

Quinazolinone derivatives as potential anti-tumor agents: Structural features and molecular mechanisms in inducing cell death (Review)

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Abstract. The quinazolinone scaffold is widely present in natural compounds and serves as a core structural unit in various alkaloids. Its structural flexibility is a major advantage in anti-tumor drug development. Characterized by a fused bicyclic system, this scaffold enables precise pharmacological modulation through targeted chemical modifications, allowing the regulation of multiple cell death pathways, including apoptosis, autophagy, ferroptosis, senescence, pyroptosis and necrosis. This review systematically describes the molecular mechanisms by which quinazolinone derivatives induce tumor cell death and critically evaluates their clinical translation potential. In addition, quinazolinone-based agents approved by the Food and Drug Administration and those in preclinical development as targeted anti-tumor therapies are summarized, providing new perspectives and methodological frameworks for advancing oncology drug discovery.

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1. Introduction

Quinazolinone and its derivatives are important heterocyclic compounds commonly found in various bioactive molecules (1). They represent a major class of biologically active compounds, with the quinazolinone nucleus attracting substantial attention due to its broad pharmacological activities (2). Studies have shown that quinazolinone and its derivatives possess diverse biological effects, including anti-HIV (3), anti-tumor (4), anti-bacterial (5), anti-inflammatory (6), anti-malarial (7), anti-convulsant (8), anti-diabetic (9), anti-oxidant (10), dihydrofolate reductase inhibition (11) and kinase inhibitory activity (12).

Chemical scaffold of quinazolinone compounds. Heterocyclic compounds represent an important class of organic chemicals. These compounds contain one or more heteroatoms, such as nitrogen, oxygen or sulfur, along with carbon atoms, forming a ring structure. Their properties are largely influenced by the number and type of heteroatoms within the ring (13). The cyclic structure strongly affects the compound's characteristics, which are primarily determined by the heteroatoms present.

The term 'cyclic' refers to the presence of at least one ring, whereas 'hetero' indicates that non-carbon atoms, or heteroatoms, are part of that ring (14). In general, heterocyclic compounds resemble cyclic organic compounds composed only of carbon atoms. However, the inclusion of heteroatoms imparts distinct physical and chemical properties, differentiating them from their all-carbon counterparts (15). These compounds are highly versatile in organic chemistry and play a key role in medicinal chemistry. They are widely used in developing bioactive synthetic compounds, pharmaceutical agents and synthetic intermediates (16). In the pharmaceutical industry, heterocyclic structures are particularly common, with >60% of top-selling drugs containing at least one heterocyclic ring (17).

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The basic structure of quinazolinone consists of a quinazoline ring and a ketone group. This bicyclic compound contains a pyrimidine ring fused with a benzene ring at the 4 and 8 positions (18). The quinazoline ring comprises six carbon atoms and two nitrogen atoms located at the 1 and 4 positions (19) (Fig. 1). As an oxidized form of quinazoline, quinazolinone retains the nitrogen atoms and is categorized as a nitrogen-containing heterocyclic compound. Quinazolinone forms the core structure of nearly 150 naturally occurring alkaloids found in various plant families, as well as in animals and microorganisms (20), including compounds such as glycyrrhizin, quinazolinone, deoxycannabinoid ketone and rutaecarpine (21). The first quinazoline alkaloid, vasicine, was isolated in 1888 from the Indian medicinal plant *Adhatoda vasica* and continues to demonstrate significant pharmacological value (22). In recent years, studies have shown that vasicine and its derivatives have potential anti-inflammatory, antioxidant, and anti-Alzheimer's disease effects (23). For instance, vasicine has been shown to alleviate atopic dermatitis induced by 2,4-dinitrochlorobenzene in BALB/c mice by inhibiting pro-Th 2 and Th 2 cytokines in both serum and skin tissues (24). Additionally, vasicine inhibits acetylcholinesterase (AChE) by specifically binding to the AChE catalytic site, such as Trp 84 and Ser 200, positioning it as a promising lead compound for Alzheimer's disease treatment (25). Furthermore, in a rat model of lung injury, *in vitro* assays of lung tissue homogenates revealed that vasicine inhibits lipid peroxidation triggered by excessive reactive oxygen species (ROS), while simultaneously restoring the activity of the endogenous antioxidant enzyme system (26). Thus, it is both a historical milestone in drug development and a starting point for research on new drugs. Later, vasicine and related quinazolinone alkaloids such as vasicinone and deoxyvasicinone were also identified in plants within the *Acanthaceae* family (27). Numerous additional natural products containing quinazoline or quinazolinone structures have since been isolated, analyzed and synthesized. The first quinazolinone compound was synthesized in the late 1860s by reacting anthranilic acid with cyanogen to produce 2-cyanoquinazolinone (28). This compound is a key precursor in quinazolinone chemistry, with its cyano group providing synthetic flexibility, making it a central molecule for constructing structurally diverse and complex quinazolinone derivatives. Systematic modification of its cyano group and the quinazolinone ring—particularly at the N-3 and C-6/C-7 positions—can efficiently generate a large library of structurally diverse compounds for high-throughput screening and structure-activity relationship (SAR) studies, supporting the discovery of new lead compounds and optimization of drug activity (29,30). It plays a pivotal role as a synthetic building block in drug discovery, particularly in the development of kinase inhibitors and related compounds. The unique structural features of quinazolinone, particularly its fused benzene and pyrimidine rings, increase the possibility and flexibility of structural modification (31). In addition, the carbonyl group at the 4-position is a strong electron-withdrawing group, markedly reducing the electron density of the quinazolinone ring and facilitating nucleophilic substitution reactions (32). A molecular docking study revealed that certain quinazolinone derivatives can form strong hydrogen bonds with LYS 630 and HIS 775 in topoisomerase II and stack π - π interactions with

