



Review

The Anticancer Effect of Natural Plant Alkaloid Isoquinolines

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Abstract: Isoquinoline alkaloids-enriched herbal plants have been used as traditional folk medicine for their anti-inflammatory, antimicrobial, and analgesic effects. They induce cell cycle arrest, apoptosis, and autophagy, leading to cell death. While the molecular mechanisms of these effects are not fully understood, it has been suggested that binding to nucleic acids or proteins, enzyme inhibition, and epigenetic modulation by isoquinoline alkaloids may play a role in the effects. This review discusses recent evidence on the molecular mechanisms by which the isoquinoline alkaloids can be a therapeutic target of cancer treatment.

Keywords: isoquinoline alkaloids; anticancer; cell cycle arrest; apoptosis; autophagy; epigenetic regulation



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1. Introduction

Cancer is a leading cause of death worldwide and has a major impact on society. It is a major barrier to increasing life expectancy this century [1]. The World Health Organization (WHO) estimates that cancer was responsible for an estimated 9.6 million deaths in 2018 [2]. Treatment varies depending on the type and stage of cancer. Most people undergo a combination of treatments, such as surgery with chemotherapy and radiation therapy. However, adverse reactions to conventional treatment and drug resistance have led some to use complementary and alternative medicine (CAM) in conjunction with conventional medical treatments [3–6]. As interest in complementary therapies increases, so has the value of natural remedies [7]. Isoquinoline alkaloids, a group of plant-derived bioactive compounds, have traditionally been used as alternative treatments for their anti-inflammatory, antimicrobial, and analgesic effects [8–12]. Recently, biomedical and pharmacological developments have begun to uncover the anticancer effects and mechanisms of isoquinoline alkaloids. In this review, we discuss the anti-cancer effects and mechanisms of isoquinoline alkaloids.

2. Isoquinoline Alkaloids Derived from Various Herb Extracts

Alkaloids that possess an isoquinoline moiety are one of the largest groups of natural substances. Isoquinoline is a heterocyclic compound consisting of a benzene and pyridine ring fused at C3/C4 of the pyridine ring [13]. The biosynthetic pathways of isoquinoline alkaloids proceed via tyrosine generating dopamine and *p*-hydroxyphenylacetaldehyde (Figure 1). Tyrosine is converted to dopamine by hydroxylation and decarboxylation, and to *p*-hydroxyphenylacetaldehyde by transamination and decarboxylation [14]. Through cyclization, hydroxylation, and methylation, dopamine and *p*-hydroxyphenylacetaldehyde are condensed to form specific scaffold molecules such as norcoclaurine, reticuline, autumnaline, deacetylisoipecoside, or norbelladine, central precursors to several thousand isoquinoline alkaloids [15,16].

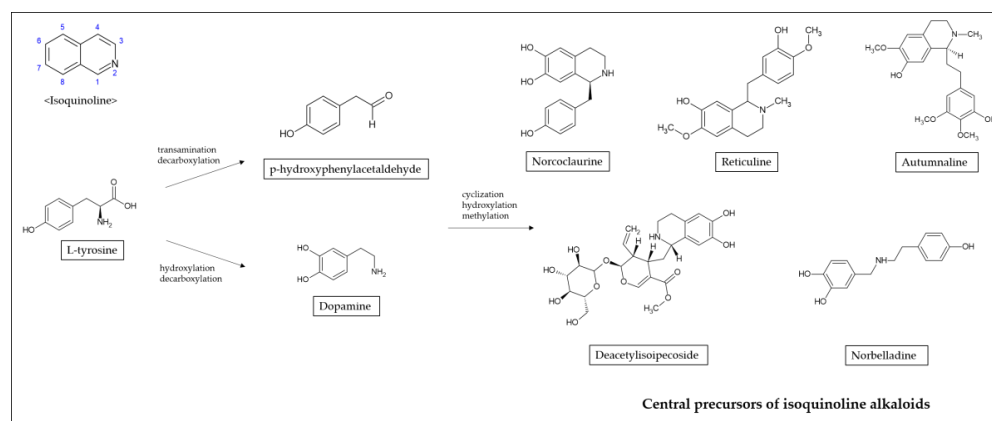


Figure 1. Synthesis of isoquinoline alkaloids.

