TC-1 cells using MTT assay. The niosomes exhibited significant stability, increased entrapment efficiency, diminished	[119]

Nanocarrier (technique) [cancer type]	Excipients	Preclinical/cell line study/in-vitro assay	Research outcomes	Ref.
			release rate, and improved cytotoxicity against TC-l cells relative to free vinblastine [170].	
Dextran-coated superparamagnetic nanoparticles (Co-precipitation method) [Pancreatic cancer]	Dextran	PANC-1 and H6C7 cell lines	These nanocarriers had a spherical shape and measured 74±13 nm in average size, 0.080 in polydispersity, and −45 mV in zeta. These nanoparticles provided effective drug delivery along with potential apoptosis and showed minimal cytotoxicity. These nanoparticles demonstrated a more potent inhibitory effect on tumor growth in PANC-1 pancreatic cancer cells.	[120]
Folic acid conjugated Bovine Serum Albumin nanoparticles (Desolvation method)	Folic Acid, Bovine Serum Albumin	4T1 mouse mammary carcinoma cell line	The drug-entrapment and loading of FA-conjugated bovine serum albumin nanoparticles were 84.83% and 42.37%, respectively. The data showed that these nanoparticles have the potential to provide targeted drug delivery to vinblastine-sensitive cancers.	[121]
PCL-PEG-PCL nanoparticles (Chemical reduction method and Co-precipitation) [leukemia]	$AgNO_3$, PEG, $NaBH_4$	K562/A02 leukemia cell line study by MTT assay	Vinblastine's solubility was increased when combined with nanoparticles as opposed to the pure drug. The medication with a silver formulation had the highest bioavailability, exhibiting maximum solubility at pH 10.4 and minimum at pH 6. Inhibition of the K562/A02 cell line was significantly higher compared to the same drug dose in solution form.	[122]
Vincristine				
Polymeric magnetic nanoparticles (Co-precipitation) [Apoptotic gene expression in tumors]	Dextran and Folate	Tera-1 and Hs1 cell lines	In citrate and phosphate buffer solutions, the nanocarrier showed controlled drug release. IC_{50} values for nanoparticles were 10-fold higher than those of the free drug. These nanoparticles decreased the number of cancer cells and suppressed tumor proliferation in TERA-1 cancer cells, correlated with expression levels of P53, P21, Caspase-9, and AKT-1 genes.	[123]
Hydroxyapatite nanoparticles (Hydrothermal method) [Bone cancer]	Sodium chloride, calcium nitrate, hexadecyltrimethylammonium bromide	In-vitro (Chorioallantoic membrane assay)	Synthesis of mesoporous hydroxyapatite nanoparticles carrying a sizable amount of the chemotherapy medication vincristine, with a mean diameter and surface area of 285.32±10.29 nm and 103.5 m^2/g, respectively. Significantly reduce endothelial cell motility by altering microtubule dynamics, inhibiting Rac1/Cdc42 activation, and impairing the actin cytoskeleton.	[124]
Solid Lipid Nanoparticles and Nanostructured Lipid Carriers (Solvent displacement and solvent diffusion method) [glioma]	Soya lecithin, Soybean phosphatidylcholine	U87 malignant glioma cells (U87 MG cells)	The zeta potential for SLNs was +35.7, while for NLCs it was +29.8 mV. NLC showed superior glioma inhibition compared to SLNs, while dual medicines showed the greatest anticancer activity. Compared to SLNs, NLCs showed higher inhibitory efficacy and were more effective in drug delivery into U87MG cells.	[125]
Folic acid chitosan conjugated nanoparticles	Sodium acetate, sodium tripolyphosphate	NCI-H460 cell line	Vincristine-loaded nanoparticles coupled with folic acid and chitosan showed anticancer effect on NCI-H460 cells in the MTT assay. The	[126]

