Review

Protein kinases as therapeutic targets to develop anticancer drugs with natural alkaloids

Hanlin Ye[1], Linlin Wang[1], Li Ma[2], Maksim Ionov[3], Gan Qiao[1], Jianlin Huang[1], Li Cheng[1], Yuxi Zhang[1], Xiaohui Yang[1], Shousong Cao[1,*], Xiukun Lin[1,*]

[1]*Department of Pharmacology, School of Pharmacy, Southwest Medical University, 646000 Luzhou, Sichuan, China,* [2]*Rizhao Hospital of Traditional Chinese Medicine, 276826 Rizhao, Shandong, China,* [3]*Department of General Biophysics, Faculty of Biology and Environmental Protection, University of Lodz, 90-236 Lodz, Poland*

TABLE OF CONTENTS

1. Abstract

Backgroud: Protein kinases play an important role in cell proliferation, differentiation, mobility and cell cycle arrest etc. These enzymes act as important targets in developing anticancer agents. Over the years, a large number of protein kinase inhibitors have been discovered and developed as anticancer agents for the treatment of cancers clinically. However, the drug-resiatance and off-targeting limit their effeciancy for the treatment of human cancer. **Materials and methods**: Alkaloids are an important class of natural products with broad spectrum biological activities. In the past decades, numerus alkaloids with significant anticancer activity by inhibiting protein kinases were identified. In the present mini-review, we will present the key enzymes including mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) and janus-activated kinases/signal transducer and activator of transcription (JAK/STAT) targeted by alkaloids and highlight the special sites targeted by alkaloids on protein kinases and/or reversing drug resistance. Additionally, the challenge and prospect of developing alkaloids as new anticancer agents are also discussed. **Conclusion**: Alkaloids suppressed tumor growth through targeting different signaling pathways mediated by protein kinases of cancer cells. It is conceivable that novel alkaloids anticancer agents with promising clinical value will be developed in the future.

2. Introduction

Protein kinases catalyze the transfer of a phosphate group to a specific amino acid in a protein molecule. Since the phosphate groups are charged negatively, the 3D structures of the specific protein will be changed when adding the phosphate group, leading to activation and inactivation of the specific proteins. There are several kinds of protein kinases with different selection towards substrates, and tyrosine protein kinases and serine threonine protein kinases are the main subfamilies [1]. It is well established that protein kinases function as a kind of important regulators in cellular events involving DNA damage-repair, cell proliferation, motility and apoptosis, etc. [2, 3]. Most protein kinases such as PI3K, Akt, EGFR and MAPK are usually highly expressed and/or activated in tumor cells, and these enzymes have been acted as major targets in developing novel anticancer agents [4]. Nowadays, almost a quarter

Submitted: 30 May 2021 Revised: 25 July 2021 Accepted: 29 September 2021 Published: 30 November 2021

of all newly developed anticancer drugs belongs to protein kinase inhibitors. Gefitinib (Iressa), a selective EGFR inhibitor, was approved in 2015 by the US Food and Drug Administration (FDA) to treat non-small cell lung cancer [5, 6]. In 2005, a multi-target tyrosine kinase inhibitor, Sorafenib (Nexavar; Onvx/Bayer), was approved by FDA to treat advanced primary liver cancer and primary kidney cancer (advanced renal cell carcinoma) [7–9]. However, the off-targets and drug resistance of protein kinase inhibitors limit their efficiency and application in the treatment of cancer patients [10, 11]. Therefore, it is urgent to develop novel agents overcoming the drawback of protein kinase inhibitors.

Alkaloids, a class of nitrogen-containing organic compounds usually with complex ring structures, are widely distributed in natural organisms. Alkaloids display diverse biological activity, including antiviral, antimicrobial, antinflammatory, and anticancer etc. [12]. Over the past decades, a large number of alkaloids have been applied clinically for the treatment of different malignant tumors [13, 14]. Taxol and vincristine, a kind of microtubule inhibitors are used to treat human cancers [15, 16]. Irinotecan and topotecan developed from camptothecin are also commonly used in cancer treatment [17]. Over the years, numerous alkaloids have been found as protein kinase inhibitors, and some of them display potent anticancer activity [18]. We discussed and highlighted the therapeutic targets according to their pathways (Fig. 1) and the special sites targeted by alkaloids on protein kinases and/or reversing drug resistance. In addition, the challenge and prospect of developing alkaloids as new anticancer agents were also presented in this mini-review.

3. Targeting MAPK pathway

MAPK, a class of serine-threonine kinases, mediates intracellular signal transduction related to cell proliferation, differentiation, death, survival and transformation [19]. The classical MAPKs consist of extracellular signal-regulated kinase (ERK), p38 MAPK and c-Jun NH2-terminal kinases (JAK)/stress-activated protein kinases (SAPK). There are many subtypes of these kinases, including ERK1-8, p38-α, -β, -γ–δ, and JNK1-3 [20, 21]. ERK1/2 are the ultimate components of the cell signal cascade of Ras/Raf/MEK/ERK signal [22]. ERK1/2 are able to phosphorylate more than 250 known substrates that regulate a variety of biological functions, including cell proliferation, gene transcription, cell cycle progression, migration, adhesion, survival and metabolism [23]. p38 MAPK is usually activated by the upstream MKK3 and MKK6 kinases, and sometimes by MKK4. Activated p38 MAPK plays an important role in cell growth, cell cycle arrest, apoptosis and differentiation [24]. Therefore, these molecules have become important targets for anticancer agents.

Over the years, numerous alkaloids affecting MAPK signaling have been identified. Dehydrocorydaline (DHC) (Fig. 2), an isoquinoline alkaloid isolated from *Corydalis yanhusuo*, *Corydalis tuber* or *Corydalis bulbosa* [25], displays diverse biological activities, including inhibition of antibody-mediated and cell-mediated allergy, inhibition of proinflammatory cytokine expression, and promotion of myoblast differentiation [26]. In recent years, the anticancer effects of DHC attract great attention; DHC was able to induce apoptosis [27], and inhibit tumor metastasis [28]. Recent study showed that DHC could inhibit the proliferation and metastasis of melanoma cells by down-regulating the MEK1/2-ERK1/2 cascade and the phosphorylation levels of MEK1/2 and ERK1/2 were down-regulated by DHC in a time-and dose-dependent manner [29]. DHC significantly inhibited the proliferation of melanoma cells with IC_{50} values of 39.73 μM. DHC was also capable of inhibiting the cell cycle-related proteins, including CDKs and cyclins, leading to cell arrest at G_0/G_1 phase in malignant melanoma.

Aconitum szechenyianum Gay, a traditional Chinese medical herb, is used to treat inflammation related diseases in China for more the 500 years [30]. Its extract displays potent anticancer activity in several cancer cells including hepatoma SMMC-7721, gastric cancer SGC-7901 and esophageal cancer Eca-109 cells both *in vitro* and *in vivo* [31]. Recent studies showed that the extracts of *Aconitum szechenyianum Gay* were able to induce apoptosis *via* targeting p38 MAPK pathway in hepatoma HepG2 cells, cervical cancer Hela cells and lung cancer A549 cells; treatment with the extract down-regulated the level of p38 MAPK phosphorylation, and induced mitochondria-dependent apoptosis. Four alkaloids (Fig. 2) responsible for the anticancer effect were isolated from its dried roots including 3-acetylaconitine ($C_{36}H_{49}NO_{12}$), songorine ($C_{22}H_{31}NO_3$), aconitine ($C_{34}H_{47}NO_{11}$) and deoxyaconitine ($C_{33}H_{45}NO_{10}$) [32].

3α-acetonyltabersonine (Fig. 2), an indole alkaloid and isolated from *Melodinus suaveolens*, showed potent anticancer effect against human promyelocytic leukemia HL-60, human liver cancer SMMC-7721, human lung cancer A549, human breast cancer MCF-7 and human colon cancer SW480 cells with IC_{50} values of 0.2–0.6 μM [33, 34]. Recent study showed that the compound is capable of inhibiting DNA damage-repair through MAPK pathway in glioblastoma U87 and T98G cells with the IC_{50} values of 1.7 μM and 4.3 μM, respectively [35]; treatment of glioblastoma U87cells with the compound led to phosphorylation of JNK and ERK, resulting in cumulative DNA damage.

Several alkaloids including isoliensinine (Fig. 2), liensinine (Fig. 2), and neferine (Fig. 2), are isolated from the seed embryo of lotus (*Nelumbo nucifera Gaertn*), and display potent anticancer activities in several cancer cells [36–38]. Neferine inhibited the proliferation of hu-