Isoquinoline alkaloids have been used in folk medicine and have attracted attention in the pharmacological industry and among researchers due to their potential medicinal benefits. Most of the isoquinoline alkaloids discovered to date have been derived from plants, such as Alangiaceae, Annonaceae, Berberidaceae, Fabaceae, Fumariaceae, Lauraceae, Menispermaceae, Papaveraceae, Ranunculaceae, and Rutaceae [17]. Opium poppy (*Papaver somniferum*) is one of the oldest plant sources of commercial isoquinolines in the world. Morphine, codeine, papaverine, noscapine, and thebaine were detected in its latex [18], and more than 40 isoquinoline alkaloids have been isolated from opium [19]. *Chelidonium majus* L., of the Papaveraceae family, contains sanguinarine, chelidonine, chelerythrine, berberine, and coptisine [20]. 8-oxoberberine, berbicine, berbamine, aromoline, obamegine, berberine, and palmatine were obtained from *Berberis vulgaris* [21].

Based on the structural diversity, isoquinoline alkaloids are classified into the subgroups benzyloisoquinoline, aporphine, protoberberine, benzo[c]phenanthridine, protopine, phthalide isoquinoline, morphine, emetine, and pavine [17,22]. Berberine, palmatine, coralyne, and coptisine are the isoquinoline alkaloids from the protoberberine class, while sanguinarine, chelerythrine, and chelidonine are the main members of the benzo[c]phenanthridine class. Noscapine and scoulerine belong to the benzyloisoquinoline alkaloid class. The most common examples of isoquinoline alkaloids (Figure 2) have been intensely investigated for their phytochemical function.

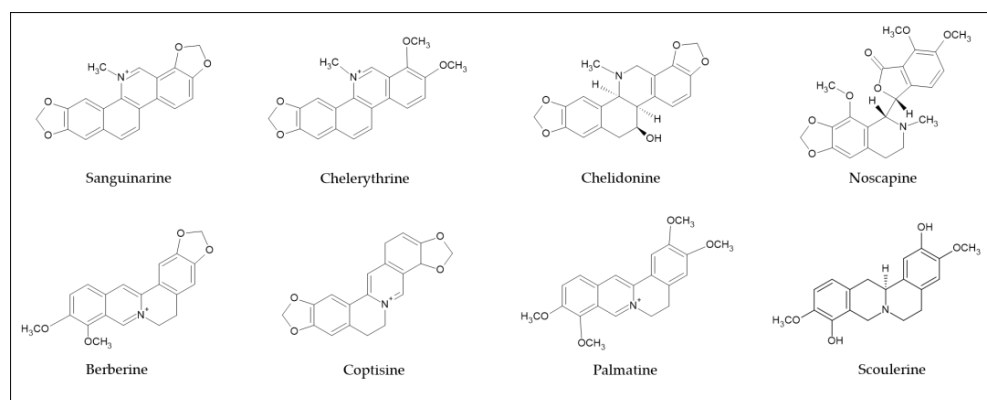


Figure 2. Examples of isoquinoline alkaloids' structures.

3. Biological Functions

Isoquinoline alkaloids have various biochemical properties related to their binding to various differential biological functional ligands [23]. Isoquinoline alkaloids intercalate with polymorphic nucleic acid structures. Berberine and palmatine bind to B-form DNA and coralyne binds to duplex B-form DNA and a single-stranded poly(A) structure [24]. Spectroscopic and thermodynamic studies suggest that sanguinarine and berberine bind

to the DNA and RNA double and triple helical structures [25] and sanguinarine binds to tRNA^{phe} [26]. Interactions between sanguinarine and chelerythrine with DNA were both enthalpy- and entropy-favored actions [27].

