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RECENT ALKALOIDS FROM *DALBERGIA SISSOO* AND VARIOUS HERBS AS ANTICANCER AGENTS

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ABSTRACT

Alkaloids are important chemical compounds that serve as a rich reservoir for drug discovery. Several alkaloids isolated from natural herbs exhibit antiproliferation and antimetastasis effects on various types of cancers both in vitro and in vivo. Alkaloids, such as camptothecin and vinblastine, have already been successfully developed into anticancer drugs. This paper focuses on the naturally derived alkaloids with prospective anticancer properties, such as berberine, evodiamine, matrine, piperine, sanguinarine, and tetrandrine, and summarizes the mechanisms of action of these compounds. Based on the information in the literature that is summarized in this paper, the use of alkaloids as anticancer agents is very promising, but more research and clinical trials are necessary before final recommendations on specific alkaloids can be made.

INTRODUCTION

Alkaloids are a highly diverse group of compounds that contain a ring structure and a nitrogen atom. In most cases, the nitrogen atom is located inside the heterocyclic ring structure [1]. A classification based on biosynthetic pathways is mostly used to categorize different alkaloid [1]. Alkaloids have a wide distribution in the plant kingdom and mainly exist in higher plants, such as those belonging to Ranunculaceae, Leguminosae, Papaveraceae, Menispermaceae,Dalbergiaceae and Loganiaceae [1]. Moreover, several alkaloids exhibit significant biological activities, such as the relieving action of ephedrine for asthma, the analgesic action of morphine, and the anticancer effects of vinblastine [1–4]. In fact, alkaloids are among the most important active components in natural herbs, and some of these compounds have already been successfully developed into chemotherapeutic drugs, such as camptothecin (CPT), a famous topoisomerase I (TopI) inhibitor [5], and vinblastine, which interacts with tubulin [4]

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Herein, we searched the PubMed database and the naturally derived alkaloids, such as berberine, evodiamine, matrine, piperine, sanguinarine, and tetrandrine (Figure 1), which have relatively more anticancer studies, have been selected for reviewing. Other alkaloids (such as chelerythrine, chelidonine, fagaronine, lycorine, nitidine chloride, and solanine) lacking systematic anticancer investigations have also been mentioned. The aim of this paper is to summarize and investigate the mechanisms of action of these compounds to accelerate the discovery of anticancer drugs derived from alkaloids.

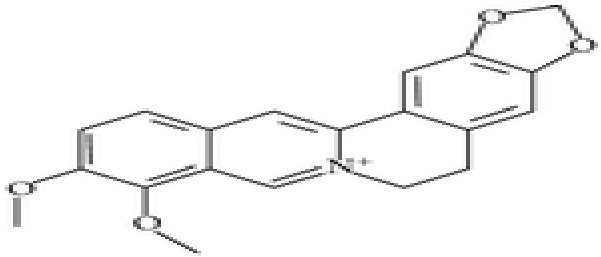
Alkaloids with Anticancer Effects and the Related Mechanisms

1. Berberine

Berberine is an isoquinoline alkaloid widely distributed in natural herbs, including *RhizomaCoptidis*, a widely prescribed Chinese herb [6]. It has a broad range of bioactivities, such as anti-inflammatory, antibacterial, antidiabetes, antiulcer, sedation, protection of myocardial ischemia-reperfusion injury, expansion of blood vessels, and inhibition of platelet aggregation, hepatoprotective, and neuroprotective effects [7–11]. Berberine has been used in the treatment of diarrhea, neurasthenia, arrhythmia, diabetes, and so forth [11]. Several studies have shown that berberine has anticancer potentials by interfering with the

multiple aspects of tumorigenesis and tumor progression in both in vitro and in vivo experiments. These observations have been well summarized in the recent reports [12–14].In addition; berberine induces endoplasmic reticulum stress [12, 13, and 15] and autophagy [17] in cancer cells. However, compared with clinically prescribed anticancer drugs, the cytotoxic potency of berberine is much lower, with an IC50 generally at 10 μM to 100 μM depending on the cell type and treatment duration in vitro [12]. Besides, berberine also induces morphologic differentiation in human teratocarcinoma cells [18]. Inhibition of tumor invasion and metastasis is an important aspect of berberine's anticancer activities [19, 20]. A few studies have reported berberine's inhibition of tumor angiogenesis [21, 22]. In addition, its combination with chemotherapeutic drugs or irradiation could enhance the therapeutic effects [23, 24]. Recently, a study reported that berberine also showed promising chemopreventive efficacy in hamster buccal pouch carcinogenesis [25].