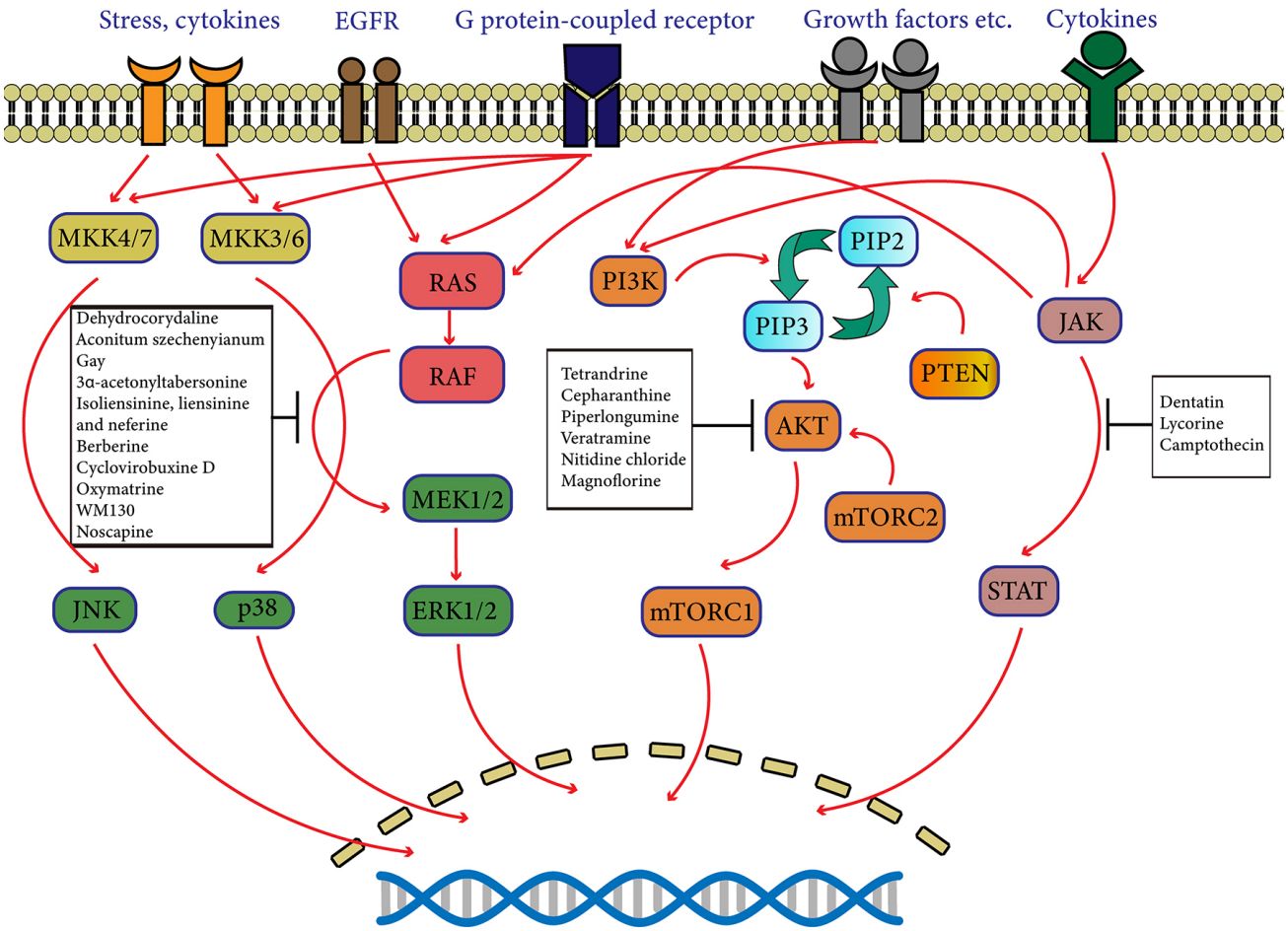

Fig. 1. Schematic diagram of protein kinase pathways targeted by natural alkaloids. The protein kinase pathways including MAPK, PI3K/AKT/mTOR, JAK/STAT pathways play a significant role in the proliferation, survival and differentiation of cells. Natural alkaloids are able to interfere with some specific molecules related to protein kinase.

man osteosarcoma cells by inducing G1 phase arrest [36]. Isoliensinine induced apoptosis in triple negative human breast cancer cells through targeting p38 MAPK and JNK pathways [38]. Treatment with isoliensinine (20 μM) resulted in increased expression of the phosphorylation of p38 and JNK in human breast cancer MDA-MB-231, MDA-MB-436, and MDA-MB-468 cells. The results suggested that isoliensinine may be developed as a novel anticancer agent for the treatment of breast cancer. Berberine (BBR) (Fig. 2), an isoquinoline alkaloid, is extracted from *Coptis chinensis*. BBR exhibits broad pharmacological effects, such as antinflammatory, anti-diabetes, antibacterial, liver protection, neuroprotection and so on [39]. In recent years, it has been proved to be a promising anticancer agent for the treatment of colon cancer, breast cancer, ovarian cancer, melanoma, adhesive tape blastoma and leukemia [40]. BBR inhibited the proliferation, invasion and metastasis of different cancer cells by inducing apoptosis, cell cycle arrest and autophagy in cancer cells. BBR was able to inhibit the growth of human non-small cell lung cancer A549 and PC-9 cells with the IC_{50}values of 58.33 μM and 49.00 μM, respectively. Recent study confirmed that berberine induced apoptosis through p38 MAPK and JNK pathways, treatment with BBR (80 μM) led to down-regulation of the expression of p-p38 MARK and p-JNK in non-small cell lung cancer [41].

4. Targeting PI3K/AKT/mTOR pathway

PI3K/AKT/mTOR pathway, activated by tyrosine kinase receptor or other cytokines, plays an essential role in regulating cell proliferation, growth, survival, exercise, metabolism and immune response [42, 43]. It is well documented that PI3K/AKT/mTOR pathway is over activated in up to 60% of cancers [44]. The activation of PI3K/AKT/mTOR pathway promotes uncontrolled proliferation, genomic instability and metabolic reprogramming of cancer cells [45]. Over the years, numerous anticancer agents are used for the treatment of human malignancies in clinic via inhiting PI3K/mTOR signaling pathway.

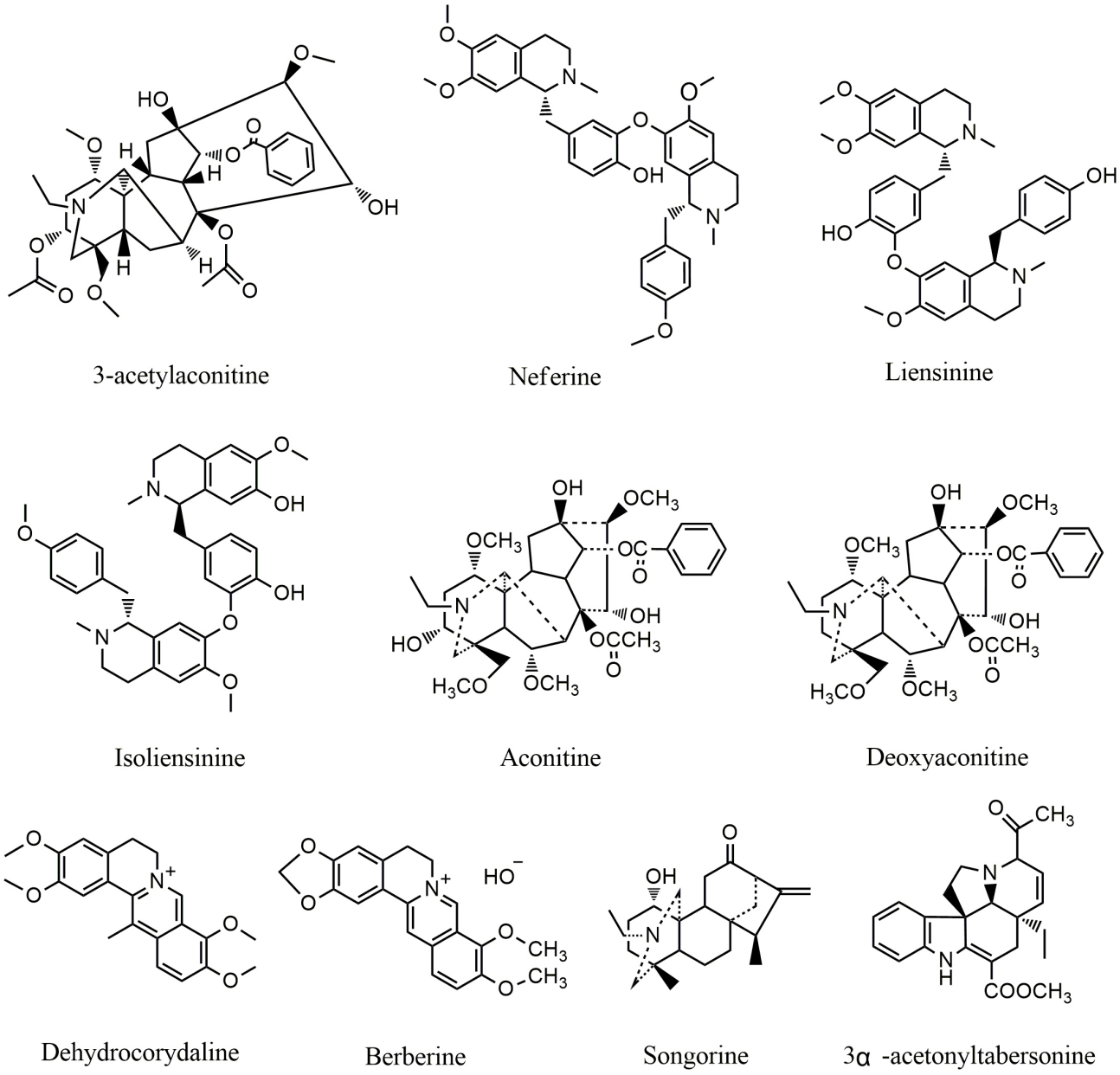

Fig. 2. Chemical structures of alkaloids targeting MAPK pathway.

Tetrandrine (TET) (Fig. 3), a bisbenzylisoquinoline alkaloid and calcium channel blocker isolated from *Stephania tetrandra S.Moore*, is used for the treatment of silicosis and rheumatoid arthritis as a traditional Chinese medicine [46]. Recent studies have shown that PI3K/AKT/mTOR Pathway plays a critical role in TET induced apoptosis in several cancer cells; treatment of human gastric cancer cells with TET resulted in inactivation of AKT/mTOR phosphorylation [47]. TET was also capable of inducing autophagy *via* targeting PI3K/AKT signaling in MCF-7 and MDA-MB-231 cell [48]. Clinical trial showed that the combination of TET and traditional cancer drugs including daunorubicin, etoposide and cytarabine (150 mg/m^2) was effective in the treatment of multidrug resistant acute myeloid leukemia, pretreatment with TET (2 mg/kg) and daunorubicin, etoposide, and cytarabine resulted in around 42% complete remission and the p-glycoprotein was decreased significantly in the tumors of acute myeloid leukemia patients [49]. Cepharanthine (CEP) (Fig. 3), another kind of bisbenzylisoquinoline alkaloid, is isolated from *Stephania cepharantha Hayata* [50]. CEP (15 μM) induced apoptosis and inhibited proliferation significantly in human leukemic Jurkat T cells. Both MAPK and PI3K/AKT/mTOR pathways play a key role in anticancer effect of CEP, treatment with CEP (15 μM) inhibited the expression of p-PI3K and p-mTOR and upregulated the expression of p-JNK and p-p38 in leukemia Jurkat T cells [51].

