· 专论与综述 ·

Review on anticancer mechanism of some plant alkaloids

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Abstracts: Alkaloids derived from natural products have long been used as a fertile source of cure for cancer, which is believed to be one of the major causes of death in this century. This article reviews the recent advances of many structures of alkaloids in understanding mechanism of action at the molecular, cellular and physiological levels. The important molecules discussed include vincristine, vinblastine, camptothecin, colchicine, ellipticine *etc*. The review also discussed the potential use of plant alkaloids on multidrug resistance.

Key words: mechanism; alkaloids; anticancer; cell cycle; DNA-topoisomerase I; apoptosis; multidrug resistance

植物生物碱抗肿瘤机制

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摘 要: 生物碱中的一些种类用于治疗癌症已有相当长的一段时间。回顾了近年来在分子、细胞及生理水平上这些生物碱抗肿瘤的作用机制, 包括长春花生物碱类、喜树碱、秋水仙碱、玫瑰树碱等。同时也涉及多药耐药现象。

关键词: 机制; 生物碱; 抗肿瘤; 细胞周期; DNA-拓扑异构酶Ⅰ; 细胞凋亡; 多药耐药

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Herbal medicine has been used for treatment of different diseases in China for thousands of years. Recent studies have demonstrated that phytochemicals of many classes in herbal medicine have therapeutic use. Numerous *in vitro* studies on different cell lines and *in vivo* study of alkaloids have reported[1~3] that alkaloids possess anticancer activities. This review aims to give an overview of the pharmacological effects of alkaloids in the treatment of cancer. Possible mechanisms of action of some alkaloids, including *V inca* alkaloids, camptothecins, ellipticine, were also discussed in the paper.

1 Mechanism of action of different alkaloids

1.1 *V inca* alkaloids Vinblastine and vincristine, commonly termed *V inca* alkaloids, are isolated from *Catharanthus roseus* (L. G. Don) leaves in the late 1950's. *V inca* alkaloids binds to tubulin, a dimeric cellular protein playing a crucial role in cell structure and in the organization of chromosomes. This binding inhibits the polymerization of tubulin into microtubules rather than interferes with the mitotic process and induces the arrest of cells in mitosis.

The tubulin isotype compostion of microtubules is an important determinant in antineoplastic activity of *V inca* alkaloids. *In vitro* study has shown that β-tubulin isotype composition affects microtubule sensitivity to *V inca* alkaloids[4]. Molecular approaches using quantitative sedimentation velocity have already proved that the tubulin isotype composition of various tissues or tumours may also determine the clinically observed drug toxicity. Thermodynamic parameters for vincristine-, vinblastine- or vinorelbine-interaction with different purified isotypes of tubulin had also been determined. Small but significant differences in certain individual thermodynamic parameters were found for vincristine and were not observed with vinblastine or vinorelbine. But in cells, microtubules are composed of a backbone of tubulin dimers and microtubule-associated proteins, termed MAPs which have been shown to regulate tubulin polymerization function and modulate the activity of tubulin-interaction agents such as *V inca* alkaloids.

On the other hand, it had been shown that *V inca* alkaloids also affected microtubules in interphase cells, which is associated with the cytoskeleton network influencing the intracellular migration of oncogenes. And such effects of *V inca* alkaloids on the microtubules of interphasic cells may also influence their antitumour activity. Activities of four *V inca*

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alkaloids on the most dynamic microtubules were investigated in mitosis and in interphase by evaluating the disturbance of the metaphase plate and the splitting of the diplosome, respectively. Cytotoxicity, mitotic disturbance and diplosome splitting were observed in vinblastine, vincristine, vindesine and vinorlbine, although these events occurred at ten times higher concentrations in the case of vinflunine. Hence, dynamic modifications of both the mitotic and interphasic microtubule cytoskeleton are compatible with *in vitro* cytotoxicity of vinflunine, raising questions about the conventional biochemical screening of these *V inca* alkaloids.