DT15, supporting the compound's ability to inhibit DNA replication and repair (33). Furthermore, the quinazolinone core adapts to the hydrophobic channel of cyclooxygenase-2, where the carbonyl group can form hydrogen bonds with Arg 121 and Tyr 356, thereby inhibiting enzyme activity (34). These properties enhance selectivity and biological activity during interactions with biomolecules, making quinazolinone a key scaffold in drug development (35).

Quinazolinones can be classified by structural features into six main groups: Those substituted at the 2- and/or 3-positions, simple 2-substituted quinazolin-4-ones and quinazolinones fused with pyrrole, pyrroloquinoline, piperidine or piperazine ring systems (36). They can also be categorized by the position of the keto or oxo group into 2(1H)-quinazolinones, 4(3H)-quinazolinones and 2,4(1H,3H)-quinazolinodiones (37). Among these, 4(3H)-quinazolinones are the most common and often serve as intermediates or natural products in proposed biosynthetic pathways (38).

The pharmacological properties of quinazolinone-based compounds can be optimized by modifying their central structure with various functional groups. For instance, introducing alkyl (39), hydrazone (40,41) or other substituents at different positions on the ring can significantly influence target interactions and therapeutic efficacy. This structural adaptability has made quinazolinones and their derivatives a central focus in research on anti-tumor, anti-bacterial and anti-inflammatory drug development.

Biological activities of quinazolinone compounds. In synthetic and medicinal chemistry, the quinazoline scaffold has attracted considerable interest due to its simple synthesis, versatile reactivity and broad pharmacological potential (42). Several quinazolinone-derived drugs, such as Idelalisib and Canertinib, demonstrate the therapeutic potential of this class in treating hematological malignancies and other cancers. In addition, prazosin is used to treat hypertension, Albaconazole for fungal infections, Balaglitazone for diabetes and Dictyoquinazol A as both a neuroprotective agent and a glutamate receptor antagonist (43). Over the past two decades, >20 drugs containing a quinazoline or quinazolinone core structure have been approved by the Food and Drug Administration (FDA) for anti-tumor use. A prominent example is Dacomitinib, approved in 2018 for the treatment of non-small-cell lung carcinoma. These agents act through various mechanisms to inhibit cancer cell growth, mainly by targeting kinases, tubulin, kinesin spindle proteins and other related molecules (44).

Natural quinazolinone compounds, derived from plants, animals and microorganisms and widely used in traditional medicine, often have complex structures that have been refined through natural selection and evolutionary processes to produce unique biological activities (45). Quinazolinone alkaloids are present in the traditional Chinese medicinal herb *Dichroae Radix*, forming the core structure of febrifugine and isofebrifugine. These compounds have been used as antimalarial agents in China for >2,000 years (46). In recent years, increasing evidence has confirmed the significant anti-tumor activity of natural quinazolinone compounds, including their ability to overcome tumor resistance (47). Several derivatives based on the quinazolinone core nucleus,

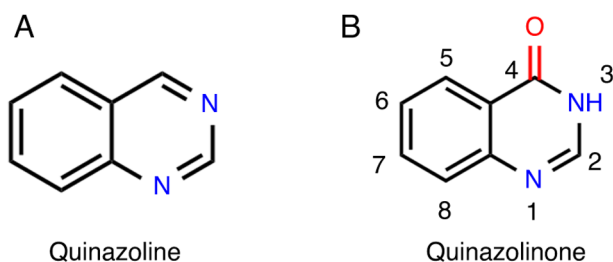


Figure 1. Chemical structures of quinazoline and quinazolinone. Chemical structures of (A) quinazoline and (B) quinazolinone. In both structures, nitrogen atoms are highlighted in blue and the carbonyl oxygen atom is highlighted in red. The numbering in panel B indicates the substitution sites of quinazolinone.

such as Bouchardatine, Luotonin F and Isofebrifugine, have been widely used in cancer treatment, underscoring the broad distribution and biological importance of this class of compounds in nature (43,48).

By contrast, the structural design of chemically synthesized quinazolinone-based drugs often involves modifications to the natural structure, with researchers selectively altering specific molecular sites (such as positions 2, 4, 6, 7 and 8) through chemical functionalization (49). These modifications can markedly influence pharmacological activity by introducing various functional groups, thereby optimizing drug efficacy, selectivity, pharmacological properties, toxicity, stability and pharmacokinetics. The choice between natural and synthetic quinazolinone drugs in therapy depends on their origins, pharmacodynamics and development strategies. Natural quinazolinones are better suited for chronic diseases that require multi-target synergy and low toxicity, such as asthma and chronic inflammation. By contrast, synthetic derivatives are more appropriate for conditions requiring targeted precision, adjustable structure and large-scale production, such as cancer therapy, anti-diabetic treatments and central nervous system disorders (50-52).