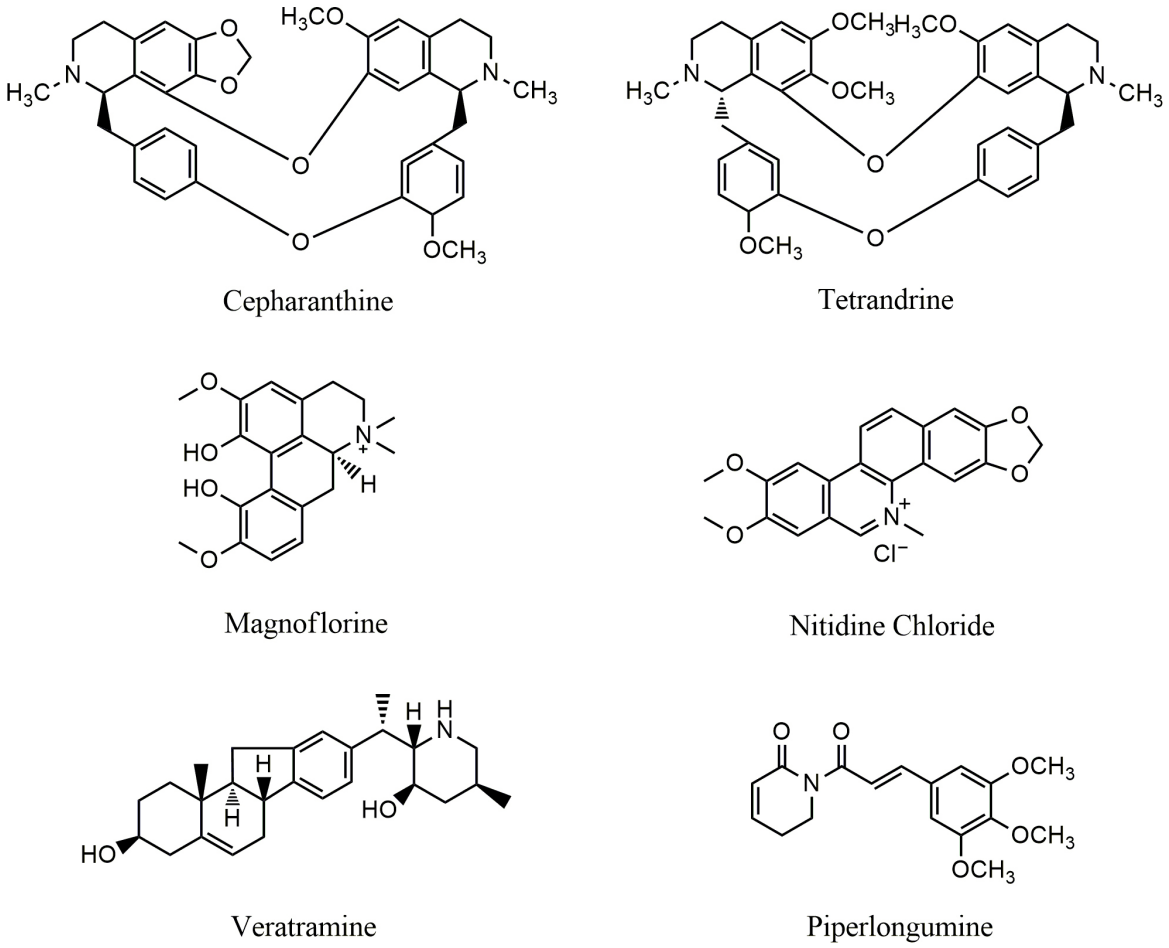

Fig. 3. Chemical structures of alkaloids targeting PI3K/AKT/mTOR pathway.

Piperlongumine (Fig. 3), a natural pyridine alkaloid, is extracted from *Piper longum* [52]. Studies have shown that piperlongumine displays broad biological activities including antianxiety, antiangiogenic, antidepressant, anticancer, antibacterial, and antidiabetic activities [53]. Piperlongumine exhibits strong cytotoxicity in various cancer cells, but it does little harm to normal human cells [54]. PI3K/AKT/mTOR play an important role in piperlongumine induced apoptosis; treatment with the compound led to down-regulation of p-Akt and p-mTOR in both A549 and U937 cancer cells [55, 56]. Studies also found that p38 was involved in piperlongumine-induced cancer cell growth inhibition; treatment with the compound (20 μM) up-regulated the expression of p-p38 [57]. The combination of piperlongumine with chemetherapeutic agents such as doxorubicin and cisplatin increased the sensitivity of cancer cells significantly [58]. Piperlongumine combined with TRAIL (TNF related apoptosis inducing ligand) or p53 activator APR-24 showed synergistic anticancer potential in several human cancer cells including human colon cancer HT-29, prostate cancer DU145, breast cancer MDA-MB-231, and head and neck squamous carcinoma (HNSC) cells [59].

Veratramine (Fig. 3), a natural steroidal alkaloid, is isolated from the plants of lily family [60, 61]. Veratramine is able to inhibit cell growth both *in vitro* and *in vivo via* targeting PI3K/Akt/mTOR; treatment with veratramine (19.81 μM) resulted in down-regulation of the phosphorylation levels of PI3K, AKT and mTOR in a concentration-dependent manner in liver cancer HepG2 cells [62]. *In vivo* study showed that the compound was capable of inhibiting the tumor growth significantly with low toxicity for the mice without obvious affection on blood cell count, body weight, and liver and kidney function [62].

Nitidine chloride (NC) (Fig. 3), a benzoanthraquinone alkaloid isolated from *Zanthoxylum nitidum (Roxb) DC*, shows significant anticancer activity against a variety of cancer cells including ovarian cancer, colorectal cancer, liver cancer, and renal carcinoma [63–66]. NC treatment led to down-regulation of AKT phosphorylation and suppressed the metastasis of renal cell carcinoma 786-O and A498 cells as well as glioblastoma U87 and U251 cells [63]. NC also inhibited the activation of STAT3 and ERK pathways and suppressed the expression of Bcl-2, Bax, cyclin D1, CDK4, VEGF-A and VEGFR2 in human hepatocellular carcinoma HepG2, HCCLM3, and Huh7 cells

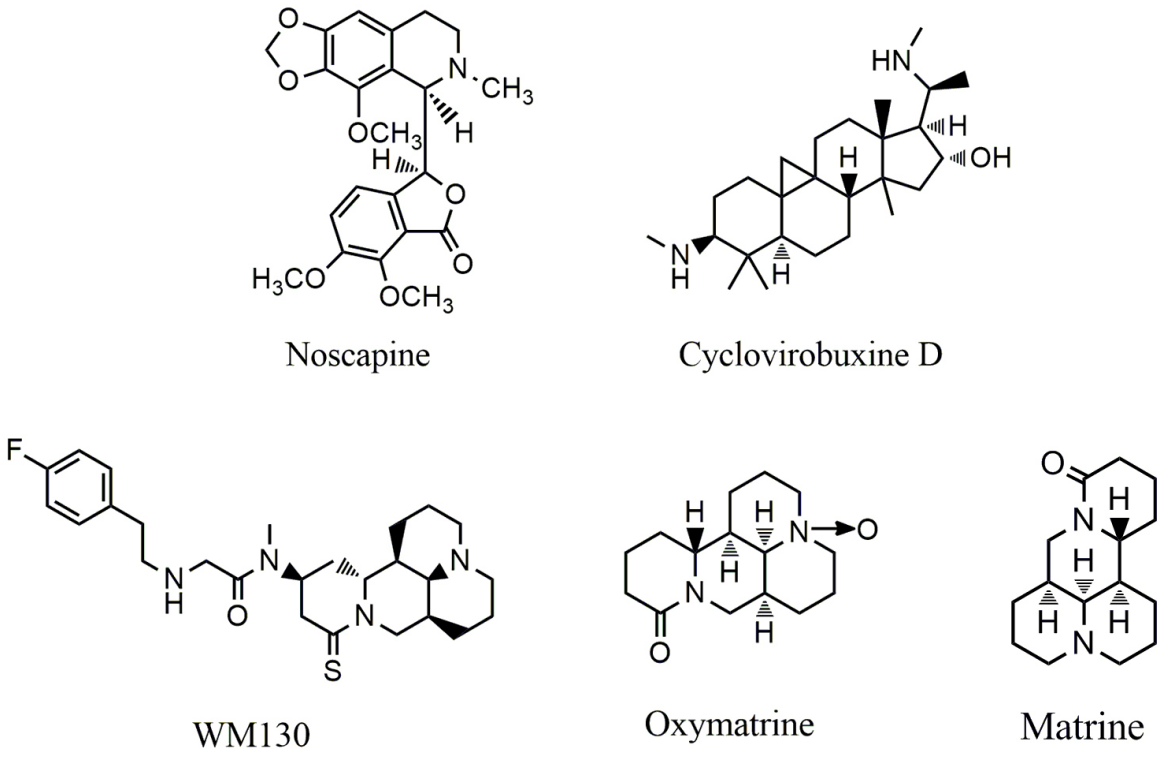

Fig. 4. Chemical structures of alkaloids that target epidermal growth factor receptor (EGFR).

[64]. Magnoflorine (MAG) (Fig. 3), an apomorphine alkaloid, is isolated from *Coptidis Rhizoma* [67]. MAG exhibits wide spectrum activities including anti-inflammatory, anti-anxiety, anticancer etc. [68, 69]. MAG induced apoptosis and autophagy *via* targeting AKT/mTOR and p38 MAPK pathways [70]. Treatment with MAG led to decreased expression of p-PI3K, p-AKT and p-mTOR. *In vivo* study showed that MAG inhibited the growth of MCF-7 tumors bearing in nude mice and reduced the side effects of doxorubicin (DOX) in experimental animals. The tumor inhibitory rate has been increased from 30% (DOX alone) to 70% when the mice were treated with the combination of Mag/DOX (both at 3 mg/kg) [70].

5. Targeting EGFR

Epidermal growth factor receptor (EGFR), a 170 *kDa* transmembrane glycoprotein, is composed of a single polypeptide chain. The occurrence and development of various cancers are associated with its mutations, overexpression or signal regulation disorders [71]. Therefore, EGFR and its related signal factors have become the critical targets for the discovery and development of novel chemotherapeutic drugs MCF-7.

