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Recent progresses and challenges in formulations of vincristine and its derivatives for hindering cancer cells

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ABSTRACT

Vincristine and its derivatives as an alkaloid have been applied in combination with chemotherapeutic drugs for the inhibition of several cancers involving small-cell lung cancer, lymphocytic leukemia, Hodgkin's disease, acute myeloid leukemia, and neuroblastoma. The main advantage of using this bioactive compound is its severe side effects specifically dose-dependent peripheral neuropathy (brain dysfunction, cranial nerve palsies, paresthesia, and gait disorder). Combination therapy using other anticancer drugs or anticancer natural compounds can synergize anticancer effects. Moreover, drug delivery systems in the nanoscale may be suitable options to decrease side effects by reducing an effective dose of vincristine. Therefore, this mini-review has tried to cover recent progress and limitations of vincristine formulations for cancers of lung cancer, acute lymphocytic leukemia, and acute myeloid leukemia.

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1. Introduction

Bioactive materials related to plants and bacteria serve as a rich source for the discovery of new therapeutic agents [1-4]. Anticancer activities of vincristine ($C_{46}H_{56}N_4O_{10}$; leurocristine, under the brand name Oncovin), as an alkaloid drug, have been confirmed by various studies (Figure 1) [5, 6]. Vincristine is prescribed intravenously for small-cell lung cancer, acute lymphocytic leukemia, Hodgkin's disease, acute myeloid leukemia, and neuroblastoma [6]. Limit dose of vincristine is 2 mg per single dose [7]. As the disadvantages, there are several side effects of vincristine chemotherapy including lung damage, peripheral neuropathy (brain dysfunction, cranial nerve palsies, paresthesia, and gait disorder), a decrease of immunity efficiency, headaches, and change in sensation, hair loss, and gastrointestinal problems such as constipation [8-10]. The main anticancer mechanism of this alkaloid metabolite is causing instability of microtubule fibers by binding vincristine to the β-subunit of the αβ tubulin heterodimer and hindering the separation of chromosomes during the metaphase [11].

2. Acute lymphocytic leukemia

Acute lymphocytic leukemia (ALL) as the leukemia is led by cancer in the lymphoid line of blood cells including lymphoblast (B lymphocyte, T lymphocyte, and natural killer cell) (Figure 3) [12]. Some medicinal plant species containing bioactive compounds may be able to synergize the anticancer effects of vincristine. Methanolic extract of aerial parts of *Artemisia Annua* species was used to increase the anticancer activity of vincristine against pre-B acute lymphoblastic leukemia cells. According to the results of quantitative real time-PCR analysis, a combination of *A. annua* extract and vincristine increased Bax (Bcl-2-associated X protein) and caspase 3 expression levels by nearly 2.72- and 2.6-fold in Reh cells (a human cell line showing lymphoblastic morphology), respectively. In the case of Nalm-6 cells (a B cell precursor leukemia cell line), mRNA expression levels of Bax and caspase 3

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genes were increased under the effects of the plant extract (40 µg/ml) in combination with vincristine [13].