The potential molecular targets and mechanisms of berberine are rather complicated. Berberine interacts with DNA or RNA to form a berberine-DNA or a berberine-RNA complex, respectively [26, 27]. Berberine is also identified as an inhibitor of several enzymes, such as N-acetyltransferase (NAT), cyclooxygenase-2 (COX-2), and telomerase [12]. Other mechanisms of berberine are mainly related to its effect on cell cycle arrest and apoptosis, including regulation of cyclin-dependent kinase (CDK) family of proteins [12, 28] and expression regulation of B-cell lymphoma 2 (Bcl-2) family of proteins (such as Bax, Bcl-2, and Bcl-xL) [12, 15, 28], and caspases [15, 28]. Furthermore, berberine inhibits the activation of the nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) and induces the formation of intracellular reactive oxygen species (ROS) in cancer cells [12, 15].

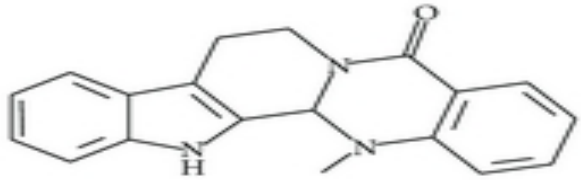


Berberine

2. Evodiamine

Evodiamine a quinolone alkaloid, is one of the major bioactive compounds isolated from the Chinese herb. Dalbergiasissooleaf It possesses antianxiety, antiobese, antinociceptive, antiinflammatory, antiallergic, and anticancer effects. Besides, it has thermoregulation, protection of myocardial ischemia-reperfusion injury and vessel-relaxing activities [11, 31–34]. Evodiamine exhibits anticancer activities both in vitro and in vivo by inducing the cell cycle arrest or apoptosis, inhibiting the angiogenesis, invasion, and metastasis in a variety of cancer cell lines [35–38]. It presents anticancer potentials at micromolar concentrations and even at the nanomolar level in some cell lines in vitro Evodiamine also stimulates autophagy, which serves as a survival function Compared with other compounds, evodiamine is less toxic to normal human cells, such as human peripheral blood mononuclear cells [37,]. It also inhibits the proliferation of adriamycin-resistant human breast cancer NCI/ADR-RES cells both in vitro and in Balb-c/nude mice Evodiamine (10 mg/kg) administrated orally twice daily significantly inhibits the tumor growth .Moreover, treatment with 10 mg/kg evodiamine from the 6th day after tumor inoculation into mice reduces lung metastasis and does not affect the body weight of mice during the experimental period [35].

Evodiamine inhibits TopI enzyme, forms the DNA covalent complex with a similar concentration to that of CPT, and induces DNA damage. Cancer cells treated with evodiamine exhibit G 2 / M phase arrest rather than S phase arrest, which is not consistent with the mechanism of classic TopI inhibitors, such as CPT. Therefore, other targets aside from TopI may also be important for realizing the anticancer potentials of evodiamine.

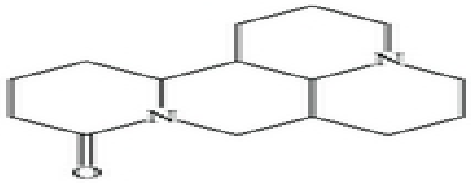


Evodiamine

3. Matrine

Matrine is a major alkaloid found in many Sophora plants, including SophoraflavescensAit.It exhibits a wide range of pharmacological properties such as antibacterial, antiviral, antiinflammatory, antiasthmatic, antiarrhythmic, antiobesity, anticancer, diuretic, choleretic, hepatoprotective, nephroprotective, and cardioprotective effects [11,]. It has been used for treatment of bacillary dysentery, enteritis, malignant pleural effusion, and so forth in China [11], and the anticancer effects have also been widely studied. Although the needed concentration of matrine to inhibit cancer cell proliferation is relatively high (i.e., at millimolar level) it has no significant effects on the viability of normal cells. Matrine inhibits the proliferation of various types of cancer cells mainly through mediation of G1 cell cycle arrest or apoptosis .Apoptosis and autophagy could be both induced by matrine in human cancer cells, such as hepatoma G2 cells and SGC-7901 cells matrine at 50 mg/kg or 100 mg/kg inhibits MNNG/HOS xenograft growth and it reduces the pancreatic tumor volumes compared to those of control at the similar doses However, the exact targets of matrine are still unclear. Matrine has been used in China for cancer therapy. The direct inhibition of cancer proliferation by

this compound seems not to be the exact mechanism that could explain the reason for its application in cancer treatment.

