Natural alkaloids: basic aspects, biological roles, and future perspectives

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[ABSTRACT] Natural products have gained popularity worldwide for promoting healthcare, as well as disease prevention. Alkaloids are important chemical compounds that serve as a rich reservoir for drug discovery. Several alkaloids isolated from natural herbs exhibit antiproliferation, antibacterial, antiviral, insecticidal, and antimetastatic effects on various types of cancers both in vitro and in vivo. This paper focuses on the naturally-derived alkaloids such as berberine, matrine, piperine, fritillarine, and rhynchophylline, etc., and summarizes the action mechanisms of these compounds. Based on the information in the literature that is summarized in this paper, the use of alkaloids as drugs is very promising, but more research and clinical trials are necessary before final recommendations on specific alkaloids can be made. Following this, it is hoped that as a result of this review, there will be a greater awareness of the excellent promise that natural alkaloids show for use in the therapy of diseases.

[KEY WORDS] Natural product; Alkaloids; Biological roles; Health benefits


Introduction

Natural products have provided considerable impetus to the discovery of drugs. In particular, the therapeutic areas of infectious diseases and oncology have benefited from numerous drug classes derived from natural product sources. Many new and interesting molecules with biological activity have been published in the past few years. Recently, natural products from traditional Chinese medicine (TCM) have become important sources for drug discovery. The status of current compound libraries and databases in China are large-scale, high-quality, comprehensive, standard, open-access, and are integrated with quality control systems, drug screening, and discovery platforms [1]. The natural products and natural products-derived compounds that have undergone clinical evaluation or registration from 2005 to 2010 by disease area, i.e. infectious, immunological, cardiovascular, neurological, inflammatory and related diseases and oncology have been reviewed [2]. As natural products continue to be evaluated for desirable therapeutic activities, significant progress in identifying new antibiotics, oncology therapeutics and other useful medicines will be made [3].

Alkaloids are present in nature primarily as a class of nitrogen-containing organic compounds in plants, fungi, bacteria, and 3 organisms. They possess significant biological activities, frequently being one of the important active ingredients in Chinese herbal medicine. With advances in the separation of natural products, and the continuing emergence of new technologies and methods, the development of alkaloid chemistry has expanded. The vast majority of alkaloids are present in higher plants, especially in dicots, and a few exist in the lower plants [4]. Alkaloids can be classified by the source combined with chemical structures, like cuscohygrine, a pyrrolidine alkaloid derived from ornithine. Leonurine is a prominent pharmacologically active guanidine alkaloid, being commonly regarded as the predominant active principle of Leonurus and Leonotis drugs. Its presence has only been unambiguously proven for the aerial parts of Leonurus japonicus Houtt. [5] Leal et al. found a decreasing

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trend in the discovery of new alkaloids between 2000 and 2009, contrasting with an increasing number of new terpenoids [6]. Alvarado et al. have reported that a sponge of the Spongosorites, which contains the nortopsentin and topsentin class of bisindole imidazole alkaloids, exhibits potent inhibition of *Plasmodium falciparum* growth [7]. The evaluation of basic, biological roles, and health benefits arising from the study of alkaloids can provide important information for future pharmaceutical research. In the present study, the trends associated with the discovery of natural alkaloids from a pharmacology and drug efficacy perspective are discussed.

**Background**

**Berberine**

Berberine (Fig. 1a) is an isoquinoline alkaloid isolated from Chinese herbs such as *Coptidis Rhizome*. It has been used for the treatment of diarrhea and other gastrointestinal infections as an antibacterial drug. In recent years, it was reported to have beneficial effects on the metabolism disorders states of diabetes. The mechanisms of action are diverse, such as regulating blood cholesterol and triglyceride, lowering blood glucose, ameliorating the insulin resistant state and influencing the function of the pancreatic beta cell [8]. Recently, berberine has been reported to possess anticancer activities. Among the various cellular targets of berberine is AMP-activated protein kinase (AMPK), which regulates tumor progression and metastasis. Berberine decreased the migration of SW480 and HCT116 cells, and activated AMPK in human colon cancer cell lines. Notably, berberine-induced activation of AMPK, reduced the integrin β1 protein levels, and decreased the phosphorylation of integrin β1 signaling targets [9].