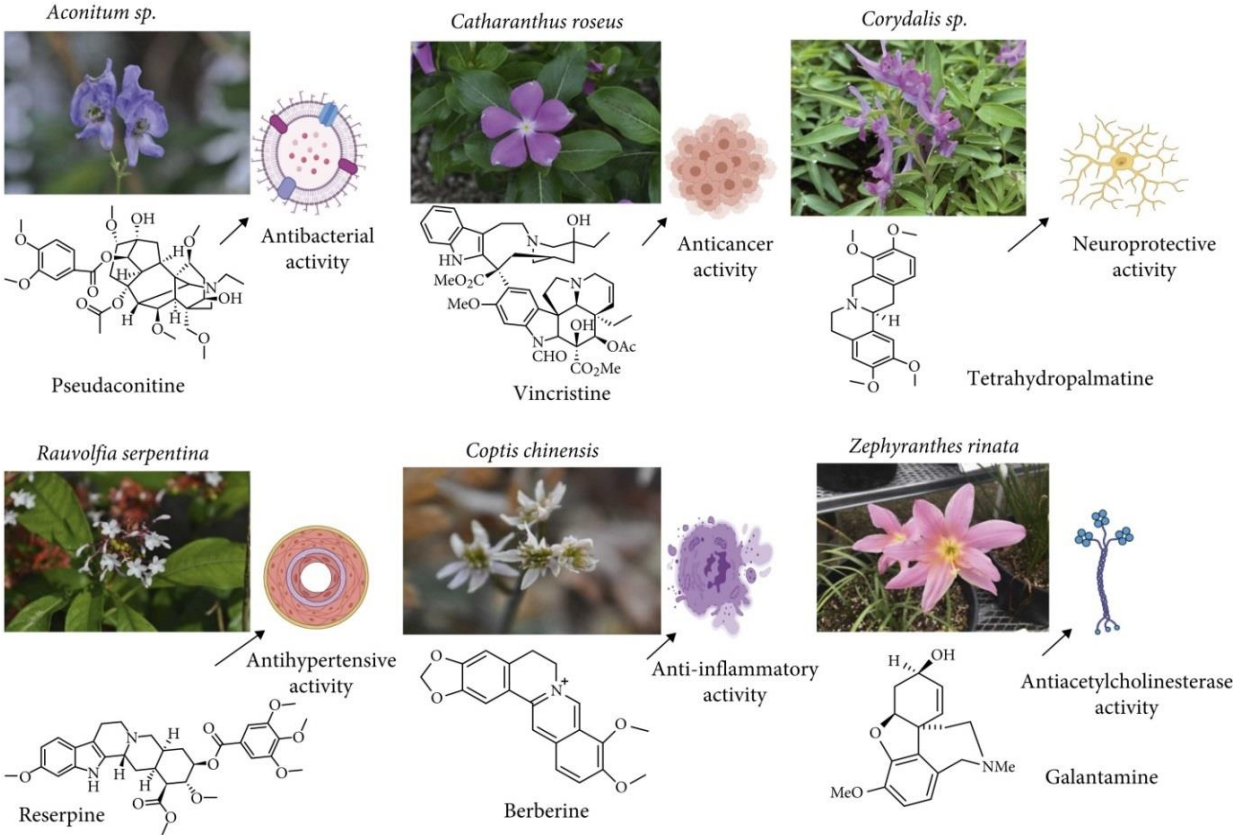

Fig. 1. The main therapeutic activities of alkaloids related to some medicinal plants (adapted from [14]).