Nanocarrier (technique) [cancer type]	Excipients	Preclinical/cell line study/in-vitro assay	Research outcomes	Ref.
(Ionic gelation method) [Non-small cell lung cancer]			erythrocyte aggregation assay proved that the nanoparticles were non-toxic.	
Lipid-polymeric nanocarriers (Nano-precipitation method) [lymphoma]	PEG2000-DSPE, cholesterol, stearic acid	Human Burkitt's Lymphoma cell line	Vincristine/Quercetin lipid-polymeric nanocarriers have zeta potentials of about 35 mVa and an *in vitro* study of these nanoparticles showed a sustained release profile.	[127]
Vinorelbine				
Solid lipid nanoparticles (Solvent diffusion method) [Breast cancer]	Glyceryl monooleate, Poloxamer-188, Vitamin E TPGS	MCF-7 cancer cell lines	It was discovered that the SLNs had spherical form and entrapment efficiency of up to 58%. A biphasic release pattern was seen in *in vitro* release tests. The efficacy of prepared nanoparticles against MCF-7 cell lines was shown to be significantly higher. MTT assay revealed that TPGS emulsified vinorelbine SLNs were 39.5-fold more effective compared to plain drug.	[128]
PLGA nanoparticles (emulsion-solvent evaporation method) [Non-small cell lung cancer]	PLGA	Preclinical studies	Lengthening of sonication time during nanoparticle preparation caused the breakdown of PLGA, which caused enhanced permeability of nanoparticles.	[129]
PEGylated liposomal (lipid film hydration method) [Hepatocellular carcinoma]	Cholesterol, mPEG2000-DSPE, distearoylphosphatidylcholine	Human hepatocellular carcinoma cell lines	While SP94-mediated targeting further boosts anticancer effectiveness by enhancing tumor targeting, combined targeted therapy showed a considerable improvement in reducing the growth of orthotopic malignancies.	[130]
Modified liposomes (Film dispersion method) [Resistant brain glioma]	Cholesterol and DSPE-PEG2000, RGD (Arg-Gly-Asp) tripeptide	Preclinical studies	The modified liposomes clustered in glioma cells and facilitated transit across the blood-brain barrier. Their elimination half-life was longer at 7.093 ± 1.311 hours, and the area under the curve (AUC0–24 h) was larger at 28.92 ± 2.66 mg/L.h. Liposomes increased the cellular uptake and triggered apoptosis by activating caspases.	[131]
Liposome encapsulating polymeric micelles (Reverse evaporation) [Non-small cell lung cancer]	DSPE-mPEG2000 and cholesterol	NSCLC cell line	Showed spherical morphology, uniform size distribution, and zeta potential of (-) 13.02±0.22 mV and mean particle size of 162.97±9.06 nm. The liposomes showed a synergistic effect of vinorelbine with cisplatin in the treatment of non-small cell lung cancer. CoNP-lips displayed anticancer action in C57BL/6 mice with tumors, and their increased permeability and retention effect led to drug accumulation in tumors.	[132]

7. Clinical Status of Nanoformulations of Vinca Alkaloids

Clinical trials on VAs such as vincristine, vinblastine, vinorelbine, and vindesine in cancer therapy are at various phases of clinical development, as listed in Table 2 [133]. The analysis revealed that the nano-liposomal formulation of vincristine, alone or in combination

therapy, has completed a few phases of clinical trials to explore its anticancer potential in refractory cancers, relapsed malignancies, non-Hodgkin lymphoma, acute lymphoblastic leukemia, retinoblastoma, and malignant melanoma. Vinblastine has been clinically tested for therapy of CNS tumors, non-seminomatous malignant germ cell tumors in children and adolescents, recurrent or refractory low-grade glioma, metastatic renal cancer, Hodgkin lymphoma, metastatic melanoma, desmoid tumors, urothelial cancer, and metastatic renal cell cancer. Vinorelbine undergoes clinical testing for efficacy in metastatic breast cancer and metastatic solid tumors. Vindesine is clinically evaluated for pancoast tumors, a type of lung cancer affecting the apex, small cell lung cancer, neuroblastoma patients, and T-cell lymphoma.

Table 2. Clinical status of vinca alkaloid in cancer therapeutics.