**Matrine**

Matrine (Fig. 1b), one of the main active components of the extracts of the dried roots of *Sophora flavescens*, has a significant anti-inflammatory, anti-arrhythmic, and anti-fibrotic effects. Furthermore, matrine significantly inhibited the expression and reduction in the central nervous system of ICAM-1 and VCAM-1, key adhesive molecules and chemokines [10]. Li et al. found that matrine protects against isoproterenol-induced myocardial infarction through the eNOS and asymmetric dimethylarginine pathway [10]. In recent years, matrine was also found to have anticancer effects, such as inhibiting proliferation, inducing differentiation and apoptosis in a dose and time-dependent manner, reducing invasion and metastasis of tumor cell. Matrine could be used as an effective antitumor agent in therapy of osteosarcoma by targeting the caspase-dependent signaling pathway [12-13].

**Fritillarine**

Verticine (Fig. 1c), verticinone (Fig. 1d), imperialine, imperialine-3β-D-glucoside, and puqietinone (Fig. 1e), purified from Bulbus Fritillariae which is used as an antitussive drug in TCM. A study suggested that the five alkaloids could significantly elevate the cAMP concentration in HEK cells transfected with muscarinic M(2) receptor plasmid [14]. Ebeinine and zhebeinine, which were isolated for the first time from *Fritillaria hupehensis*, were assayed for cytotoxic effects towards the HeLa and HepG2 cell lines. It showed significant inhibitory effects against both types of tumor cells [15]. *Fritillaria thunbergii* Miq. has been traditionally used in China as an antitussive and expectorant, and is newly used in the clinical treatment of leukemia. Verticinone, a major alkaloid isolated from the bulbs of *Fritillaria ussuriensis*, has been shown to induce differentiation in human leukemia cells [16]. It may induce apoptosis through the caspase pathway mediated by mitochondrial damage in immortalized keratinocytes and oral cancer cells [17].

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**Fig. 1** Structures of (a) berberine, (b) matrine, (c) verticine, (d) verticinone, and (e) puqietinone
Rhynchophylline

Rhynchophylline (Fig. 2a) is a neuroprotective agent isolated from the Chinese medicinal herb Uncaria rhynchophylla used in treatment of disorders of the central nervous system. Rhynchophylline is beneficial for the treatment of the psychological dependence on amphetamines, as the down regulation of n-methyl-D-aspartate receptor. The effects of rhynchophylline on the proliferation of PC12 cells were also investigated [19]. It was demonstrated that rhynchophylline suppresses GluA2/3 expression and downregulates GluN1 expression. Dai et al. had found that phyncho- phylline might promote the apoptosis of vascular adventitial fibroblasts in the thoracic aorta of spontaneously hypertensive rats by regulating the protein expressions of Bcl-2 and Bax. It also can improve the thoracic aorta wall reconstruction and decrease the tail arterial systolic pressure by attenuating the deposition of extracellular matrix [19-20]. Rhynchophylline and isorhynchophylline may be effective therapeutic candidates for use in the treatment of neurodegenerative diseases accompanied by microglial activation [21]. The potential molecular mechanism for rhynchophylline or isorhynchophylline-mediated attenuation was implicated in the suppression of iNOS protein level, phosphorylation of ERK and p38 MAPKs, and degradation of Ik Bα.

![Fig. 2 Structures of (a) rhynchophylline, (b) piperine, (c) jatrorrhizine, and (d) marine](image)

Jatrorrhizine

Jatrorrhizine (Fig. 2c), a novel tetrahydroisoquinoline alkaloid, is one of the protoberberine alkaloids derived from the plant Coptis chinensis, has been used for the treatment of a variety of diseases. It is expected to be developed as a new gastric prokinetic drug, and its metabolic characteristics in humans have been studied. Jatrorrhizine is metabolized by human CYP1A2 and multiple UGT1A isoforms [26]. Luo et al suggest that jatrorrhizine protects neuronal-like cells against H2O2-induced toxicity. It also was shown to suppress the activation of caspase-3 induced by Apoptosis and prevented cytochrome c transport into the cytosol, demonstrating the neuroprotective effects against Apoptosis-induced injury via the antioxidative potential, which may indicate a therapeutic potential for Alzheimer's disease [27].