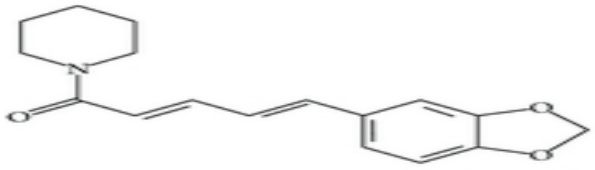


Matrine

4. Piperine

Piperine a piperidine alkaloid isolated from Piper nigrum and Piper longum, is a compound found in famous spices that have been used for centuries [34]. It exhibits antioxidant, antiinflammatory, antidiarrheal, anticonvulsant, antimutagenic, hypolipidemic, promoting bile secretion, and tumor inhibitory activities [11]. It is also a known antidepressant of the central nervous system .The chemopreventive effects of piperine against several kinds of carcinogen, such as benzo(a) pyrene, and 7,12-dimethyl benz(a)anthracene, show its potential as a cancer preventive agent .Administration of piperine (50 mg/kg or 100 mg/kg per day for 7 days) inhibits solid tumor development in mice transplanted with sarcoma 180 cells.A recent study has shown that piperine inhibits breast stem cell self-renewal and does not cause toxicity to differentiated cells. It has been demonstrated that piperine induced apoptosis and increased the percentage of cells in G 2 / M phase in 4T1 cells and induced K562 cells to differentiate into macrophages/monocytes.Piperine also has very good antimetastatic properties against lung metastasis induced by B16F-10 melanoma cells in mice (200 μM/kg and suppresses phorbol-12-myristate-13-acetate (PMA)-induced tumor cell invasion

Piperine also inhibits the functions of P-glycoprotein (P-gp) and CYP3A4, which not only affects drug metabolism but also re-sensitizes multidrug resistant (MDR) cancer cells Piperine increases the therapeutic efficacy of docetaxel in a xenograft model without inducing more adverse effects on the treated mice by inhibiting CYP3A4, one of the main metabolizing enzymes of docetaxel

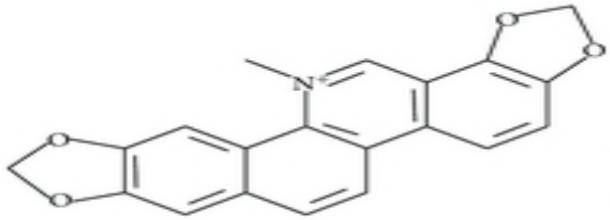


Piperine

5. Sanguinarine

modulator for the treatment of P-gp-mediated MDR cancers. Tetrandrine appears to be a promising candidate for combining with several chemotherapeutic agents, such

Sanguinarine is a benzophenanthridine alkaloid isolated from the Papaveracea family, which includes Sanguinariacanadensis L. and Chelidoniummajus L. It has antibacterial, antifungal, antischistosomal, antiplatelet, and antiinflammatory properties [11,], and is used for schistosomiasis control [11]. Sanguinarine also exhibits anticancer potentials [10–14] and is currently receiving attention from researchers. Data from in vitro studies indicates that this alkaloid presents anticancer effects at concentrations less than ten micromoles in most cases. Sanguinarine induces cell cycle arrest at different phases or apoptosis in a variety of cancer cells [11, 12, 14–17]. It remarkably sensitizes breast cancer cells to tumor necrosis factor (TNF)-related apoptosis-inducing ligand-mediated apoptosis [15]. Sanguinarine also shows antiangiogenic effects in mice (5 mg/kg), presents anti-invasive effects, and overcomes P-gp-mediated MDR phenotype .It has also been suggested that sanguinarine may be developed as an agent for the management of conditions elicited by ultraviolet exposure such as skin cancer

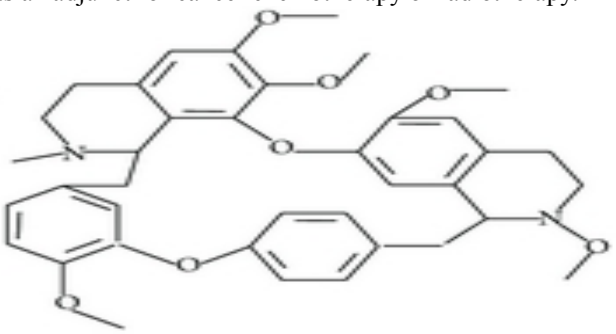


Sanguinarine

6. Tetrandrine

Tetrandrine a bisbenzylisoquinoline alkaloid from the root of Stephaniatetrandra, exhibits a broad range of pharmacological activities, including immunomodulating, antihepatofibrogenetic, antiinflammatory, antiarrhythmic, antiportal hypertension, anticancer and neuroprotective activities [11]. It generally presents its anticancer effects in the micromolar concentrations. Tetrandrine induces different phases of cell cycle arrest, depends on cancer cell types [12–14], and also induces apoptosis in many human cancer cells, including leukemia, bladder, colon, hepatoma, and lung [12–13]. In vivo experiments have also demonstrated the potential value of tetrandrine against cancer activity [16]. Coadministration of tetrandrine restores the sensitivity of MDR cancer cells to doxorubicin, paclitaxel, docetaxel, and vincristine through the inhibition of P-gp. In mice with MDR MCF-7/adr or KBv200 cell xenografts, co-administration of tetrandrine increases the anticancer activity of doxorubicin and vincristine without a significant increase in toxicity. Hence, tetrandrine holds a great promise as a MDR as 5-fluorouracil and cisplatin, in vitro or in vivo It enhances tamoxifen-induced antiproliferation by inhibiting phosphoinositide-dependent kinase 1.Tetrandrine also