Cyclovirobuxine D (CVB-D) (Fig. 4) is the main active ingredient extracted from *Buxus microphylla*. CVB-D is widely used to treat cardiovascular diseases such as coronary heart disease, angina pectoris and arrhythmia in China [72, 73]. In recent years, there are numerous reports to show that CVB-D inhibited EGFR. CVB-D can inhibit the proliferation, colony formation, cell cycle process, and induced apoptosis through mitochondrial-mediated pathway in human gastric cancer MGC-803 and MKN28 and hepatocellular carcinoma HepG2 and HCCLM3 cells [74]. Previous study revealed that CVB-D induced autophagic death through targeting AKT/mTOR signal pathway; treatment with CVB-D led to upregulation of p-AKT and p-mTOR in MCF-7 cells [75]. Recent study showed that both EGFR and PI3K/AKT were involved in CVB-D induced growth inhibition of cancer cells; treatment with CVB-D (10–40 μM) led to down-regulated expression of p-FAK, p-EGFR and EGFR proteins, inhibiting the proliferation, migration and invasion of human hepatoma HepG2 and HCCLM3 cells [76]. Oxymatrine (OM) (Fig. 4) belonged to a quinoline alkaloid is isolated from *Sophora flavescens*. OM displays diverse pharmacological effects, such as anti-inflammation, anti-virus, immune regulation and anti-apoptosis [77–80]. OM induced apoptosis in human pancreatic cancer PANC-1 cells by regulating the expression of Bcl-2, IAP families and the release of cytochrome C [81]. Both PI3K/AKT/mTOR and EGFR are involved in OM induced growth inhibition of cancer cells; treatment with OM down-regulated the phosphorylation levels of AKT and mTOR, inhibited the expression of EGFR, inhibited the invasion and metastasis of human glioblastoma U251MG cells [82]. OM can also inhibit angiogenesis of pancreatic cancer PANC-1 cells *via* targeting

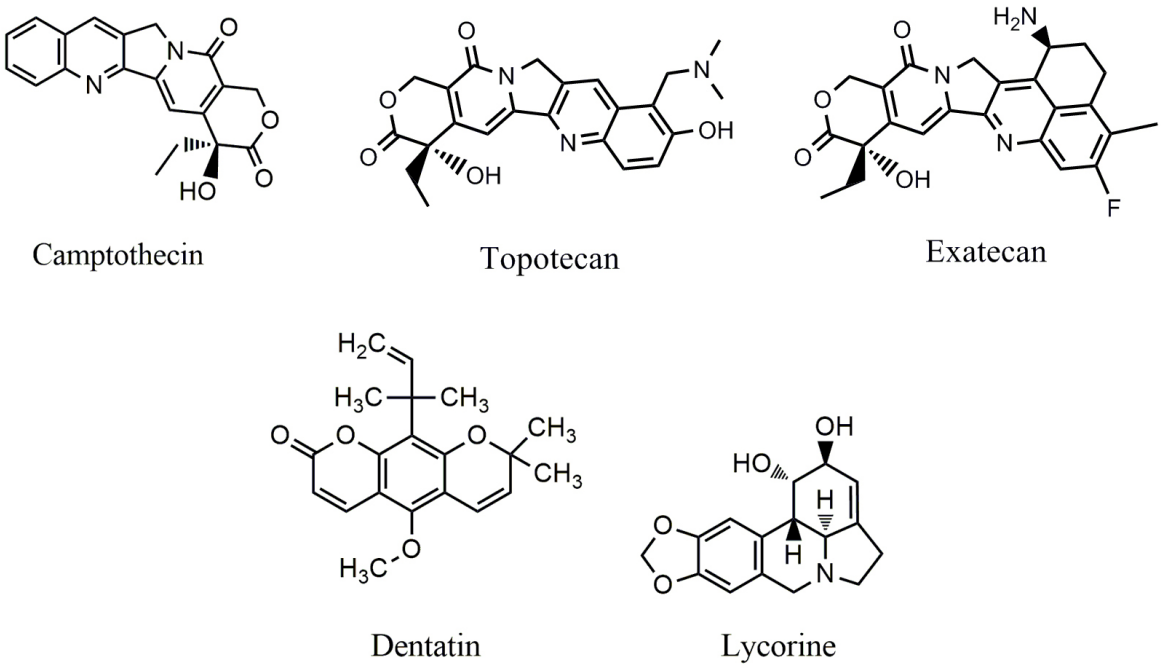

Fig. 5. Chemical structures of alkaloids targeting JAK/STAT pathway.

NF-κB pathway [83]. OM (1 mg/mL) combined with erlotinib (2 μM) exhibited a stronger inhibitory effect than erlotinib (2 μM) alone in human glioma U251MG cells [82]. The inhibitory rate was increased from 30% to around 75% in the combination treatment compared with erlotinib alone.

Matrine (Fig. 4) and oxymatrine (Fig. 4) are the main active components of *Sophora flavescens* [84]. Matrine exhibits cytotoxicity in several cancer cells including hepatocellular carcinoma [85], gastric cancer [86], breast cancer [87] and lung cancer [88]. Matrine displays anticancer activity through targeting different cellular pathways in cancer cells; matrine could inhibit cancer cell proliferation, invasion, metastasis, and angiogenesis, induce differentiation and apoptosis, reverse multidrug resistance [89]. In order to increase the anticancer activity, a derivative of matrine, WM130 ($C_{30}N_4H_{40}SO_5F$) was developed [90]. WM130 inhibited the proliferation, migration and invasion of hepatocellular carcinoma Huh-7 cells more powerful than that of the parent compound matrine with IC_{50} value around 40.61 μg/mL. EGFR plays a critical role for the effect of WM130 on the growth inhibition in cancer cells; WM130 down-regulated the level of EGFR phosphorylation in a dose-dependent. Further study showed that PI3K/Akt was also involved in WM130 induced growth inhibition in cancer cell; WM130 up-regulated the expression of PTEN resulting in the inactivation of AKT/ERK pathway [91]. *In vivo* study showed that treatment with WM130 (40 and 80 mg/kg) significantly inhibited (43.43% and 53.92%) the growth of Huh-7 tumors bearing in nude mice.

Noscapine (Fig. 4), a benzylisoquinoline alkaloid derived from the opium poppy *Papaver somniferum*, is widely used as a cough suppressant in Chinese folk medicine. Studies have shown that noscapine displays anticancer activity both *in vitro* and *in vivo* [92–95]. Noscapine induced growth inhibition of cancer cells is dependent on EGFR-related signal pathway; treatment with noscapine resulted in inactivation of EGFR and AKT, and the reduction of the expression of cyclin D1 and CDK4/6, leading to G1 arrest in osteosarcoma MG63 cells [96]. Treatment with noscapine also led to down-regulation of VEGF in hypoxic human glioma U87 cells [97, 98].

6. Targeting JAK/STAT signaling pathway

JAK/STAT signaling pathway plays an essential role in numerous cellular functions including cell proliferation, differentiation, apoptosis, immunomodulation and hematopoiesis [99]. There are four members of JAK family; JAK1, JAK2, JAK3 and TYK2. STAT families are composed of seven members; STAT1-4, STAT5A/5B and STAT6 [100]. The activation of JAK/STAT pathway depends on a variety of cytokines and growth factors including interleukin, interferon and EGF family members [101]. The binding of cytokines and other ligands to the receptor leads to the activation of janus kinase (JAK), and the activated JAK phosphorylates the tyrosine residues in the tail of the cytoplasm receptors [11]. In the process of tumorigenesis and development, over-activated JAK/STAT signals contribute to cancer cells proliferation, survival, invasion and neovascularization [102]. Therefore, this pathway has attracted more and more attention as a new target for anticancer drugs.

Dentatin (Fig. 5), a carbazole alkaloid isolated from *Murraya koenigii*, has been found to exhibit a variety of anticancer activities [103, 104]. Dentatin can induce apoptosis in prostate cancer PC-3 and LNCaP cells [105], and breast cancer MCF-7 cells [106]. Recent study showed that JAK/STAT signaling plays a critical role in dentatin induced apoptosis and autophagy in cancer cells [107]. Dentatin was able to down-regulate the phosphorylation of JAK1, JAK2, STAT1 and STAT3, and the compound is also capable of increasing the expression of Beclin-1 and LC3II, leading to autophygic cell death in HT-29 cancer cells. Dentatin can also up-regulate the expression of cyclin D1, down-regulate the expression of cyclin A/B1, induce S-phase arrest in HT-29 cells. Lycorine (Fig. 5), a isoquinoline alkaloid extracted from *Amaryl lidaceae* displays broad spectrum of pharmacological activities such as anti-inflammatory, emetic, anti-malaria, anti-viral and so on [108, 109]. Lycorine can inhibit the growth of cancer cells through different mechanisms. Lycorine inhibited the growth and metastasis of prostate cancer [110]. The compound significantly inhibited the proliferation, migration and invasion of prostate cancer PC-3M, DU145, LNCaP and 22RV1 cells with the IC_{50} values around 5–10 μM. Treatment with lycorine (5 μM) led to down-regulation of p-EGFR, p-JAK1, p-JAK2 and p-STAT3. *In vivo* trial showed that lycorine inhibited the growth of tumor significantly; administration of lycorine (10 mg/kg) by i.p. inhibited the tumor growth with an inhibition rate of 78%. Additionally, lycorine can affect the JAK/STAT3 pathway via other regulators; lycorine was able to down-regulate the expression of p-JAK2 and p-STAT3 by inhibiting HDAC in human acute myeloid leukemia K562 cells and human multiple myeloma U266, RPMI8226 and KM3 cells [111]. Lycorine was also capable of inhibiting the activation of JAK/STAT3 pathway *via* up-regulating the expression of SOCS1 in multiple myeloma cells [112].

Camptothecin (CPT) (Fig. 5), a quinoline alkaloid, was isolated from *Camptotheca acuminate*. Its analogs such as irinotecan and topotecan are used clinically for the treatment of ovarian, colorectal and other cancers by inhibiting topoisomerase-I (Top-I) [113]. Moreover, CPT is also able to inhibit the phosphorylation of JAK2 and STAT3; the level of JKA2 is closely associated with the sensitivity of CPT in colon cancer cells [114].

7. Discussion

Table 1 (Ref. [25–41, 46–70, 72–83, 90–98, 103–114]) summerizes the natural alkaloids and their main targets in protein kinase pathways. However, it should be kept in mind that some of the alkaloids are able to target multiple pathways related to protein kinases. EGFR plays critical roles in WM130 induced growth inhibition of cancer cells. However, PI3K/Akt is also involved in WM130 induced growth inhibition of cancer cells [91]. NC treatment lead to down-regulation of AKT phosphorylation and inhibition of metastasis in several cancer cells [63]. NC also inhibited the activation of STAT3 and ERK pathways in human hepatocellular carcinoma HepG2, HCCLM3, and Huh7 cells [64]. Both EGFR and PI3K/AKT were involved in CVB -D induced inhibitory effect on cancer cells [111].