Isoquinoline alkaloids inhibit the activity of some enzymes, especially acetylcholinesterase (AChE) and butylcholinesterase (BuChE) through anticholinesterase potency of alkaloid scaffolds [28–34]. This mechanism was uncovered via structure-based virtual screening [35]. Possible structure–activity relationship (SAR) investigations for active compounds predict that the protoberberine scaffold structure is associated with AChE inhibitory effects. Galanthamine from the *Hippeastrum* species inhibited the activity of AChE more than 90% compared to the control in the hippocampus of adult Wistar rats [28]. Chelidonine, 6-ethoxydihydrosanguinarine, and 6-ethoxydihydrochelerythrine, which are abundant in *Chelidonium majus* (Papaveraceae), exhibited inhibitory activity of human blood AChE and human plasma BuChE [36].

Protoberberine and coralyne are known as topoisomerase I and II inhibitors [29,30]. They exhibit intercalative and minor groove binding to duplex DNA and are involved in topoisomerase I poisoning [37]. In addition, corydine, parfumine, 8-methyl-2,3,10,11-tetraethoxyberberine, and chelidonine from the Papaveraceae family inhibit cytochrome P450 3A4 (CYP3A4) with high-affinity alkaloid interactions [31,32]. Berberine inhibited transcriptional activity of cyclooxygenase-2 (COX-2) through the binding to DNA and RNA.

Isoquinoline alkaloids reportedly have other bioactivities, including antibacterial and antifungal effects via the binding to DNA and RNA [38–40]. (+)-*N*-(methoxycarbonyl)-*N*-nordicentrin, (+)-*N*-(methoxycarbonyl)-*N*-norpredicentrin, and (+)-*N*-(methoxycarbonyl)-*N*-norglaucine in the *L. cubeba* extract inhibited the bacterium *S. aureus* and fungus *A. alternata* and *C. nicotianae* [41]. Sanguinarine and chelerythrine from *Sanguinaria canadensis* and berberine and β -hydrastine from *Hydrastis canadensis* inhibited *Staphylococcus aureus* growth [42,43]. The antifungal activity of berberine and jatrorrhizine isolated from *Mahonia aquifolium* was evaluated against *Malassezia* [44]. Berberine inhibited the growth of H1N1 influenza A [45] and the Chikungunya virus [46].

Furthermore, isoquinoline alkaloids have anti-inflammatory and antioxidant effects. Berberine hydrochloride showed significantly low expression levels of inflammation markers and toll-like receptor 4 (TLR4) protein expression in lipopolysaccharide (LPS)-induced mice [47]. The downregulation of inflammatory cytokines such as TNF α , IL-6, and C-reactive protein by berberine treatment was confirmed in vitro [48]. Chelidonine, a major compound of *Chelidonium majus*, also inhibited LPS-induced inflammatory responses through TLR4/NF- κ B signaling pathway suppression in RAW264.7 cells [49]. In a radical scavenging assay, iraqiine, muniranine, and kinabaline showed antioxidant activity [50], and stylophine, protopine, fumaritine, fumaricine, fumarophycine, fumariline, and fumarofine from two Algerian species of *Fumaria* inhibited lipid peroxidation [51].

4. Anticancer Effects of Isoquinoline Alkaloids

The anti-cancer activity of isoquinoline alkaloids is noteworthy. Isoquinoline alkaloids and/or isoquinoline-enriched plants have been investigated as alternative regimens to complement chemotherapy. They efficiently induce cell death in various cancer cell lines [52–55]. The evidence based on in vivo and in vitro models indicated isoquinoline alkaloids exert significant anti-cancer effects through cell cycle arrest, apoptosis, and autophagy (Table 1), leading to cell death.

4.1. Apoptosis-Mediated Cell Death

Apoptosis, programmed cell death, is a promising target for anticancer therapy. Apoptosis is triggered by the extrinsic and intrinsic pathways. The extrinsic pathway is triggered by external stimuli. Ligand and death receptor (DR) binding interacts with the Fas-associated death domain (FADD) and tumor necrosis factor receptor 1 (TNFR1)-associated death domain (TRADD). A death-inducing signaling complex (DISC) is then formed and

caspase-8 is recruited to DISC. This leads to the activation of caspase-8, which cleaves and activates caspase-3/6/7, initiating apoptosis [56].

