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Molecular Targets and Developmental Potential of Alkaloid Monomers from Traditional Chinese Medicine as Anticancer Agents

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Abstract: Plant-derived alkaloids exhibit significant anticancer potential, yet their multi-target mechanisms, spanning signaling pathways, programmed cell death, immunity, and metabolism, remain fragmented. This narrative review synthesizes recent preclinical evidence on five representative alkaloids: dendrobine (DDB), aloperine (ALO), levo-tetrahydropalmatine (L-THP), solamargine (SM), and cyclovirobuxine D (CVB-D). Using a dual-framework of compound-specific analysis and key regulatory modules (NF-κB, MAPK, PI3K/AKT/mTOR, JAK/STAT; apoptosis, autophagy, ferroptosis; immune checkpoints; metabolism/microbiota), the study identified convergent anticancer mechanisms with translational relevance. These alkaloids consistently suppress NF-κB, PI3K/AKT/mTOR, and MAPK pathways, and modulate JAK/STAT signaling. They induce apoptosis and ferroptosis, and block autophagic flux. Notably, EVO and SM downregulate PD-L1 via the MUC1-C/NF-κB/c-MYC axis, enhancing $CD8^+$ T cell function. L-THP activates AMPK and remodels tumor metabolism. These mechanistic insights support rational co-therapies such as L-THP plus metabolic inhibitors, or ALO combined with bispecific immune checkpoint inhibitors. Overall, these alkaloids demonstrate systemic, multi-pathway anticancer efficacy, and represent promising partners in precision combination therapy. Clinical translation should prioritize formulation and pharmacokinetic optimization, biomarker-guided stratification, and preclinical validation of synergistic regimens.

Keywords: Alkaloids; NF-κB; PI3K/AKT/mTOR; MAPK; Ferroptosis; Autophagy; PD-L1; Combination therapy

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1. Introduction

Cancer remains a leading cause of mortality and poses a major global public health challenge [1]. Although notable progress has been made in surgery, radiotherapy, targeted therapy, and immunotherapy, the prognosis of many late-

stage cancers remains unsatisfactory [2]. Consequently, there is an urgent need to develop safer, more effective, and better-tolerated therapeutic options. In recent years, traditional Chinese medicine (TCM) has attracted increasing attention in oncology due to its unique advantages of multi-component synergy, multi-target modulation, and holistic homeostatic regulation [3]. A growing body of pharmacological evidence indicates that active constituents derived from TCM not only directly inhibit tumor cell growth, but also alleviate treatment-related side effects and improve systemic physiological states, thereby serving as complementary or alternative therapies in clinical oncology [4]. Among the diverse resources in TCM, alkaloids have emerged as a prominent group of compounds with anti-inflammatory, neuroprotective, and anticancer properties [5]. Notably, recent studies suggest that alkaloid monomers may not only exert direct antiproliferative and pro-apoptotic effects, but also provide organ-protective and chemo-sensitizing benefits in combination regimens, thus improving therapeutic tolerance [6].

Plant-derived alkaloids are chemically diverse and are supported by substantial preclinical evidence in cancer research [7]. Across tumor models in the respiratory, digestive, reproductive, and urinary systems, these alkaloids demonstrate three mechanistic convergences:

(1) Inhibition of key oncogenic nodes including NF-κB, MAPK/ERK-JNK-p38, PI3K/AKT/mTOR, and JAK/STAT pathways, limiting proliferation, invasion, metastasis, and therapeutic resistance [8–17];

(2) Reprogramming of cell death and stress response pathways, including apoptosis, ferroptosis, and blockage of autophagic flux, which are particularly relevant in apoptosis-resistant tumors [18–23];

(3) Modulation of the tumor immune microenvironment, such as downregulation of PD-L1 and reactivation of $CD8^+$ T cells [24–26], alongside remodeling of tumor metabolism and microbiota–metabolism interfaces [27–29].

These shared mechanisms suggest that alkaloids possess the potential to counteract pathway crosstalk, one of the key barriers limiting the efficacy of cancer therapies in solid tumors. Nonetheless, their clinical translation faces several obstacles. Therefore, this review systematically summarizes recent preclinical advances of these five alkaloid monomers, highlights their molecular targets and signaling pathways, evaluates their potential in targeted and combination cancer therapies, and discusses key directions for advancing their clinical translation.