Although the pathways of PI3K/Akt/mTOR, JAK/STAT, EGFR and p38 MAPK account for most of the protein kinase enzymes, there are still many other protein kinases responsible for the occurrence, development, proliferation, invasion, metastasis and mitosis of cancer cells. A ser/thr protein kinase, protein kinase C (PKC) plays very important roles in regulating a variety of cellular functions in cell development and proliferation. Several pathophysiological conditions including cancers are development by the dysregulation of PKC [115]. A benzophenanthridine alkaloid, chelerythrine isolated from Chelidonium majus (L), acting as a PKC inhibitor, was able to induce apoptosis significantly in Dalton's lymphoma cells [116]. The combination of berberine (10 μM) and As_2O_3 (5 μM) inhibited the growth, migration and invasion of human malignant glioma U87 cells and decreased the expression of PKC α and ϵ [117]. CDKs, an important class of protein kinases, control key transcriptional events and critical cell cycle checkpoints in response to intracellular and extracellular signals. CDK inhibitors also act as an important class of targets for developing novel anticancer agents [118]. A vitality of alkaloids targeting the growth of CDKs-mediated cancer cells have been identified as newly discovered anticancer agents. Rohitukine, a chromone alkaloid isolated from *Amoora rohituka* (Roxb.), exhibited inhibitory effect on the growth of leukemia HL-60 and Molt-4 cells through down-regulating the expression of CDK2/A and CDK9/T1 [119]. An oxoaporphine alkaloid, lysicamine isolated from *Asimina triloba* inhibited the growth of hepatoma HepG2 and lung cancer NCI-H460 cells. Lysicamine induced S-phase arrest *via* down-regulation of the expression of cyclin A2/B1/D1/E1 and CDK2/6 [120]. FLT3, a type III receptor tyrosine kinase acts as a proto-oncogene involved in crucial steps of haematopoiesis such as proliferation, differentiation and survival. In recent years, FLT3 has been developed as an important marker in different haematological malignancies [121]. Homoharringtonine (HHT), an alkaloid isolated from Cephalotaxus species, was able to suppress the expression of FLT3/p-FLT3 and inhibit the growth of human AML MV4-11 and MOLM-13 cells in nanomolar level [122]. A benzylamine alkaloid, 2-acetyl-benzylamin, isolated from *Adhatoda vasica*, displayed potent anticancer effect by down-regulation of JAK2 and FLT3. Over the past decades, the development of protein kinase inhibitors as novel anticancer drug has advanced dramatically, and many kinase inhibitors have been approved by the US FDA to treat various human disorders; among them more than forty protein kinase inhibitors are used for cancer treatment [4]. Even though significant ad-

Table 1. Summary of alkaloids as protein kinase inhibitors and their specific targets.

Name of Alkaloids	Sources	Targets and cell lines	References
Dehydrocorydaline	*Corydalis yanhusuo*	MEK1/2 and ERK1/2 A375, MV3 cells	[25–29]
Aconitum szechenyianum Gay	*Aconitum pendulum* Busch	p38 MAPK SMMC-7721, SGC-7901, Eca-109, HepG2, Hela and A549 cells	[30–32]
3α-acetonyltabersonine	*Melodinus suaveolens*	p38 MAPK HL60, SMMC-7721, A549, MCF-7 and SW480 cells	[33–35]
Isoliensinine, liensinine and neferine	*Nelumbo nucifera* Gaertn	p38 MAPK MDA-MB-231, MDA-MB-436, MDA-MB-468 and MCF-7 cells	[36–38]
Berberine	*Coptis chinensis*	p38 MAPK A549, PC-9 cells	[39–41]
Tetrandrine	*Stephania tetrandra* S.Moore	PI3K/AKT MCF-7, MDA-MB-231 and HGC-27 cells	[46–49]
Cepharanthine	*Stephania cepharantha* Hayata	PI3K/AKT/mTOR Jurkat T cells	[50, 51]
Piperlongumine	*Piper longum*	PI3K/AKT/mTOR A549, U937, HT29, DU145, MDA-MB-231 and K562/A02 cells	[52–59]
Veratramine	Plants of the lily family	PI3K/AKT/mTOR HepG2 cells	[60–62]
Nitidine chloride	*Zanthoxylum nitidum (Roxb) DC*	PI3K/AKT/mTOR U87, U251, 786-O and A498 cells	[63–66]
Magnoflorine	*Coptidis Rhizoma*	AKT/mTOR MDA-MB-231, MDA-MB-453 and MCF-7 cells	[67–70]
Cyclovirobuxine D	*Buxus microphylla*	EGFR MGC-803, MKN28, HepG2 and HCCLM3 cells	[72–76]
Oxymatrine	*Sophora flavescens*.	EGFR and VEGF PANC-1 and U251MG cells	[77–83]
WM130	*Sophora flavescens*.	EGFR and ERK Huh-7 cells	[90, 91]
Noscapine	*Papaver somniferum*	EGFR MG63 and U87 cells	[92–98]
Dentatin	*Murraya koenigii*	JAK/STAT HT29 cells	[103–107]
Lycorine	*Amaryllidaceae*	JAK/STAT PC-3M, DU145, LNCaP and 22RV1, U266, RPMI8226 and KM3 cells	[108–112]
Camptothecin	*Camptotheca acuminata*	JAK/STAT Lovo, SW48, HCT116, HCT8, HT29 and WiDr cells	[113, 114]

vancement has been made in the development of kinase inhibitors as novel anticancer agents, the drug resistance and off-targets hinder the application of these kinds of drugs. Several approaches have been developed to overcome the drug resistance or off-targets of protein kinase inhibitors; targeting alternative binding sites on the protein kinases or affecting other pathways that are required for the kinase transformation [123]. Nuciferine, an alkaloid isolated from *nelumbo nucifera* and *nymphaeacaerulea*, was able to inhibit the tumor growth *via* inhiting PI3K/AKT/mTOR pathway, and the compound can also overcome the drug resistance *via* inhibiting the P-gp expression in several cancer cells [124]. Bisindololylmaleimide alkaloid (BMA), isolated from *Streptomyces staurosporeus*, is considered as a PKC inhibitor, and a newly synthesized BMA analogue, BMA097, exhibits anticancer effects both *in vitro* and *in vivo*. BMA is able to bind directly to the SH2 domain of STAT3 and inhibit the phosphorylation of STAT3 [125]. These drugs provide an alternative approaches for overcoming the drug resistance associated with protein kinase inhibitors.

Isoquinoline represents one of the most important class of alkaloids in cancer therapy. The structure/activity relationship (SAR) of isoquinoline has been investigated and the result revealed that the substitutions of 11H-benzothieno [3, 2-b]quinoline-4-carboxamides and indolo[1,2-b]quinoline-6-carboxamides at the pseudo-peri position to the carboxamide side chain is crucial for its cytotoxicity against several cancer cells [126]. Moreover, in protoberberine alkaloids, substitution of methoxyl to hydroxy group at the C-9 position was very important for their anticancer efficacy [127]. DHC and BBR share similar

structure as that of isoquinoline and both of the compounds inhibited the cancer cell growth by inhibiting p38MAPK pathway significantly. CPT and its analogs as TOP-1 inhibitor display similar anticancer effect.

The anticancer alkaloids reviewed here are found from different kinds of natural organisms and display diverse mechanisms for their anticancer activities. Several anticancer agents developed from alkaloids exhibit unique anticancer mechanism. For example, 3α-acetonyltabersonine could inactivate the DNA damage-repair by inhibiting MAPK signaling pathway. In the past several decades, alkaloids from the nature resource have served as an important class of agents in the treatment of different human diseases. It should be predicated that in the future nature alkaloids will provides us more and more novel anticancer drugs with significant therapeutic efficacy and low side effects considering the wide distribution and broad activities of alkaloids.

8. Author contributions

XL and SC designed the work. HY, LW, LM, MI, GQ, JH, LC, YZ, XY, SC and XL collected and reviewed the references. HY wrote the first draft. XL and SC wrote and reviewed the final version of the manuscript. All authors discussed and contributed to the manuscript.

9. Ethics approval and consent to participate

Not applicable.

10. Acknowledgment

Not applicable.

11. Funding

The study was supported the International Collaborative Project of the MOST of China (No#: 2017YFE0195000). We are also grateful for the support by the Taishan Talents project of Shandong province and the Natural Sci. Foundation in Shandong Province of China (No#: ZR2020MH421, ZR2020MH420, ZR2020QH360).

12. Conflict of interest

The authors declare no conflict of interest.

13. References

[1] Fischer PM. Approved and Experimental Small-Molecule Oncology Kinase Inhibitor Drugs: a Mid-2016 Overview. Medicinal Research Reviews. 2016; 37: 314–367.

[2] Alonso A, Sasin J, Bottini N, Friedberg I, Friedberg I, Osterman A, *et al*. Protein tyrosine phosphatases in the human genome. Cell. 2004; 117: 699–711.

[3] Roskoski R. A historical overview of protein kinases and their targeted small molecule inhibitors. Pharmacological Research. 2015; 100: 1–23.

[4] Roskoski R. Properties of FDA-approved small molecule protein kinase inhibitors. Pharmacological Research. 2019; 144: 19–50.

[5] Cohen MH, Williams GA, Sridhara R, Chen G, McGuinn WD, Morse D, *et al*. United States Food and Drug Administration Drug Approval summary: Gefitinib (ZD1839; Iressa) tablets. Clinical Cancer Research. 2004; 10: 1212–1218.

[6] Kazandjian D, Blumenthal GM, Yuan W, He K, Keegan P, Pazdur R. FDA Approval of Gefitinib for the Treatment of Patients with Metastatic EGFR Mutation-Positive Non-Small Cell Lung Cancer. Clinical Cancer Research. 2016; 22: 1307–1312.

[7] Di Lorenzo G, Buonerba C, Biglietto M, Scognamiglio F, Chiurazzi B, Riccardi F, *et al*. The therapy of kidney cancer with biomolecular drugs. Cancer Treatment Reviews. 2010; 36: S16–S20.

[8] Roskoski R. Vascular endothelial growth factor (VEGF) and VEGF receptor inhibitors in the treatment of renal cell carcinomas. Pharmacological Research. 2017; 120: 116–132.