In addition to their antimitotic effects, the effects of vinblastine on angiogenesis were specifically studied: *in vitro*, vinblastine had inhibitory effect at non-cytotoxic doses and in a concentration-depedent fashion, on endothelial cell proliferation, chemotaxis, spreading on fibronectin and morphogenesis on Matrigel; the antiangiogenic effects of vinblastine were confirmed *in vitro* using the chick embryo chorioallantoic membrane model and these effects were rapidly abolished when vinblastine was removed. The antivascular effects of other newer *V inca* alkaloids, such as vinorelbine and vinflunine, were also established using the MAC 15A transplantable murine colon adenocarcinoma model[5]. Furthermore, it was emphasized that for vinflunine there was a clear separation between the antiangiogenic dose and the maximum tolerated dose. In addition, reduced tumour oxygenation by treatment with vinblastine was recently observed *in vivo*[6]. This study using non-invasive techniques such as magnetic resonance imaging and electron paramagnetic resonance oxymetry, demonstrated that vinblastine caused a profound reduction in tumour blood flow and oxygenation which could have resulted from the effects of vinblastine on tumour vasculature. New *V inca* alkaloids should certainly be screened for any novel antiangiogenic properties.

By flow cytometry using nuclear staining and annexin V, vinorelbine and vincristine had been demonstrated to induce both mitotic arrest and apoptosis in leukemia and lymphoma cells, in a drug exposure time dependent manner. CPP32 or caspase-3 was a critical apoptosis inducer. Its active subunits p20 and p11 were up-regulated in chemo- and apoptosis-sensitive lymphoma and leukemia cells treated with vinorelbine. These observations suggested that widely divergent exogenous stimuli and chemotherapeutic agents can affect apoptosis in cancer cells via different pathways involving the caspases.

Fukuoka *et al*.[7] reported that vinorelbine at a minimally toxic concentration moderately sensitized human non-small cell lung cancer cells to radiation by causing accumulation of cells in the G_2/M-phase of the cell cycle. Prolonged G_2/M accumulation concomitant with continuous polyploidization and increased susceptibility to induction of apoptosis may be associated with the cellular mechanism of radio-sensitization produced by vinorelbine.

1.2 Camptothecins Camptothecin (CTP) is a naturally occurring cytotoxic alkaloids derived from the Chinese tree *Camptotheca acuminata* Decne. It is an effective inhibitor of intranuclear enzyme topoisomerase I, which is involved in reducing the torsional stress of supercoiled DNA during the replication, recombination, transcription, and repair of DNA.

The camptothecins trap and stabilize the normally transient DNA-topoisomerase I cleavable complex, which leads to the accumulation of single-stranded breaks of the DNA. Collision of the DNA replication fork with the ternary drug-enzyme-DNA complex produces an irreversible double-strand break that ultimately leads to cell death. The camptothecins are S-phase-specific anticancer agents. Irreversible DNA double-strand breaks are produced during DNA synthesis in the presence of camptothecin. And recent studies of low-dose, protracted administration of camptothecin analogues in mice bearing xenografts of human tumors have shown less toxicity and equal to or better antitumor activity than shorter, more intense dosing schedules. However, camptothecin-induced cytotoxicity had also been observed in nondividing cells, such as neurons. It was characteried by chromatin condensation, cytoplasmic shrinking, plasma membrane blebbing, and fragmentation of neurites. DNA fragmentation was also confirmed by the use of the *in situ* DNA end labeling assay.

CPT effectively kills human gastric cancers by activating cell cycle withdrawal and cell death through induction of $p21^{Waf1/Cip1}$ and down regulation of Bcl-2. Meanwhile, the transcription factor complex E2F-1/DP-1 regulates the G_1-to-S-phase transition and has been associated with sensitivity to the S-phase-specific anticancer agent camptothecin. Hofland *et al*.[8] reported that camptothecin-induced toxicity in their experiments was due to the activation of an E2F-1/DP-1-induced post-DNA damage pathway rather than an increase in the number of replication forks caused by the S-phase initiation. In addition, Adams *et al*.[9] found that CPT-based drug development and resulting chemotherapy could benefit from evaluation of differential activity at acidic versus physiological pH. It has been identified that analogues could have improved therapeutic indices based on the pH gradient that selectively exists in human tumors. Final-

ly, recent reports have suggested that the camptothecins may also have an antiangiogenesis effect. The pharmacological interest of camptothecin has generated a large number of derivatives and analogues endowed with potent cytotoxic activity, including 9-AC, 9-NC, irinotecan, CPT-11, 7-substituted camptothecins, 10-hydroxycamptothecin, exatecan mesylate, and karenitecin.