2. Representative plant-derived alkaloid monomers

DDB is a sesquiterpene alkaloid primarily derived from Dendrobium nobile, representing one of the earliest isolated and most extensively studied active compounds [30]. ALO, a quinolizidine alkaloid isolated from Sophora alopecuroides L [31,32]. L-THP is an isoquinoline alkaloid extracted from Corydalis yanhusuo, a plant of the Papaveraceae family [33]. SM, a naturally occurring alkaloid extracted from Solanum nigrum, exhibits anti-inflammatory, antioxidant, and anticancer properties [34]. CVB-D is a steroidal alkaloid isolated from Buxus microphylla and related species [35].

3. Molecular mechanisms and therapeutic targets of anticancer alkaloids

3.1. NF-κB signaling pathway

3.1.1. Respiratory system cancers

CVB-D downregulates the expression of phosphorylated p65 (p-p65), interfering with NF-κB signaling transmission [36,37]. SM reduces p65 protein levels, suppressing NF-κB pathway activation [38]. These alkaloids offer novel molecular strategies for lung cancer therapy by intervening at multiple levels of the NF-κB signaling cascade.

3.1.2. Digestive system cancers

In colorectal cancer, DDB downregulates mRNA expression levels of NF-κB pathway-related genes such as NF-κB, COX-2 (Cyclooxygenase-2), and PGE2 (Prostaglandin E2) [39].

3.1.3. Reproductive system cancers

In prostate cancer, L-THP enhances phosphorylation of Akt while suppressing NF-κB expression, thereby inhibiting cancer cell proliferation [40].

3.2. MAPK signaling pathway

3.2.1. Respiratory system cancers

SM suppresses the expression of EP4, enhances ERK1/2 phosphorylation, and inhibits lung cancer proliferation [41]. DDB increases JNK phosphorylation and induces CHOP, thereby inhibiting the proliferation of lung cancer cells [42].

3.2.2. Digestive system cancers

In hepatocellular carcinoma, CVB-D binds to Leukemia Inhibitory Factor at Val145, inducing mitophagy and inhibiting cell invasion and migration [43]. In gastric cancer, SM suppresses ERK1/2 phosphorylation while upregulating long non-coding RNAs lncPINT and lncNEAT1_2 [44]. In colorectal cancer, CVB-D downregulates phosphorylated ERK1/2, thereby suppressing migration and invasion [45]. Moreover, Huangqin Decoction—composed of betulinic acid, L-THP, and quercetin—exerts synergistic effects on HIF-1/MAPK pathways and multiple core targets to inhibit colorectal cancer progression [46].

3.3. PI3K/AKT/mTOR signaling pathway

3.3.1. Respiratory system cancers

SM acts via a dual mechanism—reducing Akt phosphorylation at Ser473 and suppressing pathway activation via PDPK1 [41,47]. ALO also inhibits the PI3K/Akt/mTOR pathway and decreases transcription and translation of MM*P*-2 [48].

3.3.2. Digestive system cancers

ALO suppresses the expression and release of HMGB1 and its receptor RAGE, leading to inactivation of the PI3K/Akt/mTOR pathway and inhibition of gastric cancer growth [49]. In hepatocellular carcinoma, ALO downregulates p110α, p85, Akt, and p-Akt, thereby inhibiting cell proliferation [50]. Both in vitro and in zebrafish tumor models, ALO exerts anticancer effects by suppressing the PI3K/Akt pathway, inducing apoptosis, G2/M cell cycle arrest, mitochondrial membrane potential loss, and changes in cell cycle distribution [51]. In colorectal cancer, ALO downregulates Stat3 and PI3KC3, inhibiting pathway activation and tumor cell proliferation [31]. SM inhibits PI3K/Akt/mTOR signaling and upregulates PTEN expression, effectively suppressing colorectal cancer cell proliferation and invasion and promoting apoptosis both in vitro and in vivo [52].

3.3.3. Reproductive system cancers

In prostate cancer, ALO inhibits Akt phosphorylation, reduces p-Akt expression, and induces apoptosis [53]. SM blocks PI3K/Akt signaling, suppresses cell proliferation, and enhances the antitumor effect of docetaxel in vivo [54]. In breast cancer, CVB-D exerts its effects by reducing phosphorylation of the autophagy-related suppressors AKT

and mTOR, thus disrupting the autophagic process [55].

3.3.4. Urinary system cancers

In renal cell carcinoma, DDB inhibits the expression of p-PI3K, p-Akt, and p-Erk, thereby suppressing the proliferation, migration, and invasion of 786-O and A498 cells [8].

3.3.5. Other systemic cancers

In osteosarcoma, ALO significantly reduces PI3K and p-Akt1 levels, thereby inhibiting tumor cell proliferation [31]. In thyroid cancer, ALO downregulates p-Akt expression and induces cell death by suppressing the Akt pathway [31].