[9] Likhitsup A, Razumilava N, Parikh ND. Treatment for Advanced Hepatocellular Carcinoma: Current Standard and the Future. Clinical Liver Disease. 2019; 13: 13–19.

[10] Ceramella J, Iacopetta D, Barbarossa A, Caruso A, Grande F, Bonomo MG, *et al*. Carbazole Derivatives as Kinase-Targeting Inhibitors for Cancer Treatment. Mini-Reviews in Medicinal Chemistry. 2020; 20: 444–465.

[11] Deng J, Grande F, Neamati N. Small molecule inhibitors of Stat3 signaling pathway. Current Cancer Drug Targets. 2007; 7: 91–107.

[12] Liu C, Yang S, Wang K, Bao X, Liu Y, Zhou S, *et al*. Alkaloids from Traditional Chinese Medicine against hepatocellular carcinoma. Biomedicine & Pharmacotherapy. 2019; 120: 109543.

[13] Iacopetta D, Grande F, Caruso A, Mordocco RA, Plutino MR, Scrivano L, *et al*. New insights for the use of quercetin analogs in cancer treatment. Future Medicinal Chemistry. 2017; 9: 2011–2028.

[14] Grande F, Rizzuti B, Occhiuzzi MA, Ioele G, Casacchia T, Gelmini F, *et al*. Identification by Molecular Docking ofHomoisoflavones from Leopoldia comosa as Ligands of Estrogen Receptors. Molecules. 2018; 23: 894.

[15] Shah NN, Merchant MS, Cole DE, Jayaprakash N, Bernstein D, Delbrook C, *et al*. Vincristine Sulfate Liposomes Injection (VSLI, Marqibo®): Results from a Phase I Study in Children, Adolescents, and Young Adults with Refractory Solid Tumors or Leukemias. Pediatric Blood & Cancer. 2016; 63: 997–1005.

[16] Yang CH, Horwitz SB. Taxol®: the first Microtubule Stabilizing Agent. International Journal of Molecular Sciences. 2017; 18: 1733.

[17] Martino E, Della Volpe S, Terribile E, Benetti E, Sakaj M, Centamore A, *et al*. The long story of camptothecin: from traditional medicine to drugs. Bioorganic & Medicinal Chemistry Letters. 2017; 27: 701–707.

[18] Schläger S, Dräger B. Exploiting plant alkaloids. Current Opinion in Biotechnology. 2016; 37: 155–164.

[19] McCubrey JA, Lahair MM, Franklin RA. Reactive oxygen species-induced activation of the MAP kinase signaling pathways. Antioxidants & Redox Signaling. 2006; 8: 1775–1789.

[20] Schaeffer HJ, Weber MJ. Mitogen-activated protein kinases: specific messages from ubiquitous messengers. Molecular and Cellular Biology. 1999; 19: 2435–2444.

[21] Dhillon AS, Hagan S, Rath O, Kolch W. MAP kinase signalling pathways in cancer. Oncogene. 2007; 26: 3279–3290.

[22] Roskoski R. ERK1/2 MAP kinases: structure, function, and regulation. Pharmacological Research. 2012; 66: 105–143.

[23] Sever R, Brugge JS. Signal transduction in cancer. Cold Spring Harbor Perspectives in Medicine. 2015; 5: a006098.

[24] Brancho D, Tanaka N, Jaeschke A, Ventura J, Kelkar N, Tanaka

Y, *et al*. Mechanism of p38 MAP kinase activation in vivo. Genes & Development. 2003; 17: 1969–1978.
[25] Kurahashi K, Fujiwara M. Adrenergic neuron blocking action of dehydrocorydaline isolated from Corydalis bulbosa. Canadian Journal of Physiology and Pharmacology. 1976; 54: 287–293.
[26] Matsuda H, Tokuoka K, Wu J, Shiomoto H, Kubo M. Inhibitory effects of dehydrocorydaline isolated from Corydalis Tuber against type i-IV allergic models. Biological & Pharmaceutical Bulletin. 1997; 20: 431–434.
[27] Xu Z, Chen X, Fu S, Bao J, Dang Y, Huang M, *et al*. Dehydrocorydaline inhibits breast cancer cells proliferation by inducing apoptosis in MCF-7 cells. The American Journal of Chinese Medicine. 2012; 40: 177–185.
[28] Lee J, Sohn EJ, Yoon SW, Kim CG, Lee S, Kim JY, *et al*. Anti-Metastatic Effect of Dehydrocorydaline on H1299 Non-Small Cell Lung Carcinoma Cells via Inhibition of Matrix Metalloproteinases and B Cell Lymphoma 2. Phytotherapy Research. 2017; 31: 441–448.
[29] Hu H, Dong Z, Wang X, Bai L, Lei Q, Yang J, *et al*. Dehydrocorydaline inhibits cell proliferation, migration and invasion via suppressing MEK1/2-ERK1/2 cascade in melanoma. OncoTargets and Therapy. 2019; 12: 5163–5175.
[30] Qu W, Mou Z, Cui H, Zhang Z. Analysis of fatty acids in a. szechenyianum Gay. by microwave-assisted extraction and gas chromatography-mass spectrometry. Phytochemical Analysis. 2011; 22: 199–204.
[31] Duan J, Liu X, Li Q. A Study of the effectiveness of Aconitum szechnyianum gay. On anti-tumour. Shenzhen Journal of Integrated Traditional Chinese and Western Medicine. 1998; 1: 13–16. (In Chinese)
[32] Fan Y, Jiang Y, Liu J, Kang Y, Li R, Wang J. The antitumor activity and mechanism of alkaloids from Aconitum szechenyianum Gay. Bioorganic & Medicinal Chemistry Letters. 2016; 26: 380–387.
[33] Chen Y, Yang K, Yang X, Khan A, Liu L, Wang B, *et al*. New Cytotoxic Tigliane Diterpenoids from Croton caudatus. Planta Medica. 2017; 82: 729–733.
[34] Kong L, Feng T, Wang Y, Li X, Ye Z, An T, *et al*. Bisleuconothine a, a bisindole alkaloid, inhibits colorectal cancer cell in vitro and in vivo targeting Wnt signaling. Oncotarget. 2016; 7: 10203–10214.
[35] Li Y, Zhao Y, Zhou X, Ni W, Dai Z, Yang D, *et al*. Cytotoxic Indole Alkaloid 3α-Acetonyltabersonine Induces Glioblastoma Apoptosis via Inhibition of DNA Damage Repair. Toxins. 2017; 9: 150–167.
[36] Zhang X, Liu Z, Xu B, Sun Z, Gong Y, Shao C. Neferine, an alkaloid ingredient in lotus seed embryo, inhibits proliferation of human osteosarcoma cells by promoting p38 MAPK-mediated p21 stabilization. European Journal of Pharmacology. 2012; 677: 47–54.
[37] Law BYK, Chan WK, Xu SW, Wang JR, Bai LP, Liu L, *et al*. Natural small-molecule enhancers of autophagy induce autophagic cell death in apoptosis-defective cells. Scientific Reports. 2014; 4: 5510.
[38] Zhang X, Wang X, Wu T, Li B, Liu T, Wang R, *et al*. Isoliensinine induces apoptosis in triple-negative human breast cancer cells through ROS generation and p38 MAPK/JNK activation. Scientific Reports. 2015; 5: 12579.
[39] Imenshahidi M, Hosseinzadeh H. Berberis Vulgaris and Berberine: an Update Review. Phytotherapy Research. 2016; 30: 1745–1764.
[40] Liu D, Meng X, Wu D, Qiu Z, Luo H. A natural isoquinoline alkaloid with antitumor activity: Studies of the biological activities of berberine. Frontiers in Pharmacology. 2019; 10: 9–31.
[41] Chen Q, Shi J, Ding Z, Xia Q, Zheng T, Ren Y, *et al*. Berberine induces apoptosis in non-small-cell lung cancer cells by upregulating miR-19a targeting tissue factor. Cancer Management and Research. 2019; 11: 9005–9015.
[42] Guerrero-Zotano A, Mayer IA, Arteaga CL. PI3K/AKT/mTOR: role in breast cancer progression, drug resistance, and treatment. Cancer and Metastasis Reviews. 2016; 35: 515–524.
[43] Fruman DA, Chiu H, Hopkins BD, Bagrodia S, Cantley LC, Abraham RT. The PI3K Pathway in Human Disease. Cell. 2017; 170: 605–635.
[44] Engelman JA. Targeting PI3K signalling in cancer: opportunities, challenges and limitations. Nature Reviews Cancer. 2009; 9: 550–562.
[45] Lien EC, Dibble CC, Toker A. PI3K signaling in cancer: beyond AKT. Current Opinion in Cell Biology. 2017; 45: 62–71.
[46] Xu W, Meng K, Tu Y, Tanaka S, Onda K, Sugiyama K, *et al*. Tetrandrine potentiates the glucocorticoid pharmacodynamics via inhibiting P-glycoprotein and mitogen-activated protein kinase in mitogen-activated human peripheral blood mononuclear cells. European Journal of Pharmacology. 2017; 807: 102–108.
[47] Bai X, Liu Y, Song W, Li Y, Hou D, Luo H, *et al*. Anticancer activity of tetrandrine by inducing pro-death apoptosis and autophagy in human gastric cancer cells. Journal of Pharmacy and Pharmacology. 2018; 70: 1048–1058.
[48] Wong VKW, Zeng W, Chen J, Yao XJ, Leung ELH, Wang QQ, *et al*. Tetrandrine, an Activator of Autophagy, Induces Autophagic Cell Death via PKC-α Inhibition and mTOR-Dependent Mechanisms. Frontiers in Pharmacology. 2019; 8: 351.
[49] Xu W, Shen H, Ao Z, Chen B, Xia W, Gao F, *et al*. Combination of tetrandrine as a potential-reversing agent with daunorubicin, etoposide and cytarabine for the treatment of refractory and relapsed acute myelogenous leukemia. Leukemia Research. 2006; 30: 407–413.
[50] Xu W, Meng K, Kusano J, Matsuda H, Hara Y, Fujii Y, *et al*. Immunosuppressive efficacy of tetrandrine combined with methylprednisolone against mitogen-activated peripheral blood mononuclear cells of haemodialysis patients. Clinical and Experimental Pharmacology & Physiology. 2017; 44: 924–931.
[51] Xu W, Wang X, Tu Y, Masaki H, Tanaka S, Onda K, *et al*. Tetrandrine and cepharanthine induce apoptosis through caspase cascade regulation, cell cycle arrest, MAPK activation and PI3K/Akt/mTOR signal modification in glucocorticoid resistant human leukemia Jurkat T cells. Chemico-Biological Interactions. 2019; 310: 108726.
[52] Bezerra DP, Pessoa C, de Moraes MO, Saker-Neto N, Silveira ER, Costa-Lotufo LV. Overview of the therapeutic potential of piplartine (piperlongumine). European Journal of Pharmaceutical Sciences. 2013; 48: 453–463.
[53] Pei S, Minhajuddin M, Callahan KP, Balys M, Ashton JM, Neering SJ, *et al*. Targeting aberrant glutathione metabolism to eradicate human acute myelogenous leukemia cells. The Journal of Biological Chemistry. 2013; 288: 33542–33558.
[54] Ranjan A, Ramachandran S, Gupta N, Kaushik I, Wright S, Srivastava S, *et al*. Role of phytochemicals in cancer prevention. International Journal of Molecular Sciences. 2019; 20: 4981–4998.
[55] Seok JS, Jeong CH, Petriello MC, Seo HG, Yoo H, Hong K, *et al*. Piperlongumine decreases cell proliferation and the expression of cell cycle-associated proteins by inhibiting Akt pathway in human lung cancer cells. Food and Chemical Toxicology. 2018; 111: 9–18.
[56] Wang H, Wang Y, Gao H, Wang B, Dou L, Li Y. Piperlongumine induces apoptosis and autophagy in leukemic cells through targeting the PI3K/Akt/mTOR and p38 signaling pathways. Oncology Letters. 2018; 15: 1423–1428.
[57] Liu JM, Pan F, Li L, Liu QR, Chen Y, Xiong XX, *et al*. Piperlongumine selectively kills glioblastoma multiforme cells via reactive oxygen species accumulation dependent JNK and p38 activation. Biochemical and Biophysical Research Communications. 2013; 437: 87–93.
[58] KANG Q, YAN S. Piperlongumine reverses doxorubicin resistance through the PI3K/Akt signaling pathway in K562/a02 human leukemia cells. Experimental and Therapeutic Medicine. 2015; 9: 1345–1350.
[59] Li J, Sharkey CC, King MR. Piperlongumine and immune cytokine TRAIL synergize to promote tumor death. Scientific Reports. 2015; 5: 9987.
[60] Bai F, Liu K, Li H, Wang J, Zhu J, Hao P, *et al*. Veratramine