The intrinsic pathway is triggered by exogenous and endogenous stimuli, including DNA damage and oxidative stress. The Bcl family members, Bax and Bcl-2, act as pro- or anti-apoptotic regulatory proteins through binding to the mitochondrial membrane. The release of cytochrome C in the cytoplasm recruits Apaf-1 and procaspase-9 to form the apoptosome, which triggers downstream caspase-9/3 cascades [57].

4.1.1. Caspase-Dependent Apoptosis

Caspase activation is a central process for apoptosis. All caspases are produced as catalytically inactive zymogens and are cleaved and activated during apoptosis [58]. Chelerythrine-induced apoptosis was accompanied by a decrease in the mitochondrial membrane potential (MMP), the release of cytochrome c, activation of caspase-3 and poly ADP-ribose polymerase (PARP), and downregulation of Bcl-2 in BGC-823 cells [59]. Sanguinarine inhibited tumor growth in vivo and in vitro in various cancers, including prostate [60], cervical [61], pancreatic [62], and colorectal cancers [63]. AsPC-1 and BxPC-3 growth were suppressed via an increase in Bax, Bid, and Bak and decreases in the anti-apoptotic Bcl-2 and Bcl-xL proteins [62]. Sanguinarine also decreased the tumor size in orthotopic colorectal carcinoma bearing BALB/c-nu mice through increased caspase 3, PARP, and mitochondrial reactive oxygen species (ROS) cleavage [63]. The effect of chelerythrine on A549 and H1299 leads to increased protein levels of cleaved PARP and cleaved caspase 3 [64]. Chelidonine inhibited non-small cell lung cancer growth via regulating epidermal growth factor receptor/AMP-activated protein kinase (EGFR/AMPK) signaling pathways in vivo and in vitro [65]. Berberine induced caspase 3, 8, and 9 mediated apoptosis in A549 and H1299 xenograft mice models [66,67] and triple-negative breast cancer cells [68].

4.1.2. MAPK-Mediated Apoptosis

Mitogen-activated protein kinase (MAPK) signaling pathways regulate fundamental cellular processes such as growth, proliferation, differentiation, and migration [69]. MAPK subfamilies consist of extracellular signal-regulated kinases (ERKs), c-Jun N-terminal kinases (JNKs), and p38-MAPKs. ERKs are important for cell survival, while JNKs and p38-MAPKs are stress-responsive and mediate apoptotic processes triggered by numerous stimuli [70]. The major cellular receptor protein kinase C (PKC) activates the MAPK/ERK pathway via c-Raf [71]. Berberine treatment of A549 cells showed indication of apoptosis with increased phosphorylation of p38-MAPK and induced protein expression of p53 and forkhead box class O 3a (FOXO3a) [72]. Berberine affected PKC, glycogen synthase kinase 3 beta (GSK-3 β), ERK activity, and (NSAID) activated gene-1 (NAG-1) expression, resulting in apoptosis in HCT-116 cells [73].

4.2. Cell Cycle Arrest

The cell cycle is regulated by several cyclin-dependent kinases and controls cell division and proliferation. Induction of cell cycle arrest and inhibition of cell proliferation by regulation of cell cycle checkpoints is a therapeutic target for treating cancer [74]. Berberine leads to G1 cell cycle arrest with the induction of NAG1 and activating transcription factor 3 (ATF3) expression on HCT116 cells [73]. An antitumor effect has been demonstrated in human colorectal adenocarcinoma by inducing G2/M phase arrest in vivo and in vitro studies [75]. Berberine treatment also caused G2 phase arrest in U251 cells and significantly inhibited tumor progression in the glioma mouse model [76]. Chelerythrine treatment induced S phase arrest to inhibit BGC-823 cell proliferation [59]. Moreover, sanguinarine arrested AsPC-1 and BxPC-3 cells in the G0–G1 phase through modulation of the Bcl-2 family [62].