1.3 Colchicine Colchicine exerts its biological effects through binding to the soluble tubulin heterodimer, the major component of the microtubule. Specifically, it interferes with microtubule growth and therefore affects mitosis and other microtubule-dependent functions. The kinetic mechanisms of the binding to tubulin of colchicine and eight different analogues had been studied. All of the analogues follow a two step binding mechanism, i.e. binding occurs via an initial step with low affinity, followed by an isomerisation of the initial complex leading to the final high affinity state. Morphological analysis of MCF-7 ADRr cells revealed that thiocolchicone is able to induce apoptosis in this multidrug resistance (MDR)-bearing model and they also demonstrated that thiocolchicone interacts with α- and β-tubulin by using flow cytometry. In addition, colchicine also has significant effects on tubulin conformation, but the regions which are affected have not been identified. Chaudhuri *et al.* [10] reported for the first time that the interaction of the B-ring of colchicine with the α- subunit affects a domain of tubulin which appears to be far from its binding site. Furthermore, they also found that the B-ring of colchicine plays a major role in the stability of tubulin while the A and the C-rings have little effect on it. Levchenko *et al.* [11] used a positron-emitting MDR tracer, 11C-colchicine (CHC), to evaluate MDR by PET imaging. They observed an approximately 2-fold difference between 11C-CHC accumulation in sensitive and resistant tumors. These *in vivo* experiments provided additional evidence for the indirect effect of P-gp action on CHC-to-tubulin binding, which in turn determines CHC uptake in tumors.

1.4 Harringtonine Harringtonine (HT), homoharringtonine (HHT) and isoharringtonine (IHT) are cephalotaxine alkaloids with anticancer activities which were isolated from *Cephalotaxus hainanensis* L. indigenous to China. Since the 1970s, HT and HHT have been developed as effective anticancer drugs in China and have been used widely in the treatment of acute nonlymphoid leukemia and chronic granulocyte leukemia. The *Cephalotaxus* alkaloids inhibit the elongation phase of translation by preventing substrate from binding to the acceptor site on the 60-S ribosome subunit and therefore block aminoacyl-tRNA binding and peptide bond formation. The mechanism of the antitumor action of harringtonine is considered to be an effect on protein synthesis and is characterized by breakdown of polysomes to monosomes. In addition, IHT shows significant and rapid apoptotic inductive effect on HL-60 cells in both concentration- and time-dependent fashion. Typical DNA ladder in agarose gel electrophoresis and pre-G_1 peak in flow cytometric analysis are also observed in the cells exposed to IHT.

1.5 Ellipticine Ellipticine is one of the simplest naturally occurring alkaloids isolated in 1959 from the leaves of *Ochrosia elliptica* (Labill.) (Apocynaceae), which grows wildly in Oceania. Studies on the mechanisms of cytotoxicity and anticancer activity of the ellipticine analogues indicate a complex set of effects, including DNA intercalation and inhibition of topoisomerase Ⅱ. Ellipticine does not impair topoisomerase Ⅱ-mediated DNA religation and presumably increases levels of DNA cleavage complexes primarily by stimulating the forward rate of scission. Wild-type p53 causes cell-cycle arrest at late G_1 phase and induction of apoptosis by up-regulation of WAF 1 and BAX, respectively, but in many cancer cells p53 is frequently mutated and loses its functions. Mizumoto *et al.* [12] suggests that 9-hydroxy ellipticine may cause G_1 arrest and induction of G_1 phase-restricted apoptosis by restoring the wild-type function of mutant p53 protein. Recently, Frei *et al.* found that ellipticine also forms covalent DNA adducts and that the formation of the major adduct is dependent on the activation of ellipticine by cytochrome P450 (CYP) [13, 14].

1.6 Cepharanthin Cepharanthin is one of the biscoclaurine alkaloids widely used for treatment of many acute and chronic diseases; snakebite, bronchial asthma, alopecia areata, leukopenia during radiation therapy or anticancer treatment. Recently, it has been reported that cepharanthin exerts antitumour effects by increasing immunological competence of the host or apoptosis-inducing activity. Cepharanthin induces G_1 arrest via expression of p21 (WAF1) and apoptosis through caspase 3 against a human adenosquamous cell carcinoma cell line (TYS) [15].

1.7 Solamargine Solamargine, a herbal and molluscicidal medicine derived from *Solanum incanum* L., is a steroidal alkaloid glycoside. To characterize the anticancer mechanism of solamargine on human hepatoma cells (Hep 3B), changes of cell morphology, DNA content, and gene expression of cells after solamargine treatment were studied. The appearance in solamargine-treated cells of chromatin condensation, DNA fragmentation, and a sub-G_1 peak in a DNA histogram suggest that solamargine induce cell death by apoptosis [16]. In addition, the gene expression of tumour

necrosis factor receptor Ⅰ (TNFR Ⅰ) is up-regulated with solamargine treatment. Since TNFR Ⅰ has been involved in apoptosis, the overexpression of TNFR Ⅰ may be related with the mechanism of cytotoxicity of solamargine.