Marine alkaloids

The marine ecosystem and its organisms produce a large group of structurally unique natural products encompassing a wide variety of alkaloids, having diverse pharmacological activities. Manzamines are a unique class of β-carboline marine alkaloids with an unusual tetra- or pentaacyclic system. They have shown a variety of bioactivities against malaria, infectious diseases, cancer, and inflammatory diseases. Three new alkaloids, hyrtimomines A-C, were isolated from an Okinawan marine sponge Hyrtios sp. [29]. Hyrtimomines A and B are heteroaromatic alkaloids possessing a fused hexacyclic ring system, while hyrtimomine C is an alkaloid consisting of hydroxyindole and azepino-hydroxyindole moieties. Hyrtimomine A exhibited cytotoxicity against KB and L1210 cells [29]. It is normal that nitrogen-containing pyrroles, indoles, carbolines, tryptamines, tyrosines, and tyramines are excellent platforms for biohalogenation, particularly in the marine environment. Natural organohalogens of all types, especially marine halogenated alkaloids, comprise a rapidly expanding class of natural products, in many cases expressing powerful biological activity [30-31].

Other Alkaloids

Vincristine (VCR, Fig. 3a), which is a widely used antineoplastic drug, was integrated with a submicron-emulsion drug-delivery system to enhance the anticancer effect [32]. A new aporphine alkaloid, vireakine, along with two known alkaloids stephanine and pseudopalmaritine, described for the first time in Stephania rotunda, and five known alkaloids tetrahydropalmaritine (Fig. 3b), xylopinine (Fig. 3c), roemerine (Fig. 3d), cepharanthine (Fig. 3e), and palmaritine (Fig. 3f) were identified. The alkaloids were evaluated for their in vitro antiplasmodial and cytotoxic activities [33]. Chen et al have tested a series of benzylisoquinoline and phenanthrene alkaloids for their antiplatelet and vasorelaxing actions [34]. Zeph-grabatine has seven cytotoxic activities. A dose dependent cytotoxic effect was exhibited by all of the alkaloids on the cancer cell lines with lycorine (Fig. 3g) and haemanthamine showing prominent activity [35].
Biological Roles

Antitumor activity

Cancer is a major killer disease all over the world and more than six million new cases are reported every year. Alkaloids have played an important role in the development of several clinically useful anti-cancer agents. The Catharanthus alkaloids are established as antimitotic agents, inhibiting the polymerization of tubulin, like vinblastine. Structure-activity relationships indicate that electron-withdrawing substituents on the ring contribute to the enhancement of the antitumor activities [36]. Elamin MH et al. have shown that curcumin has cytotoxic effects on medulloblastoma cells, and suppressed cell proliferation and triggered cell-cycle arrest at G(2)/M phase. Furthermore, curcumin inhibited the Shh-Gli1 signaling pathway by down-regulating the Shh protein, and represents great promise as Shh-targeted therapy for medulloblastomas [37]. Berberine could decrease the migration of SW480 and HCT116 cells. Berberine-induced AMPK activation inhibits the metastatic potential of colon cancer cells by decreasing integrin β1 protein levels and downstream signaling [38]. Rizo et al. have tested the cytotoxic activity of the indole alkaloids heyneanine, coronaridine, and voacangine against HeLa and B-1 cell lines [39]. Results suggest that further investigation of coronaridine as an antitumor agent has merit.

Central nervous system effects

Sotoing et al. had examined the alkaloid fraction prepared from the leaves of Crassocephalum bauchiense (Hutch.) Milne-Redh (Asteraceae) which possessed antipsychotic and sedative properties in rodents. It suggested that the alkaloid fraction from C. bauchiense could cause dose-dependent inhibition of rearing behavior, decrease the apomorphine-induced stereotypy and fighting, and produced a significant fall in the body temperature [41]. Exposure to high altitudes can cause neurological dysfunction due to decreased oxygen availability to the brain. A study suggests that huperzine A supplementation can improve cognitive deficits, reduce oxidative stress, and inhibit the apoptotic cascade induced by acute hypobaric hypoxia [42]. A research study investigated the effects of strictosidinic acid isolated from Psychotria myriantha Müll.-Arg. (Rubiaceae) leaves, on monoamine levels in the rat hippocampus and on monoamine oxidase activity [43]. Stricosidinic acid seems to act on the 5-HT system in the rat hippocampus, possibly inhibiting precursor enzymes of 5-HT biosynthesis.