4.3. Autophagy-Mediated Cell Death

Autophagy is a response to a range of cellular stressors to maintain cellular homeostasis. Therefore, autophagy is a critical mechanism of cancer treatments. Mechanistic target of rapamycin (mTOR), a molecular regulator of autophagy, is associated with cell proliferation and is regulated by AMPK. Inhibition of mTORC1 and increased AMPK induces autophagy [77], during which autophagosomes are formed to digest cytoplasmic components and LC3I is converted to LC3II [78,79]. Berberine upregulated LC3-II and induced autophagy in glioblastoma through the regulation of the AMPK/mTOR/unc-51 like autophagy activating kinase 1 (ULK1)-pathway [80] and repressed human gastric cancer cell proliferation through inactivation of the MAPK/mTOR/p70S6K/Akt signaling pathway in vivo and in vitro [81]. In chelerythrine-treated A549 and H1299 cells, LC3-II expression was enhanced [64]. Similarly, neferine upregulated LC3-II and downregulated the phosphoinositide 3-kinase (P13K), Akt, and mTOR pathways, inducing autophagy [82].

Table 1. Current evidence on anticancer effects of isoquinoline alkaloids.

Mechanisms	Cancer Type	Effect	Compounds	Reference
Apoptosis	Colorectal cancer	Accumulation of cells in sub G0 phase Increase in Bax expression	Berberine	[73]
	Breast cancer	Condensed chromatin with fragmented nuclei Accumulation of cells in sub G0 phase	Noscapine	[83]
	Gastric cancer		Chelerythrine	[59]
	Breast cancer Liver cancer Lung cancer Prostate cancer	Decrease of mitochondrial membrane potential Increased release of cytochrome c Activation of caspase-3/8/9 and PARP	Berberine	[66–68,84–86]
	Leukemia	Decrease in Bcl-2 expression Increase in Bax expression Apoptotic DNA fragmentation	Berberine Scoulerine	[87,88]
	Colorectal cancer		Noscapine Sanguinarine	[41,63]
	Breast cancer	Decrease of mitochondrial membrane potential Increased phosphorylation of JNK Increased release of cytochrome c and AIF Activation of caspase-3	Berberine	[89]
	Colorectal cancer	Decrease in Bcl-2 expression Increase in Bax expression	Liensinine	[90]
	Lung cancer	Increased phosphorylation of p38 MAPK Increase in transcriptional activity of FoxO3a	Berberine	[72]
	Liver cancer	Suppressed PI3K/Akt/mTOR pathway Increased phosphorylation of JNK Reactive oxygen species (ROS) generation Increase in Bim expression and transcriptional activity of FoxO	Berberine	[91]

Table 1. Cont.

Mechanisms	Cancer Type	Effect	Compounds	Reference
	Prostate cancer	Decrease of mitochondrial membrane potential Decrease in Bcl-2, Bcl-XL, and XIAP expression Increase in Bax, Bad, and Apaf-1 expression Increased cytochrome c and AIF release	Sinomenine	[92]
	Liver cancer	Activation of caspase-3 and PARP Suppression of PI3K/Akt pathway	Tetrandrine	[93]
	Lung cancer	Reactive oxygen species (ROS) generation Activation of caspase-3/8/9 and PARP	Chelerythrine	[64]
	Liver cancer Colorectal cancer	Endoplasmic reticulum (ER) stress activation	Coptisine	[94,95]
	Colorectal cancer	Increased phosphorylation of JNK Suppression of PI3K/Akt pathway	Scoulerine	[96]
	Renal cancer	Decreased phosphorylation of ERK and Akt Decrease in Bcl-2 expression Increase in Bax and p53 expression	Chelerythrine	[97]
	Oral cancer	Increase in FasL expression Decrease in Bcl-2 and Bcl-xL expression Increase in Bax, Bad, and Apaf-1 expression Activation of caspase-3/8/9 and PARP Increased phosphorylation of p38 MAPK	Berberine	[98]
	Breast cancer Colorectal cancer Gastric cancer Pancreatic cancer Prostate cancer	G1 phase cell cycle arrest	Berberine Sanguinarine Chelerythrine	[57,60,61,86,99]
	Colorectal cancer Glioblastoma Lung cancer	G1 phase cell cycle arrest induction of p21 inhibition of cyclin D1	Tetrandrine Berberine	[59,76,100,101]
Cell cycle arrest	Gastric cancer Ovarian cancer	S phase cell cycle arrest	Chelerythrine Liriodenine	[59]
	Glioblastoma		Chelidoneine	[102]
	Colorectal cancer	G2/M phase cell arrest	Liensinine Noscapine Berberine	[41,58,92]
	Leukemia	Enhanced cyclin dependent kinase 1 (Cdk1)/cyclin B1 complex activity	Scoulerine	[88]
	Breast cancer		Noscapine	[83]
	Prostate cancer		Protopine	[103]
Autophagy	Breast cancer Gastric cancer Glioblastoma cancer Liver cancer Lungcancer	Enhanced expression of LC3-II Increase of AMPK activity Downregulated expression of PI3K, Akt, and mTOR Activation of Beclin-1	Berberine Neferine Sanguinarine Chelerythrine	[64,80–82,86,99,100]