1.8 Sanguinarine Sanguinarine, which is derived from the root of *Sanguinaria canadensis* L. and other poppy fumaria species, is a benzophenathridine alkaloid and a structural homologue of chelerythrine. Sanguinarine has been shown to possess antimicrobial, antioxidant, and anti-inflammatory properties. A recent study has shown that sanguinarine is a potent inhibitor of the activation of nuclear transcription factor NF-κB, which has been implicated to play a key role in the regulation of cell growth, cell cycle regulation, and apoptosis. But the antitumor properties of this alkaloid are not well established. Ahmad *et al.* [17] compared the antiproliferative and apoptotic potential of sanguinarine against human epidermoid carcinoma (A431) cells and normal human epidermal keratinocytes (NHEKs). Sanguinarine treatment was found to result in a dose-dependent decrease in the viability of A431 cells as well as NHEKs albeit at different levels because sanguinarine-mediated loss of viability occurred at lower doses and was much more pronounced in the A431 carcinoma cells than in the normal keratinocytes. Weerasinghe *et al.* [18] demonstrated that sanguinarine treatment at a low level induces apoptosis or programmed cell death (PCD) in the Bcl-2 low-expressing K562 human erythroleukemia cells, and that a high level induces blister cell death (BCD); whereas the over-expression of anti-apoptotic Bcl-2 may have prevented sanguinarine from inducing PCD and BCD in JM1 cells[19].

1.9 Others Inhibition of cancer cell's growth in a common approach to treat cancer. Recently, it was reported that the aqueous extract of *Rhizoma Coptidis* and berberine have potent inhibitory effect on the proliferation of esophageal cancer cells (ECCs) lines[20]. Cell cycle analysis of *Rhizoma Coptidis*-treated cancer cells showed the accumulation of cells in the G_0/G_1 phase.

Tetrandrine, a calcium channel antagonist, is a natural lipid-soluble alkaloid with a low molecular weight, possessing various pharmacological activities including antitumor activity. Tetrandrine inhibits both proliferation and clonogenicity of human leukemic U937 cells at an optimal concentration. This growth inhibition is dose-and time dependent, and is accompanied with evidence of apoptotic changes. The induction of apoptosis by tetrandrine would appear to proceed via non-Ca^{2+}-dependent pathways. Moreover, tetrandrine enhances the radiosensitivity in human glioblastoma U138MG cells and eliminated the cell cycle perturbation induced by radiation.

Cryptolepine and neocryptolepine are two indoloquinoline derivatives isolated from the roots of the African plants *Cryptolepis sanguinolenta* (Lindl.) Schlechter, which display potent cytotoxic activities against tumour cells. Studies on molecular level indicated that these two natural products intercalate into DNA and interfere with the catalytic activity of human topoisomerase Ⅱ. Western blotting analysis revealed that cryptolepine induces cleavage of poly (ADP-ribose) polymerase but both alkaloids induce the release of cytochrome c from the mitochondria[21].

Originally isolated from an Australian plant, acronycine in an antitumor alkaloid wiht poor water solubility and low potency. The modest antitumor activity of this compound was markedly improved by the total synthesis of original analogs resulting in the selection of S23906-1. The molecular mechanism of action of S23906-1 could involve DNA alkylation, modulation of cyclin E protein levels and inhibition of DNA synthesis leading to apoptosis[22].

The whole plant of *Sedum sarmentosum* Bunge has been traditionally used for the treatment of chronic viral hepatitis in China and South Korea. Certain hepatitis virus causes acute and chronic hepatitis and induces hepatocellular carcinoma (HC). Antiproliferative effects of the crude alkaloid fracion of *S. sarmentosum* are associated with an increase in the number of cells in the G_1 phase of cell cycle. This study suggests that *S. sarmentosum* may improve survival of hepatoma patients via the inhibition of excessive growth of tumor cells[23].