modulates AP-1-dependent gene transcription by directly binding to programmable DNA. Nucleic Acids Research. 2017; 46: 546–557.
[61] Kudo M. Systemic Therapy for Hepatocellular Carcinoma: Latest Advances. Cancers. 2018; 10: 142–158.
[62] Yin L, Xia Y, Xu P, Zheng W, Gao Y, Xie F, *et al*. Veratramine suppresses human HepG2 liver cancer cell growth in vitro and in vivo by inducing autophagic cell death. Oncology Reports. 2020; 44: 477–486.
[63] Fang Z, Tang Y, Jiao W, Xing Z, Guo Z, Wang W, *et al*. Nitidine chloride inhibits renal cancer cell metastasis via suppressing AKT signaling pathway. Food and Chemical Toxicology. 2013; 60: 246–251.
[64] Lin J, Shen A, Chen H, Liao J, Xu T, Liu L, *et al*. Nitidine chloride inhibits hepatic cancer growth via modulation of multiple signaling pathways. BMC Cancer. 2014; 14: 729.
[65] Sun X, Lin L, Chen Y, Liu T, Liu R, Wang Z, *et al*. Nitidine chloride inhibits ovarian cancer cell migration and invasion by suppressing MMP-2/9 production via the ERK signaling pathway. Molecular Medicine Reports. 2016; 13: 3161–3168.
[66] Zhai H, Hu S, Liu T, Wang F, Wang X, Wu G, *et al*. Nitidine chloride inhibits proliferation and induces apoptosis in colorectal cancer cells by suppressing the ERK signaling pathway. Molecular Medicine Reports. 2016; 13: 2536–2542.
[67] Kim J, Ha Quang Bao T, Shin Y, Kim K. Antifungal activity of magnoflorine against Candida strains. World Journal of Microbiology & Biotechnology. 2018; 34: 167.
[68] Cai Z, Feng Y, Li C, Yang K, Sun T, Xu L, *et al*. Magnoflorine with hyaluronic acid gel promotes subchondral bone regeneration and attenuates cartilage degeneration in early osteoarthritis. Bone. 2018; 116: 266–278.
[69] Guo S, Jiang K, Wu H, Yang C, Yang Y, Yang J, *et al*. Magnoflorine Ameliorates Lipopolysaccharide-Induced Acute Lung Injury via Suppressing NF-κB and MAPK Activation. Frontiers in Pharmacology. 2018; 9: 982.
[70] Wei T, Xiaojun X, Peilong C. Magnoflorine improves sensitivity to doxorubicin (DOX) of breast cancer cells via inducing apoptosis and autophagy through AKT/mTOR and p38 signaling pathways. Biomedicine & Pharmacotherapy. 2020; 121: 109139.
[71] Arteaga CL, Engelman JA. ERBB receptors: from oncogene discovery to basic science to mechanism-based cancer therapeutics. Cancer Cell. 2014; 25: 282–303.
[72] Yu B, Fang T, Lü G, Xu H, Lu J. Beneficial effect of Cyclovirobuxine D on heart failure rats following myocardial infarction. Fitoterapia. 2011; 82: 868–877.
[73] Yu B, Ruan M, Zhou L, Xu L, Fang T. Influence of cyclovirobuxine D on intracellular [Ca(2+)] regulation and the expression of the calcium cycling proteins in rat myocytes. Fitoterapia. 2012; 83: 1653–1665.
[74] Wu J, Tan Z, Chen J, Dong C. Cyclovirobuxine D Inhibits Cell Proliferation and Induces Mitochondria-Mediated Apoptosis in Human Gastric Cancer Cells. Molecules 2015; 20: 20659–20668.
[75] Lu J, Sun D, Gao S, Gao Y, Ye J, Liu P. Cyclovirobuxine D induces autophagy-associated cell death via the Akt/mTOR pathway in MCF-7 human breast cancer cells. Journal of Pharmacological Sciences. 2014; 125: 74–82.
[76] Zhang J, Chen Y, Lin J, Jia R, An T, Dong T, *et al*. Cyclovirobuxine D Exerts Anticancer Effects by Suppressing the EGFR-FAK-AKT/ERK1/2-Slug Signaling Pathway in Human Hepatocellular Carcinoma. DNA and Cell Biology. 2020; 39: 355–367.
[77] Wang B, Wang GJ, Jun XU. Inhibitory effect of Oxymatrine on vascular endothelial cell proliferation induced by tumor. Journal of Practical Oncology. 2000; 15: 297–300.
[78] Deng ZY, Li J, Jin Y, Chen XL, Lü XW. Effect of oxymatrine on the p38 mitogen-activated protein kinases signalling pathway in rats with CCl4 induced hepatic fibrosis. Chinese Medical Journal. 2009; 122: 1449–1454.
[79] Cao Y, Jing S, Li L, Gao J, Shen Z, Liu Y, *et al*. Antiarrhythmic effects and ionic mechanisms of oxymatrine from Sophora flavescens. Phytotherapy Research. 2010; 24: 1844–1849.
[80] Fan H, Li L, Zhang X, Liu Y, Yang C, Yang Y, *et al*. Oxymatrine downregulates TLR4, TLR2, MyD88, and NF-kappaB and protects rat brains against focal ischemia. Mediators of Inflammation. 2010; 2009: 704706.
[81] Ling Q, Xu X, Wei X, Wang W, Zhou B, Wang B, *et al*. Oxymatrine induces human pancreatic cancer PANC-1 cells apoptosis via regulating expression of Bcl-2 and IAP families, and releasing of cytochrome c. Journal of Experimental & Clinical Cancer Research. 2011; 30: 66.
[82] Dai Z, Wang L, Wang X, Zhao B, Zhao W, Bhardwaj SS, *et al*. Oxymatrine induces cell cycle arrest and apoptosis and suppresses the invasion of human glioblastoma cells through the EGFR/PI3K/Akt/mTOR signaling pathway and STAT3. Oncology Reports. 2018; 40: 867–876.
[83] Chen H, Zhang J, Luo J, Lai F, Wang Z, Tong H, *et al*. Antiangiogenic effects of oxymatrine on pancreatic cancer by inhibition of the NF-kappaB-mediated VEGF signaling pathway. Oncology Reports. 2013; 30: 589–595.
[84] Li Y, Wang B, Zhou C, Bi Y. Matrine induces apoptosis in angiotensin II-stimulated hyperplasia of cardiac fibroblasts: effects on Bcl-2/Bax expression and caspase-3 activation. Basic & Clinical Pharmacology & Toxicology. 2010; 101: 1–8.
[85] Zhang J, Li Y, Liu T, He W, Chen Y, Chen X, *et al*. Antitumor effect of matrine in human hepatoma G2 cells by inducing apoptosis and autophagy. World Journal of Gastroenterology. 2010; 16: 4281–4290.
[86] Zhang J, Li Y, Chen X, Liu T, Chen Y, He W, *et al*. Autophagy is involved in anticancer effects of matrine on SGC-7901 human gastric cancer cells. Oncology Reports. 2011; 26: 115–124.
[87] Li L, Li X, Wang L, Du W, Guo R, Liang H, *et al*. Matrine inhibits breast cancer growth via miR-21/PTEN/Akt pathway in MCF-7 cells. Cellular Physiology and Biochemistry. 2012; 30: 631–641.
[88] Zhang Y, Zhang H, Yu P, Liu Q, Liu K, Duan H, *et al*. Effects of matrine against the growth of human lung cancer and hepatoma cells as well as lung cancer cell migration. Cytotechnology. 2009; 59: 191–200.
[89] Liu Y, Xu Y, Ji W, Li X, Sun B, Gao Q, *et al*. Anti-tumor activities of matrine and oxymatrine: literature review. Tumour Biology. 2014; 35: 5111–5119.
[90] Qian L, Liu Y, Xu Y, Ji W, Wu Q, Liu Y, *et al*. Matrine derivative WM130 inhibits hepatocellular carcinoma by suppressing EGFR/ERK/MMP-2 and PTEN/AKT signaling pathways. Cancer Letters. 2015; 368: 126–134.
[91] Liu H, Fu X, Ji W, Liu K, Bao L, Yan Y, *et al*. Human sulfatase-1 inhibits the migration and proliferation of SMMC-7721 hepatocellular carcinoma cells by downregulating the growth factor signaling. Hepatology Research. 2013; 43: 516–525.
[92] Morozevich GE, Kozlova NI, Ushakova NA, Preobrazhenskaya ME, Berman AE. Integrin $\alpha5\beta1$ simultaneously controls EGFR-dependent proliferation and Akt-dependent pro-survival signaling in epidermoid carcinoma cells. Aging. 2012; 4: 368–374.
[93] Mueller KL, Powell K, Madden JM, Eblen ST, Boerner JL. EGFR Tyrosine 845 Phosphorylation-Dependent Proliferation and Transformation of Breast Cancer Cells Require Activation of p38 MAPK. Translational Oncology. 2012; 5: 327–334.
[94] Xiao L, Lin P, Lin F, Liu X, Qin W, Zou H, *et al*. ADAM17 targets MMP-2 and MMP-9 via EGFR-MEK-ERK pathway activation to promote prostate cancer cell invasion. International Journal of Oncology. 2012; 40: 1714–1724.
[95] Pal HC, Sharma S, Strickland LR, Agarwal J, Athar M, Elmets CA, *et al*. Delphinidin reduces cell proliferation and induces apoptosis of non-small-cell lung cancer cells by targeting EGFR/VEGFR2 signaling pathways. PLoS ONE. 2013; 8: e77270.
[96] He M, Jiang L, Ren Z, Wang G, Wang J. Noscapine targets EGFRp-Tyr1068 to suppress the proliferation and invasion of MG63 cells. Scientific Reports. 2016; 6: 37062.
[97] Pedersen MW, Tkach V, Pedersen N, Berezin V, Poulsen HS. Expression of a naturally occurring constitutively active variant of the epidermal growth factor receptor in mouse fibroblasts