5. Molecular Mechanisms of Anticancer Effects

The molecular or cellular mechanisms behind these anti-cancer effects are of great interest. Molecular functions, such as binding to nucleic acids or proteins and enzyme inhibition, have been suggested as potential anti-cancer mechanisms.

5.1. Binding to Polynucleic Acids

Interactions of the alkaloids with DNA and RNA may be responsible for anticancer effects. Specific binding to nucleic acids regulates polynucleic acid stability and may be the therapeutic target of isoquinoline alkaloids with anticancer effects. These bindings disrupt the structure of duplex B-form DNA and affect their interaction with DNA replication, repair, or transcription-related proteins. Sanguinarine and chelerythrine preferred double-helical regions for binding [27] and DNA adduct formed from both isoquinoline alkaloids [101].

5.2. Binding to Microtubules

Microtubule polymerization plays a pivotal role in chromosomal segregation during mitosis [104]. Specific binding to mitotic microtubules has been considered the therapeutic target of isoquinoline alkaloids with anticancer effects. Sanguinarine caused microtubule depolymerization and conformational changes in tubulin through tubulin binding and inhibited cell proliferation in Hela cells [105]. Noscapine-treated MCF-7, MDA-MB-231, and CEM cells displayed higher tubulin-binding activity and mitotic arrest followed by apoptosis [83,106]. Chelidonine [107] and hydroxy-substituted indolo[2,1-a]isoquinolines [108] disrupt microtubular structure and inhibit tubulin polymerization.

5.3. Inhibition of Enzyme Activity

Inhibition of enzyme activity is associated with anticancer activities. The abilities of protoberberine and coralyne as topoisomerase I and II inhibitors are well known [29,30]. Berberrubine's inhibition of DNA topoisomerase II induced DNA cleavage through stabilization of the enzyme–DNA complexes [109,110].

Telomere shortening is evident in MCF-7 cells upon chelidonine treatment [111]. A new berberine derivative synthesized telomeric quadruplex ligands and led to inhibitory effects on telomerase activity [112,113]. Berberine also downregulates nucleophosmin/B23 and inhibits telomerase activity and induces apoptosis of HL-60 cells [114].

Corydine, parfumine, 8-methyl-2,3,10,11-tetraethoxyberberine, and chelidonine from the Papaveraceae family inhibit CYP3A4, indicating a high-affinity interaction with this enzyme and demonstrating an anticancer effect [31,32]. The binding of chelerythrine to Bcl-2 and apoptotic processes were observed in a dose-dependent manner [115,116]. Berberine inhibited cyclooxygenase-2 (COX-2) transcriptional activity with the regulation of I kappa B kinase (IKK) and nuclear factor-kappa B (NF- κ B), and induced apoptosis [33,34]. However, inhibition of AChE and BuChE activity is not related to anticancer effects. Studies have shown that AChE is upregulated in response to apoptotic induction [117]. Its inhibition is considered a potential treatment of Alzheimer's disease (AD). AD is characterized by a loss of neurotransmission due to abnormal synaptic acetylcholine levels [118]. AChE and BuChE are enzymes that break down the neurotransmitter acetylcholine and regulate cholinergic levels in the brain [119].