Study title	Intervention	NCT Number	Phase
Vincristine (Nanoformulations)			
To evaluate the safety, activity, and pharmacokinetics of marqibo in children and adolescents with refractory cancer	Marqibo® (liposomal Injection of vincristine sulfate)	NCT01222780	1
Liposomal vincristine for pediatric and adolescent patients with relapsed malignancies	Liposomal vincristine	NCT00038207	2
Liposomal vincristine in treating patients with refractory or relapsed non-Hodgkin's lymphoma	Liposomal vincristine sulfate	NCT00006383	2
Safety and efficacy of Marqibo in relapsed acute lymphoblastic leukemia	Marqibo®	NCT00495079	2
Safety and efficacy of Marqibo in metastatic malignant uveal melanoma	Marqibo®	NCT00506142	2
Vincristine, carboplatin, and etoposide or observation only in treating patients who have undergone surgery for newly diagnosed retinoblastoma	Liposomal vincristine sulfate/carboplatin/ etoposide	NCT00335738	3
Liposomal vincristine plus dexamethasone in patients with relapsed or refractory acute lymphoblastic leukemia	Vincristine Sulfate Liposomes Injection/ Dexamethasone	NCT00144963	2
Pharmacokinetic study of liposomal vincristine in patients with malignant melanoma & hepatic dysfunction	Vincristine Sulfate Liposomes Injection	NCT00145041	1
Hyper-CVAD with liposomal vincristine in acute lymphoblastic leukemia	Marqibo®	NCT01319981	2
Vinblastine (conventional)			
Vinblastine and temsirolimus in pediatrics with recurrent or refractory lymphoma or solid tumors, including CNS tumors	Vinblastine, Temsirolimus	NCT02343718	1
A multicenter study to evaluate a risk-adapted strategy for the treatment of extracranial non-seminomatous malignant germ cell tumors in children and adolescents	Combination of (Vinblastine, Bleomycin, Cisplatin) and (etoposide, ifosfamide, and cisplatin)	NCT02104986	2
Study of nivolumab alone, or in combination with vinblastin, in patients with classical Hodgkin lymphoma	Nivolumab, Vinblastine	NCT03580408	2
PAZOPANIB efficacy and tolerance in desmoid tumors (DESMOPAZ)	PAZOPANIB versus Vinblastine and Methotrexate	NCT01876082	2
Vinorelbine (conventional)			
Temsirolimus and Vinorelbine Ditartrate in treating patients with unresectable or metastatic solid tumors	Temsirolimus, Vinorelbine ditartrate	NCT01155258	1
Study of oral vinorelbine and erlotinib in non-small cell lung cancer	Vinorelbine, Erlotinib	NCT00702182	1
Vindesine (conventional)			
Trial of pre-operative chemoradiotherapy followed by surgical resection in pancoast tumors (JCOG 9806)	Mitomycin C, Vindesine, Cisplatin, Radiotherapy	NCT00128037	2
Combination chemotherapy followed by stem cell transplant in high-risk neuroblastoma patients (NB2004-HR)	Combination of cisplatin, etoposide, and vindesine with other drugs	NCT03042429	3
Study of bortezomib combined with ACVBP in peripheral T-cell lymphoma.	Bortezomib, Doxorubicin, Prednisone, Cyclophosphamide, Vindesine, Bleomycin	NCT00136565	2

8. Patent Status of Nanoformulations of Vinca Alkaloids

To examine and organize previous research on nanoformulations of VAs for cancer therapy, searches for patents and related information were conducted using analytics on the World Intellectual Property Organization's official website from 2007 to date (Table 3). These published patents on VAs belong to nanoformulations such as polymeric micelles, lipid polymer hybrid nanoparticles, polymer nanoparticles, nanoemulsions, and solid lipid nanoparticles.

Table 3. Published patent literature in the context of nanotechnological facets of vinca alkaloid for cancer management.

Patent name	Patent number [Publication date]	Applicant	Ref.
Vincristine in nano-formulation			
Small molecular drug-loaded polymer vesicle, preparation method therefor, and use thereof.	US20240099977 [28.03.2024]	Soochow University	[134]
Method for formation of lipid-polymer hybrid nanoparticles for combinatorial vincristine sulfate and lomustine drug delivery	AU2021101545 [15.04.2021]	Chouhan, Disha, Mujariya, Rajesh	[135]
Lipid-polymer hybrid nanoparticles for vincristine sulfate and lomustine drug delivery	IN202121044871 [29.10.2021]	Rajesh Mujoriya, Disha Chouhan, Manjeet Singh	[136]
Vincristine-containing medicine, as well as preparation method, medicine composition, and application thereof	CN111097051 [05.05.2020]	Baiyao Zhida (Beijing) Nano Biotechnology Co., Ltd.	[137]
Preparation for treating oncological diseases	WO2020046163 [05.03.2020]	Limited Liability Company Industrial Research Company "Alpha-Oncotechnologies	[138]
Polymer nanoparticles for loading alkaline antitumor drugs	CN102697735 [03.10.2012]	The Affiliated Drum Tower Hospital of Nanjing University Medical School	[139]
Vinblastine in nano-formulation			
Nanoparticle-anticancerous drug nanoformulations AUNPS-FA-VBLS AND CSNPS -VBLS-FA	IN201821002413 [09.02.2018]	Dipali Bharat Nagaonkar Prof. Mahendra Rai	[140]
Drug delivery system for targeting and a method for preparing the same	KR1020110117769 [28.10.2011]	Industry-Academic Cooperation Foundation, Yonsei University	[140]
Vinorelbine in nano-formulation			
Vinorelbine solid lipid nano granule, freeze-drying formulated product, and method of preparing the same	CN101129375 [27.02.2008]	Zhejiang University	[141]
Polyglycol derivatization of phospholipid-loaded vinorelbine nano-micelle preparations.	CN101138548 [12.03.2008]	Beijing Dekerui Medical Technology Co., Ltd.	[142]
Vinca alkaloids in nano-formulation			
Nano anticancer micelles of VAs entrapped in polyethylene glycolylated phospholipids	WO2007028341 [15.03.2007]	Beijing Diacrid Medical Technology Co. Ltd.	[143]
Nanomicelle preparation of *Catharanthus roseus* alkaloids antineoplastic drugs with coating of phospholipid derived from polyethylene glycol	CN1927203 [14.03.2007]	Liang Wei	[144]
A nano-emulsion injection of VAs and the preparation method thereof	EP2428203 [14.03.2012]	Jiangsu Hengrui Medicine Co Shanghai Hengrui Pharm Co Ltd	[145]
Nanometer drug loading system co-loading cytarabine and Vinca, as well as preparation method and application of the nanometer drug loading system	CN116212043 [06.06.2023]	Shandong University Qilu Hospital	[146]