enhances the radio sensitivity of various cancer cells mainly by affecting the radiation-induced cell cycle arrest and redistributing the cell cycle .All these observations are rational evidence supporting the application of tetrandrine as an adjunct for cancer chemotherapy or radiotherapy.



Tetrandrine

Side effects:-

Berberine :- side effects of include anaphylaxis, constipation, and skin allergies Berberine can displace bilirubin from serum-binding proteins and cause kernicterus, jaundice, and brain damage in infants Neurotoxicity, immunotoxicity,[12-14]

Piperine:- Reproductive toxicity induced by piperine have been reported and hepatotoxicity and embryonic toxicity [12-14].

Sanguinarine:- hepatotoxicity and embryonic toxicity .Therefore, alkaloids isolated from natural herbs are not always safe. The dosages, the routes of administration and the treatment procedures, among others, are very important. The transformation of chemical structures and the application of new drug delivery systems may reduce the toxicities of these compounds [12-14].

Finally, though there are several clinical studies of the alkaloids for the treatment of other diseases, for example, berberine for the treatment of diabetes or metabolic syndrome, there is no report about the clinical trial for cancer prevention or treatment using the aforementioned alkaloids. As there is a big jump from experiment researches to clinical ones, it is necessary to carry out some clinical anticancer trials for these alkaloids, such as berberine and tetrandrine.

Other Alkaloids with Anticancer Effects

Aside from the aforementioned alkaloids, other alkaloids such as chelerythrine isolated from Toddaliaasiatica (L.) Lam, chelidonine isolated from Chelidoniummajus L., fagaronine isolated from Fagarazanthoxyloides Lam., lycorine isolated from Lycoris, nitidine chloride isolated from Zanthoxylumnitidum (Roxb.) DC., solanine isolated from Solanumtuberosum, sophocarpine isolated from Sophoraalopecuroides L., trigonelline isolated from trigonellafoenum-graecum also present anticancer potentials with diversiform mechanisms [11]. However, reports on the anticancer activities and underlying mechanism of actions of these compounds are limited

DISCUSSION

In this paper, we summarized the recent progress of several typical alkaloids with anticancer activities and presented some characteristics of these compounds. On the basis of the previous studies, alkaloids with anticancer activities reflect diversity at least in three aspects.

First, the source of alkaloids with anticancer potentials is very extensive. Most of the aforementioned alkaloids are from different families, and the biosynthesis of these compounds is also varied. For example, berberine is isolated from Ranunculaceae and roots in phenylalanine and tyrosine, whereas evodiamine is isolated from Rutaceae and roots in tryptophan [1]. Second, the pharmacological activities of these alkaloids are varied [11, 12, 14]. For instance, piperine and berberine are used to treat epilepsy and diarrhea, respectively [15,16], and both of these compounds show anticancer and other pharmacological effects. Third, the research focuses of these anticancer alkaloids are also very different. Research on piperine is usually focused on cancer prevention whereas that on most other alkaloids is mainly focused on cancer chemotherapy, especially on the evaluation of antiproliferative activity [12,37,].

Berberine, evodiamine, matrine, piperine, sanguinarine, and tetrandrine restrain cancer by modulating multiple signaling pathways, resulting in the inhibition of the initiation of carcinogenesis, induction of cell cycle arrest, apoptosis, autophagy, or differentiation, and inhibition of metastasis, angiogenesis.

In addition to their diversity, the anticancer alkaloids also have several other characteristics or/and issues which should be addressed. First, the range of alkaloid concentration necessary to elicit the anticancer effects is wide [4, 5, 12,]. The needed concentration is relatively higher for most of the aforementioned alkaloids to produce anticancer effects, compared with the widely used chemotherapeutic drugs such as CPT [5] and vinblastine [4], although both are also naturally derived alkaloids. The concentration of matrine used to produce anticancer effects even reaches millimole. Therefore, modification of the compound via chemical methods may be a good strategy. This observation also indicates that combination therapy probably provides an optimal venue for the clinical application of these compounds because most of these alkaloids exhibit synergistic or enhancement effects when combined with chemotherapeutic drugs in both in vitro and in vivo experiments.

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