Noscapine, a phthalideisoquinoline alkaloid derived from opium, has been used as an oral anti-tussive agent and has shown very few toxic effects in animals or humans. Recently, Ke *et al.* [24] reported that noscapine binds stoichiometrically to tubulin and promotes microtubule polymerization. Noscapine causes growth arrest of tumor cells in mitosis and induces apoptosis of tumor cells *in vitro*. It is noteworthy that, noscapine shows little or no toxicity to kidney, liver, heart, bone marrow, spleen or small intestine at tumor-suppressive doses. Furthermore, oral noscapine does not inhibit primary immune responses, which are critically dependent upon proliferation of lymphoid cells.

2 Multidrug resistance

Multidrug resistance (MDR) is one of the main obstacles in the chemotherapy of cancer. MDR's inhibition effect and combination of chemosensitizers with antitumor compounds is an active field of research, since safe and potent reversal agents would be beneficial for clinical use. The mostly investigated mechanisms with clinical significance

are: 1) activation of transmembrane proteins effluxing different chemical substances from the cells (P-glycoprotein is mostly known as efflux pump); 2) activation of the enzymes of the glutathione detoxification system; 3) alterations of the genes and the proteins involves into the control of apoptosis (especially p53 and Bcl-2).

P-glycoprotein is a member of the ATP-binding cassette (ABC) transport superfamily. It plays an important role in the development of MDR in cancers by effluxing a wide variety of anticancer drugs. Some alkaloids have little or no cytotoxic action by themselves, but inhibit (P-gp) or MRP (multidrug resistance-associated protein)-mediated drug export and are capable of sensitizing MDR cells to the cytotoxic effects of chemotherapeutic drugs. Kopsiflorine, an indole alkaloid of the aspidofractinine-type isolated from *Kopsia dasyrachis* L., interacts directly with P-glycoprotein and inhibits the efflux of antitumor agents in drug-resistant cells. Lavie *et al*[25] examined the ability of steroidal alkaloids of plant origin, namely the *Veratrum* sp. alkaloid cyclopamine and the *Lycopersicon* sp. alkaloid tomatidine, to act as potent and effective chemosensitizers in MDR tumor cells. It is concluded that both of them act as inhibitors of P-gp-mediated drug transport and MDR and therefore may serve as chemosensitizers in combination chemotherapy with conventional cytotoxic drugs for treating MDR cancer. Pervilleine A, a novel tropane alkaloid obtained from a chloroform extract of *Erythroxylum pervillei* Baill. as the result of bioactivity-guided fractionation, was found to restore the vinblastine sensitivity of cultured MDR KB-V1 and CEM/VLB (100) cells[26]. Tetrandrine inhibits the P-gp-mediated drug efflux and lowered cell membrane fluidity in a concentration-dependent manner. It is an extremely potent MDR modulator both *in vitro* and *in vivo*, without apparently enhancing the toxicity of the co-administered drugs. Hence, tetrandrine holds great promise as a MDR modulator for the treatment of P-gp-mediated MDR cancers[27].

3 Perspectives

Alkaloids derived from various plants produces different effects on the treatment of cancer, including reactions with microtubules, inhibition of angiogenesis, inhibition of DNA-topoisomerase Ⅰ, mitotic arrest and induction of apoptosis.

Furthermore, studies on structure/activity relationships (SAR) of alkaloids have discovered some therapeutically useful compounds and their semisynthetic derivatives, including *Vinca* alkaloids, camptothecins, ellipticine, *etc*. In other words, plant alkaloids provided basic structures of bioactivity and pharmacokinetic properties but more practical approach is the optimization of these structures. Meanwhile, a better understanding of SAR will lead to suppress or circumvent MDR mechanisms because the MDR tumor cells are resistant to drugs which are structurally unrelated and functionally divergent. Nevertheless, the exact mechanisms of some alkaloids still remain unclear. In view of the above mentioned mechanisms of action, combination/parallel methods should be applied in large-scale laboratory experiments and detailed clinical studies. Finally, plant alkaloids can be used as lead structures for the development of further anticancer agents with improved physicochemical and pharmacological properties.

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龙血树属植物化学成分及药理活性研究进展

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摘 要: 龙血树属植物含有黄酮类、酚类、三萜及其皂苷等化学成分。本属部分植物木质部分泌出的树脂在各产地均做药用, 具有抗炎止痛、抗真菌、抗心律失常、抗血栓、止血等多种药理活性, 并可作为中药"血竭"的代用品。现对龙血树属植物的化学成分及药理活性等方面进行概述。

关键词: 龙血树属植物; 化学成分; 药理活性

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Advances in study on chemical constituents and pharmacological activities in plants of *Dracaena* Vand. ex L.

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