5.4. Epigenetic Modulation

Epigenetics is defined as the heritable changes in gene expression without alteration of the DNA sequence itself [120]. Epigenetic dysregulation of gene expression occurs during stages of cell proliferation, invasion, metastasis, and cancer development [121–123]. DNA methylation and histone modifications, as main epigenetic mechanisms, induce chromatin remodeling followed by changes in cellular phenotypes [124]. These mechanisms regulate proto-oncogene, tumor suppressor gene, and DNA repair gene expression.

Natural products including the secondary metabolites found in plants are reported to reverse cancer progression through modulation of epigenetic events, such as modulation of the activities of DNA methyltransferases (DNMTs) and histone deacetylases (HDACs) [125,126]. Remarkably, isoquinoline alkaloids act as putative targets in cancer drug development by affecting epigenetic modulation (Table 2).

Particularly, berberine's anticancer effects have been associated with DNA and histone modifications [127–130]. In berberine-treated HepG2 cells, inhibition of DNA methylation in promoter regions of the cytochrome P450 2B6 (CYP2B6) and CYP3A4 genes mediated an anti-proliferative effect [127]. In U266 cells, berberine induced apoptosis by suppression of NF- κ B nuclear translocation through Set9-mediated lysine methylation and decreased miR21 levels [129]. Treatment with berberine affected DNMT1, DNMT3A, DNMT3B, miR-152, miR-429, and miR-29a expression, which are critical regulators of colon cancer initiation and progression [130]. Berberine also repressed HDAC activity and triggered sub-G0/G1 cell cycle arrest in A549 cells [128]. Sanguinarine inhibited H3K9, H3K4, and H3R17 methylation in vivo and in vitro [131].

Table 2. Epigenetic modulation in isoquinoline-induced cell death.

Tumor Type	Compounds	Effect	Reference
Liver cancer	Berberine	Reduced DNA methylation level in promoter regions of CYP2B6 and CYP3A4 genes	[127]
Myeloma	Berberine	Increased the level of Set9 (lysine methyltransferase) Increased the level of methylation of the RelA subunit Inhibited NF- κ B nuclear translocation and miR-21 transcription Hypomethylation of p53 promoter	[129,132]
Colorectal cancer	Berberine	Increased the level of DNMT1, DNMT3A, DNMT3B Increased the level of miR-152, miR-429, miR-29a	[130]
Lung cancer	Berberine	Decrease of HDAC activity Hyperacetylated histones H3 and H4 Decreased level of tumor necrosis factor- α (TNF- α), COX-2, MMP-2, and MMP-9 Increased the level of p21 and p53	[128]
Cervical cancer	Sanguinarine	Reduced H3K9, H3K4, and H3R17 methylation	[131]

6. Conclusions

Current evidence demonstrates that isoquinoline alkaloids have anticancer effects such as induction of cell cycle arrest, apoptosis, and autophagy (Figure 3), suggesting their potential as a cancer therapeutic agent. The effects are, at least in part, attributed to their binding to DNA or proteins, inhibition of enzyme activity, or epigenetic modulation. Further studies are needed to fully discover the underlying mechanisms of isoquinoline alkaloid-mediated cell death against cancer.