Anti-inflammatory effects

Oxymatrine is extracted from the traditional Chinese herb Sophora flavescens Ait., and possesses anti-inflammatory, anti-oxidative and anti-apoptotic properties, and has been used for the treatment of chronic viral hepatitis and many other diseases. The effect of oxymatrine on inflammation is mediated by toll-like receptor4 (TLR4) and nuclear factor kappa-B (NF-xB) oxidative injury. Oxymatrine at 120 mg·kg⁻¹ following ICH inhibits inflammatory responses, oxidative injury, and neuronal cell apoptosis [44]. Lee et al. found that lycorine has inhibited LPS-induced production of pro-inflammatory mediators, suggesting that lycorine could play an anti-inflammatory role in response to LPS [45]. Ace-tylcorynoline, a major alkaloid component derived from Corydalis bungeana, has the capability to regulate lipopolysaccharide-stimulated activation of mouse bone marrow, which are major modulators in the immune system [46].

Antibacterial and antiviral insecticidal effects

A study has showed that the benzol[c]phenanthridine alkaloids effectively inhibited the growth of Mycocystis.
Clinical drug-resistant yeast isolates [48]. The results provided important information for the potential application of the 8-hydroxylated alkaloids from C. majus in the therapy of serious infection caused by drug-resistant fungi. Harringtonine, a cephalotaxane alkaloid, displayed potent inhibition of CHIKV infection with minimal cytotoxicity, and was selected for elucidation of its antiviral mechanism. Harringtonine exerts antiviral effects by inhibiting CHIKV viral protein synthesis [49].

**Hypoglycemic effects**

Piperine, the major alkaloid in *Piper nigrum* (black pepper), has been studied for effects on blood glucose level in alloxan-induced diabetic mice. Piperine has statistically significant anti-hyperglycemic activity, while acutely it raises blood glucose at high doses [50]. Berberine has been demonstrated to possess anti-diabetic activities. Berberine affects the AMP-activated protein kinase (AMPK)/glucose-neogenesis pathway, and could suppress hepatic gluconeogenesis in a rat model of diabetes at least in part through stimulation of AMPK activity [51]. Nguyen et al. found that nuiferine, extracted from *Nelumbo nucifera*, can stimulate both phases of insulin secretion in isolated islets. It was found to stimulate insulin secretion by closing potassium-adenosine triphosphate channels [52].

**Future Perspectives**

Natural alkaloids derived from plants may be lead compounds, and have begun to gain popularity worldwide for promoting health care as well as disease prevention [53-55]. They offer a diverse range of structurally distinctive bioactive molecules, have been used as a major source of innovative and effective therapeutic agents. In-depth study on metabolic transformation, efficacy and safety of alkaloids, will accelerate their natural resource development and utilization of alkaloids. Furthermore, the biological screening of active alkaloids, using a wide variety of scientific tools and the in vitro methods will become research hotspot, providing new and essential healthcare opportunities.

**References**


al cells and the molecular mechanism [J]. *Int Immunopharmaco-


[23] Nirmal SA, Ingale JM, Pattan SR, et al. *Amaranthus roxburgh-


[26] Wang X, Cheng N. CYP450 1A2 and multiple UGT1A isoforms are responsible for jatrorrhizine metabolism in human liver micro-


[33] Baghdikian B, Mahiou-Leddet V, Bory S, et al. New antiplas-


ified Vinca alkaloids as antmitotic agents based on pharmaco-


[38] Park JJ, Seo SM, Kim EJ, et al. Berberine inhibits human colon cancer cell migration via AMP-activated protein kinase-mediated downregulation of integrin β1 signaling [J]. *BiochimBio-