3.4. JAK/STAT signaling pathway

3.4.1. Respiratory system cancers

Aberrant activation of the JAK/STAT pathway is effectively inhibited by several alkaloids. DDB suppresses the expression of PD-L1, p-JAK1/JAK1, and p-JAK2/JAK2 proteins in lung cancer cells, thereby modulating tumor immune escape and progression [56].

3.5. Other signaling pathways

3.5.1. Respiratory system cancers

DDB inhibits the SULF2-mediated signaling pathway, thereby reducing ionizing radiation-induced migration and invasion of lung cancer cells [42]. ALO targets VPS4A, interfering with autophagosome sealing and autophagosome–lysosome fusion, leading to mitochondrial ROS accumulation, G0/G1 arrest, and apoptosis. It induces autophagy blockade, exhibits strong antitumor activity in lung cancer models, and synergizes with the bispecific PD-L1/TGF-β antibody YM101 [18]. DDB downregulates PD-L1 expression and modulates immune cell infiltration, and when combined with PD-L1 blockade, displays synergistic inhibition of tumor growth [56]. DDB also synergizes with cisplatin by modulating Treg/Th17 balance, prolonging survival and inhibiting tumor progression in vivo [57]. CVB-D activates the p65/BNIP3/LC3 axis to induce mitophagy, enhance apoptosis of A549 and H446 lung cancer cells, and suppress tumor growth in vivo [36]. SM enhances the antitumor efficacy of gefitinib in NSCLC by regulating the MALAT1/miR-141-3p/Sp1/IGFBP1 axis and upregulating IGFBP1 expression in vitro and in vivo [58]. SM also inhibits STAT1 activation and downregulates PD-L1 expression, thereby enhancing the efficacy of PD-L1 immunotherapy without additional toxicity [59]. Furthermore, SM reverses cisplatin resistance by inducing G0/G1 arrest, promoting apoptosis, and inhibiting the Hedgehog pathway, showing synergistic effects with cisplatin [60].

3.5.2. Digestive system cancers

L-THP promotes apoptosis in hepatocellular carcinoma by reducing phosphorylated AMPK levels [31]. It also activates AMPK-dependent autophagy while inhibiting mitochondrial respiration and glycolysis, inducing "bioenergetic deprivation." Co-administration with the metabolic inhibitor DPI enhances its therapeutic efficacy [11,29,61]. SM modulates the LIF/miR-192-5p/CYR61/AKT axis to induce apoptosis and autophagy, while reprogramming tumor-associated macrophages in liver cancer [23]. CVB-D induces ferroptosis by suppressing GPX4 and FSP1, elevating Fe^{2+}, MDA, and ROS levels, and apoptosis rates in HepG2 and Huh-7 cells. It also shows strong antitumor efficacy in a C-NKG xenograft model [62]. SM inhibits HCC growth and enhances the efficacy of sorafenib by modulating the HOTTI*P*-TUG1/miR-4726-5p axis and downregulating MUC1

expression [63]. In gastric cancer, SM downregulates PD-L1 by inhibiting the STAT3/PD-L1 pathway and reverses IL-6-induced immunosuppression, thereby reducing proliferation, migration, and invasion [64].

3.5.3. Reproductive system cancers

In breast cancer, CVB-D binds directly to YAP, suppressing nuclear translocation of YAP/TAZ and downstream oncogenic transcription. It also triggers mitophagy via the FOXO3a/PINK1–Parkin axis, promoting apoptosis [65]. ALO suppresses phosphorylation of Ras pathway components [31]. In cervical cancer, ALO inhibits the IL-6–JAK1–STAT3 feedback loop, significantly reducing HeLa cell proliferation, migration, invasion, and enhancing apoptosis [66]. SM targets CXCL3 and inhibits the ERK pathway, effectively reducing cervical cancer proliferation and metastasis both in vitro and in vivo [67].

3.5.4. Urinary system cancers

In bladder cancer, ALO upregulates TIM*P*-4 while downregulating MM*P*-2 and MM*P*-9, thereby inhibiting migration, invasion, and adhesion [68]. Nanoparticles co-loaded with solasonine and SM demonstrate synergistic antitumor effects against bladder cancer [69].

4. Conclusion and outlook

In summary, plant-based alkaloids hold important supplementary and synergistic potential in modern cancer therapy. By integrating traditional medicinal knowledge with cutting-edge biomedical technologies, particularly multi-omics analysis, targeted delivery systems, and mechanism-driven combination approaches, we can accelerate the translation of these natural compounds into effective, low-toxicity, and personalized cancer treatments.

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Disclosure statement

The authors declare no conflict of interest.

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