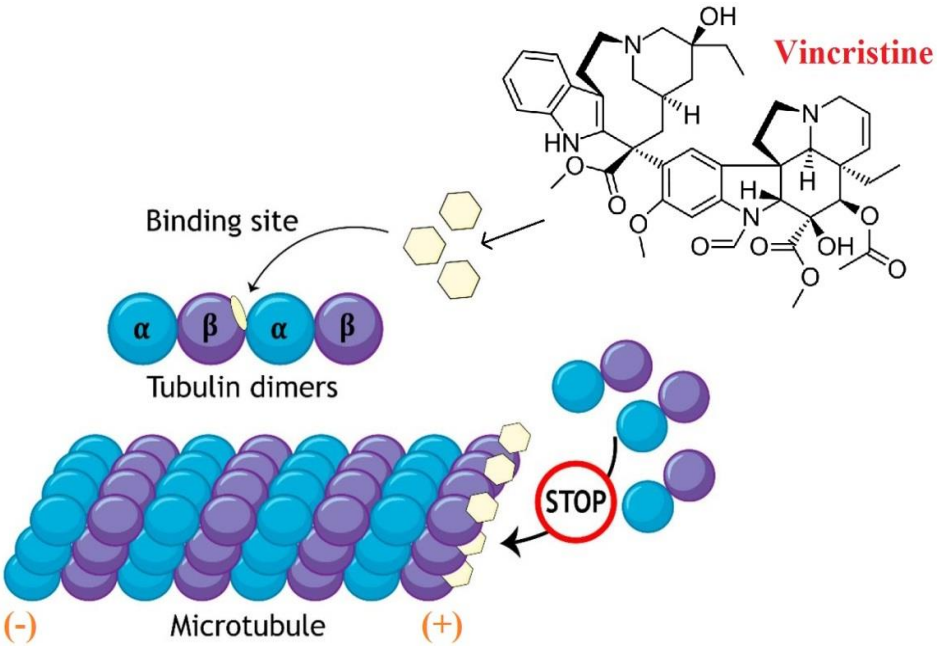

Fig. 2. Binding vincristine with the β-subunit of a tubulin dimer (the αβ tubulin heterodimer) and inhibiting binding free tubulin dimers to the microtubule (adapted and modified from [6]).

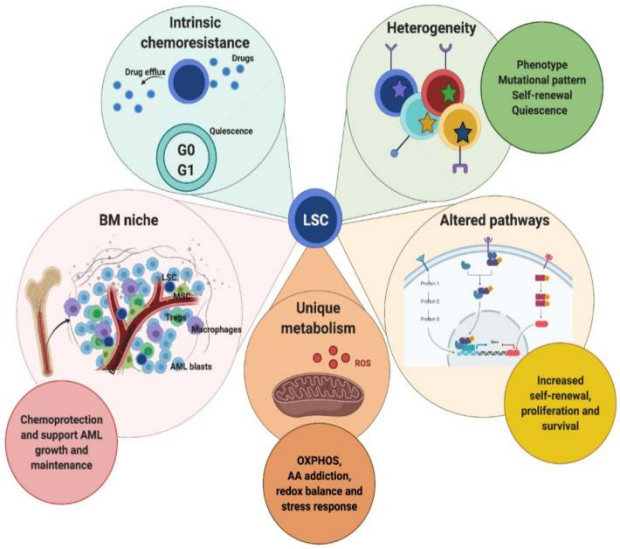

Fig. 3. Leukemic stem cell properties for AML (adapted from [12]).

3. Acute myeloid leukemia

Acute myeloid leukemia (AML) is the most common leukemia that results from cancer in the myeloid line of blood cells (a type of blood cell that originates in the bone marrow and matures into adult blood cells of erythrocyte, platelets, and granulocytes) (Figure 3) [12]. Various soft nano drug delivery systems such as liposomes, polymerosomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs) are employed to load and encapsulate anticancer agents [15, 16]. A6 peptide-tagged polymerosomes composed of poly(aspartic acid) (PAsp) as inner shell and PEG (polyethylene glycol)-P(trimethylene carbonate (TMC)-dithiolane trimethylene carbonate (DTC)) were applied to encapsulate vincristine sulfate [17]. This formulation was used to target CD44+ acute myeloid leukemia because of the ability of A6 peptide, eight l-amino acid peptide (Ac-KPSSPPEE-NH2), for binding to CD44 leading to the modulation of CD44-mediated cell signaling and the hindering of migration, invasion, and metastasis of cancer cells [17, 18].