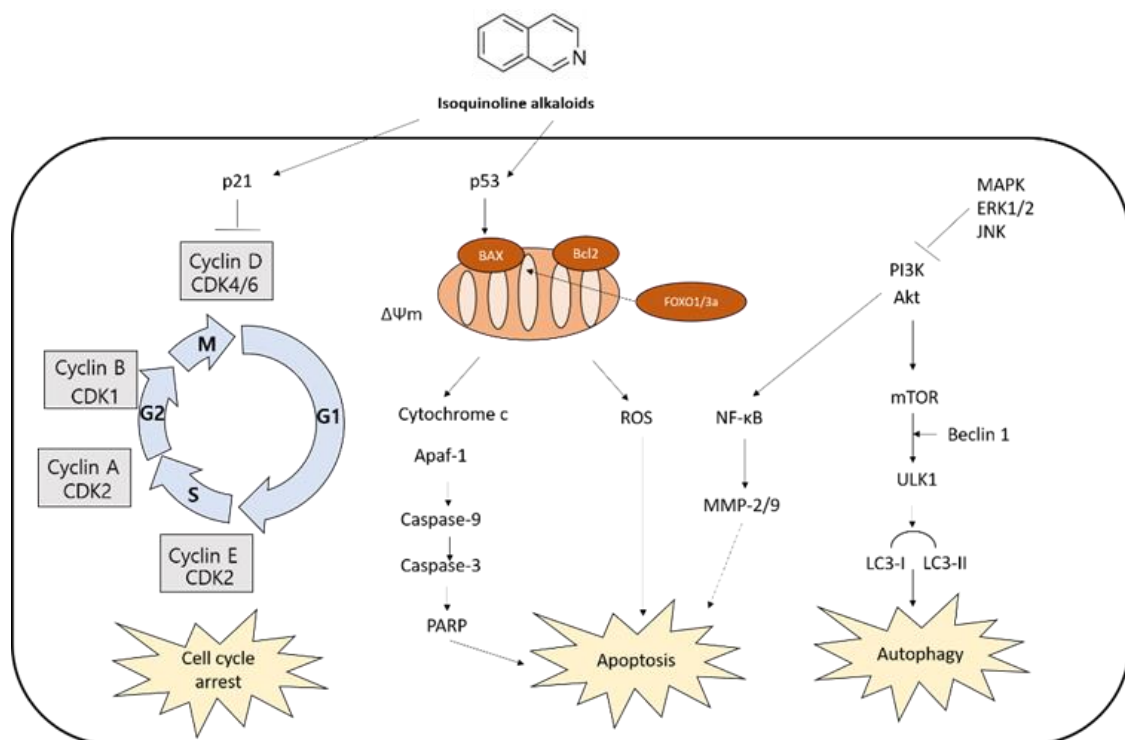


Figure 3. Molecular pathways involved in anticancer mechanisms.

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Abbreviations

AChE	Acetylcholinesterase
AD	Alzheimer's disease
AMPK	AMP-activated protein kinase
ATF3	Activating transcription factor 3
BuChE	Butylcholinesterase
CAM	Complementary and alternative medicine
CDK1	Cyclin Dependent Kinase 1
COX-2	Cyclooxygenase-2
CYP2B6	Cytochrome P450 2B6
CYP3A4	Cytochrome P450 3A4
DISC	Death-inducing signaling complex
DNMT	DNA methyltransferase
DR	Death receptor
EGFR	Epidermal growth factor receptor
ERK	Extracellular signal-regulated kinase

FADD	Fas-associated death domain
FOXO3a	Forkhead box class O 3a
GSK-3 β	Glycogen synthase kinase 3 beta
HDAC	Histone deacetylase
IKK	I kappa B kinase
JNK	Jun N-terminal kinase
LPS	Lipopolysaccharide
MAPK	Mitogen-activated protein kinase
mTOR	Mechanistic target of rapamycin
NAG-1	(NSAID) activated gene-1
NF- κ B	Nuclear factor-kappa B
PARP	Poly ADP-ribose polymerase
PI3K	Phosphoinositide 3-kinase
PKC	Protein kinase C
ROS	Reactive oxygen species
SAR	Structure–activity relationship
TLR4	Toll-like receptor 4
TNFR1	Tumor necrosis factor receptor 1
TNF- α	Tumor necrosis factor- α
TRADD	TNFR1-associated death domain protein
ULK1	Unc-51 Like Autophagy Activating Kinase 1

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