increases motility. International Journal of Cancer. 2004; 108: 643–653.
[98] Cai X, Tao B, Wang L, Liang Y, Jin J, Yang Y, *et al*. Protein phosphatase activity of PTEN inhibited the invasion of glioma cells with epidermal growth factor receptor mutation type III expression. International Journal of Cancer. 2000; 117: 905–912.
[99] Thomas SJ, Snowden JA, Zeidler MP, Danson SJ. The role of JAK/STAT signalling in the pathogenesis, prognosis and treatment of solid tumours. British Journal of Cancer. 2015; 113: 365–371.
[100] Svinka J, Mikulits W, Eferl R. STAT3 in hepatocellular carcinoma: new perspectives. Hepatic Oncology. 2014; 1: 107–120.
[101] Rosmorduc O, Desbois-Mouthon C. Targeting STAT3 in hepatocellular carcinoma: Sorafenib again… Journal of Hepatology. 2011; 55: 957–959.
[102] Siveen KS, Sikka S, Surana R, Dai X, Zhang J, Kumar AP, *et al*. Targeting the STAT3 signaling pathway in cancer: role of synthetic and natural inhibitors. Biochimica Et Biophysica Acta. 2014; 1845: 136–154.
[103] Thakur A, Singla R, Jaitak V. Coumarins as anticancer agents: a review on synthetic strategies, mechanism of action and SAR studies. European Journal of Medicinal Chemistry. 2015; 101: 476–495.
[104] Ng RC, Kassim NK, Yunie Soon YY, Gwendoline Cheng LE, Yazan SL, Musa KH. Isolation of Carbazole Alkaloids and Coumarins from Aegle marmelos and Murraya koenigii and their Antioxidant Properties. Sains Malaysiana. 2018; 47: 1749–1756.
[105] Mohan DS. Dentatin induces apoptosis in prostate cancer cells via Bcl-2, Bcl-xL, survivin downregulation, caspase-9, -3/7 activation and NF-kB inhibition. Evidence-Based Complementary and Alternative Medicine. 2012; 2012: 1–15.
[106] Arbab IA, Abdul AB, Sukari MA, Abdullah R, Syam S, Kamalidehghan B, *et al*. Dentatin isolated from Clausena excavata induces apoptosis in MCF-7 cells through the intrinsic pathway with involvement of NF-κB signalling and G0/G1 cell cycle arrest: a bioassay-guided approach. Journal of Ethnopharmacology. 2013; 145: 343–354.
[107] Xiong W, Dong J, Kong S. Dentatin exerts anticancer effects on human colon cancer cell lines via cell cycle arrest, autophagy, inhibition of cell migration and JAK/STAT signalling pathway. Journal of BUON. 2019; 24: 1488–1493.
[108] Wang P, Li L, Wang Q, Shang L, Shi P, Yin Z. Anti-dengue-virus activity and structure-activity relationship studies of lycorine derivatives. ChemMedChem. 2014; 9: 1522–1533.
[109] Wang P, Yuan H, Zhang X, Li Y, Shang L, Yin Z. Novel lycorine derivatives as anticancer agents: synthesis and in vitro biological evaluation. Molecules. 2014; 19: 2469–2480.
[110] Hu M, Peng S, He Y, Qin M, Cong X, Xing Y, *et al*. Lycorine is a novel inhibitor of the growth and metastasis of hormone-refractory prostate cancer. Oncotarget. 2015; 6: 15348–15361.
[111] Li L, Dai H, Ye M, Wang S, Xiao X, Zheng J, *et al*. Lycorine induces cell-cycle arrest in the G0/G1 phase in K562 cells via HDAC inhibition. Cancer Cell International. 2012; 12: 49.
[112] Jin Z, Zhou S, Zhang Y, Ye H, Jiang S, Yu K, *et al*. Lycorine induces cell death in MM by suppressing Janus Kinase/signal transducer and activator of transcription via inducing the expression of SOCS1. Biomedicine & Pharmacotherapy. 2016; 84: 1645–1653.
[113] Zhou Y, Gwadry FG, Reinhold WC, Miller LD, Smith LH, Scherf U, *et al*. Transcriptional regulation of mitotic genes by camptothecin-induced DNA damage: microarray analysis of dose- and time-dependent effects. Cancer Research. 2002; 62: 1688–1695.
[114] Yun HJ, Kim SY, Kwon YY, Kim C, Kang C, Kim EJ. Janus-activated kinases and signal transducer and activator of transcription control tumor growth response to camptothecin in human colon cancer cells. Cancer Biology & Therapy. 2010; 10: 354–361.
[115] Heinisch JJ, Rodicio R. Protein kinase C in fungi-more than just cell wall integrity. FEMS Microbiology Reviews. 2018; 42: 1–63.
[116] Kumar S, Deepak P, Kumar S, Gautam PK, Acharya A. A benzophenanthridine alkaloid, chelerythrine induces apoptosis in vitro in a Dalton's lymphoma. Journal of Cancer Research and Therapeutics. 2013; 9: 693–700.
[117] Lin T, Kuo H, Chou F, Lu F. Berberine enhances inhibition of glioma tumor cell migration and invasiveness mediated by arsenic trioxide. BMC Cancer. 2008; 8: 58.
[118] Whittaker SR, Mallinger A, Workman P, Clarke PA. Inhibitors of cyclin-dependent kinases as cancer therapeutics. Pharmacology & Therapeutics. 2017; 173: 83–105.
[119] Kumar V, Guru SK, Jain SK, Joshi P, Gandhi SG, Bharate SB, *et al*. A chromatography-free isolation of rohitukine from leaves of Dysoxylum binectariferum: Evaluation for in vitro cytotoxicity, Cdk inhibition and physicochemical properties. Bioorganic & Medicinal Chemistry Letters. 2016; 26: 3457–3463.
[120] Qin J, Meng T, Chen Z, Xie X, Qin Q, He X, *et al*. Facile total synthesis of lysicamine and the anticancer activities of the RuII, RhIII, MnII and ZnII complexes of lysicamine. Oncotarget. 2017; 8: 59359–59375.
[121] Meshinchi S, Appelbaum FR. Structural and Functional Alterations of FLT3 in Acute Myeloid Leukemia. Clinical Cancer Research. 2009; 15: 4263–4269.
[122] Wu Z, Zhuang H, Yu Q, Zhang X, Jiang X, Lu X, *et al*. Homoharringtonine Combined with the Heat Shock Protein 90 Inhibitor IPI504 in the Treatment of FLT3-ITD Acute Myeloid Leukemia. Translational Oncology. 2019; 12: 801–809.
[123] Hantschel O. Unexpected off-targets and paradoxical pathway activation by kinase inhibitors. ACS Chemical Biology. 2015; 10: 234–245.
[124] Liu R, Xu P, Chen Q, Feng S, Xie Y. A multiple-targets alkaloid nuciferine overcomes paclitaxel-induced drug resistance in vitro and in vivo. Phytomedicine. 2020; 79: 153342.
[125] Li X, Ma H, Li L, Chen Y, Sun X, Dong Z, *et al*. Novel synthetic bisindolylmaleimide alkaloids inhibit STAT3 activation by binding to the SH2 domain and suppress breast xenograft tumor growth. Oncogene. 2018; 37: 2469–2480.
[126] Kumar EVKS, Etukala JR, Ablordeppey SY. Indolo[3,2-b]quinolines: synthesis, biological evaluation and structure activity-relationships. Mini Reviews in Medicinal Chemistry. 2008; 8: 538–554.
[127] Qing ZX, Huang JL, Yang XY, Liu JH, Cao HL, Xiang F, *et al*. Anticancer and reversing multidrug resistance activities of natural isoquinoline alkaloids and their structure-activity relationship. Current Medicinal Chemistry. 2018; 25: 5088–5114.

Keywords: Alkaloids; Protein kinase inhibitors; Anticancer activity; MAPK; PI3K/AKT/mTOR; JAK/STAT

Send correspondence to:

Xiukun Lin, Department of Pharmacology, School of Pharmacy, Southwest Medical University, 646000 Luzhou, Sichuan, China, E-mail: xiukunlin@swmu.edu.cn

Shousong Cao, Department of Pharmacology, School of Pharmacy, Southwest Medical University, 646000 Luzhou, Sichuan, China, E-mail: shousongc@gmail.com