4. Lung cancer

Vincristine is an alkaloid, and similar to vinblastine, it is extracted from the apokinaceae plant and is applied as an intravenous injection solution [19]. This metabolite has severe side effects in high doses and can be toxic to human cells, so it should be used in low doses and together with other therapeutic agents specifically antioxidant and anticancer compounds. For example, vincristine has been prescribed with basilcophosphamide, doxorubicin, prednisone, methotrexate, procarbazine, and dacarbazine. This bioactive metabolite has mainly been combined with DNA-interacting compounds such as cyclophosphamide or medications having the ability to interfere with DNA synthesis and methylation such as methotrexate. In addition, the simultaneous administration of vincristine with monoclonal antibodies such as the anti-CD20 antibody rituximab can be used to treat cancers [20]. Vincristine is injected at intervals of 1 or 2 weeks in a cycle with other agents, it must be intravenous because if it is intraspinal, it will cause progressive neurological syndrome [21]. Vincristine exerts its antitumor activity by inducing microtubule disruption and mitosis inhibition, thereby leading to cell apoptosis [22]. This drug has many side effects, the most important of which are: stomach cramps, constipation, increased uric acid, and peripheral neuropathy [23]. Vincristine can increase the possibility of infection and has drug interactions with some drugs such as digoxin, atropinen, and carboplatin [24]. In a study related to a vincristine-resistant cancer cell called A549/VCR, the sensitivity of these lung cancer cells' resistance to vincristine was markedly modulated by survivin (the inhibitor of apoptosis protein family) expression [25]. In a nano aspect, vincristine can be loaded on various nanocarriers. For instance, vincristine was loaded on folic acid (folate or vitamin B_9)-chitosan conjugated nanoparticles with a high loading capacity of 48.65 %. In addition to significant anticancer activity as apoptotic morphological changes and decreased mitochondrial transmembrane potential, this nanoformualtion had no toxicity as erythrocyte aggregation [26]. In another trial study, a combination of vincristine, etoposide, and carboplastin showed effective anticancer activity with fewer side effects in treating 84% of patients with small-cell lung cancer [27]. In another study, the combination of gemcitabine and vincristine demonstrated significant anticancer results with low myelotoxicity in patients at stage IV non-small cell lung cancer [28]. Moreover, a combination of vincristine with doxorubicin [29],

docrobsin, and cyclophosphamide [30] led to improved conditions in patients with small-cell lung cancer. Herbal metabolites may be useful to decrease the side effects of vincristine. For example, the hepatotoxic effect of subacute vincristine administration was reduced by Indian mustard and broccoli [31].

5. Conclusions

Apoptotic effects in cell lines of acute lymphocytic leukemia can be resulted from a combination of vincristine with *A. annua* extract via increasing mRNA expression levels of Bax and caspase 3 genes. A synergistic effect is expected for the combination therapy of vincristine with other anticancer drugs or anticancer bioactive compounds. In addition, drug delivery systems in the nanoscale can reduce side effects by decreasing an effective therapeutic dose of this metabolite. For example, A6 peptide-functionalized polymerosomes encapsulating vincristine sulfate have shown specific anticancer activity against $CD44^+$ acute myeloid leukemia. The emerging discussion about vincristine is the combination of vincristine with monoclonal antibodies, which is currently undergoing clinical trials. Because a complete replacement for vincristine has not yet been suggested, it is combined with other mentioned drugs. In future investigations, it is hoped that the targeting of tumor cells and drug development will increase with specific antibodies and ligands. In general, due to its side effects, vincristine is prescribed in a low dose and with other anticancer and antioxidant drugs for decreasing liver and kidney disorders. In this regard, the modification of micro and nanoformulations by the monoclonal antibodies may be an effective alternative strategy for reducing the side effects of vincristine.

Study Highlights

- A synergistic effect is expected for the combination therapy of vincristine with other anticancer drugs or anticancer bioactive compounds.
- In cell lines of acute lymphocytic leukemia, apoptosis can be resulted from a combination of vincristine with *A. annua* extract via increasing mRNA expression levels of Bax and caspase 3 genes.
- Due to its side effects, vincristine is prescribed in a low dose and with other anticancer and antioxidant drugs for reducing liver and kidney disorders.
- The modification of micro and nanoformulations by the monoclonal antibodies may be an effective alternative strategy for reducing the side effects of vincristine.

Abbreviations

ALL: Acute lymphocytic leukemia
AML: Acute myeloid leukemia
Bax: Bcl-2-associated X protein
DTC: Dithiolane trimethylene carbonate
NLCs: Nanostructured lipid carrier
PAsp: Poly(aspartic acid)
PEG: Polyethylene glycol
SLNs: Solid lipid nanoparticles
TMC: Trimethylene carbonate

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with animals or human participants performed by any of the authors.

Author Contributions

Both authors: conceptualization, writing the first draft, and revising the manuscript.

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