9. Vinca Alkaloids in Combination Therapy

Combination therapy, integrating VAs with additional chemotherapy agents to improve antitumor efficacy, represents a promising approach for minimizing associated side effects [147-151]. CVP (vincristine, cyclophosphamide, and prednisone) is the primary treatment for follicular B-cell lymphoma. Front-line therapy employs CHOP, which consists of cyclophosphamide, doxorubicin, vincristine, and prednisone, for the treatment of patients with

follicular or diffuse large B-cell lymphoma. Patients diagnosed with diffuse large B-cell lymphoma and follicular lymphoma may benefit from first-line treatment with a combination of Rituximab and CVP or CHOP [152–154]. In recent years, the CHOP regimen has been used in conjunction with rituximab, an anti-CD20 IgG1 monoclonal antibody [155]. Treatment for IIIA and IIIB non-small-cell lung cancer includes VCRT, which consists of vinblastine, cisplatin, and radiation therapy [156]. Cytostatic therapeutics consist of VAs combined with cytostatic agents that can reduce cell death and produce better antitumor effects [157]. Nanoparticle-assisted chemoimmunotherapy represents a promising strategy for cancer treatment, which integrates chemotherapy agents with immunotherapeutic components such as cytokines, immune adjuvants, and monoclonal antibodies [158]. It also employs anti-HER2 immunoliposomal-VBL [158], anti-CD166 scFv immunoliposomes of vinorelbine [159], VNC-loaded F56 peptide-conjugated nanoparticles [160], and aptamer-nanoparticles of vinorelbine [161]. Procarbazine, vincristine, and lomustine are another well-known combination approach used to treat various CNS cancers [162–164].

10. Conclusions

Cancer is the leading cause of disease-related death worldwide and is typified by the unchecked and fast growth of abnormal cells. Inflammatory mediators, such as chemokines, growth factors like VEGF, inflammasomes, and cytokines, are involved in the progression of cancer-related inflammation. VAs produce anticancer effects via binding to microtubules, essential components of the cytoskeleton. These complexes impede cancer cell migration, leading to apoptosis and programmed cell death. These alkaloids do not confer cross-resistance to commonly utilized DNA alkylating agents, allowing their concurrent usage with chemotherapy regimens. VAs currently represent the second most utilized class of drugs for cancer therapy. VAs have limited clinical applications because of certain issues, which include their limited ability to penetrate the body, undergo high first-pass metabolism in the liver, severe adverse effects, and develop multidrug resistance. According to this review, a number of preclinical and clinical investigations using VAs-based nanoformulations have demonstrated promise as cancer treatments. This review highlights that nanoformulations of VAs offer specific advantages such as improved pharmacokinetics, enhanced tumor targeting, and reduced systemic toxicity, which can potentially overcome the conventional limitations. Additionally, clinical investigations have shown that liposomal vincristine, both alone and in combination, has strong anticancer potential in refractory cancer, non-Hodgkin lymphoma, acute lymphoblastic leukemia, retinoblastoma, and malignant melanoma. Future research should focus on developing site-specific and stimuli-responsive delivery systems to maximize therapeutic outcomes while minimizing toxicity. Equally important is the need to evaluate the long-term safety, regulatory feasibility, and cost-effectiveness of these nanoformulations. Nanoformulations of VAs with anticancer effects have also been published as patents in recent years. This review demonstrated unequivocally that using nanotechnology to deliver VAs has enormous potential for cancer treatment.

Author Contributions

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Conflict of Interest

The authors declare no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

Abbreviation	Definition
VEGF	Vascular Endothelial Growth Factor
TNFs	Tumor Necrosis Factors
VBL	Vinblastine
VNC	Vincristine
PLGA	Polylactide-co-glycolide
PEG	Polyethylene Glycol
SLNs	Solid Lipid Nanoparticles
NLCs	Nanostructured Lipid Carriers
PCL	Polycaprolactone
DSPE	1,2 distearoyl-sn-glycero-3 Phosphatidylethanolamine

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