Although quinazolinones display a wide range of biological activities, this review focuses specifically on their anti-tumor properties, particularly the mechanisms through which they induce tumor cell death. It summarizes key quinazolinone derivatives known to induce cell death and aims to provide insights for designing structures that help elucidate the mechanisms involved in tumor cell death.

2. Quinazolinone and its derivatives in inducing cell death

Apoptosis. Apoptosis is a gene-regulated, self-controlled and orderly form of cell death that maintains internal homeostasis (53). It is regulated by multiple genes, many of which are highly conserved across species. Apoptosis enables multicellular organisms to remove damaged or unnecessary cells, playing a critical role in tissue remodeling during embryonic development and in maintaining tissue stability throughout life (54). There are two major apoptotic pathways: Intrinsic and extrinsic (55).

The intrinsic pathway is mainly triggered by internal signals such as cellular stress, DNA damage or oxidative stress. It involves the release of pro-apoptotic factors, including cytochrome c, from mitochondria, which activate caspases

that execute cell death. Proteins of the Bcl-2 family are central regulators of this pathway, controlling mitochondrial membrane permeability (56). The extrinsic pathway is activated by external stimuli through membrane-bound death receptors, the most well-known being Fas and tumor necrosis factor (TNF) receptors. Ligand binding to these receptors activates a signaling cascade, including caspases, that leads to apoptosis (57).

Over the past decade, most quinazolinone derivatives have been shown to induce apoptosis through intrinsic pathways, including mitochondrial and endoplasmic reticulum (ER) stress pathways (Table I, Fig. 2). Regarding targeting the intrinsic pathway, Liang *et al* (58) synthesized four novel series of quinazolinone-based compounds by adding alkynyl functional groups at the C8 position. Among them, compound 9b showed the highest affinity for PI3K γ and induced apoptosis in leukemic cells by simultaneously modulating the PI3K-AKT and MAPK signaling pathways. Similarly, Kim *et al* (59) modified substituents at the C-5/6 positions and optimized side-chain positioning within a hydrophobic binding region to develop a selective PI3K δ inhibitor. This compound suppressed the PI3K pathway in SUDHL-5 and MOLT-4 cell models, reduced phosphorylation of AKT, S6 and eukaryotic translation initiation factor 4E-binding protein 1, and triggered apoptosis in malignant cells.

Wani *et al* (60) developed a new quinazolinone-chalcone derivative, 3-(3-((E)-3-(4-hydroxy-3-methoxyphenyl)-2-propenoyl)phenyl)-2-methyl-3,4 dihydro-4-quinazolinone (QC). QC suppressed the mitochondrial anti-apoptotic protein Bcl-2. At the same time, it promoted the translocation of Bax from the cytoplasm to the mitochondria. Bax forms oligomers on the mitochondria, leading to an increase in mitochondrial membrane permeability. This results in the release of cytochrome C from the mitochondria into the cytoplasm. Cytochrome C binds to apoptotic protease activating factor 1 (Apaf-1) to form an apoptosome, which recruits and activates caspase-9. Activated caspase-9 then further activates downstream caspases, including caspase-3, caspase-6 and caspase-7, ultimately triggering cell apoptosis (60). Similarly, Madbouly *et al* (61) synthesized a related quinazolinone-chalcone compound [(E)-2-((4-acetylphenoxy)methyl)-3-phenylquinazolin-4(3H)-one], which induced apoptosis by promoting caspase-3 and poly(ADP-ribose) polymerase 1 (PARP-1) cleavage in A431 carcinoma cells. Some quinazolinone derivatives regulate apoptosis by modulating Bcl-2 family proteins. Xie *et al* (62) synthesized a series of MITC [4-((α -L-rhamnose oxy)benzyl)] quinazolinone derivatives. Among them, MITC-12 induced apoptosis in U251 cells by increasing caspase-3 expression and elevating the Bax/Bcl-2 ratio. Qiu *et al* (63) introduced alkoxy substituents and showed that compound 5k induced concentration-dependent apoptosis in HepG2 cells by increasing pro-apoptotic proteins Bad and Bax and decreasing anti-apoptotic proteins Bcl-2 and Bcl-xL. El-Shafey *et al* (64) demonstrated that novel compounds with a 2-thioquinazolinone scaffold triggered mitochondrial apoptosis by increasing ROS accumulation, elevating the Bax/Bcl-2 ratio and activating caspases 6, 7 and 9.

A smaller group of quinazolinone derivatives induce apoptosis via the extrinsic pathway. HMJ-38 [2-(3'-methoxyphenyl)-6-pyrrolidinyl-4-quinazolinone], a quinazolinone

Table I. Apoptosis pathway changes following quinazolinone derivative treatment.

Authors, year	Cancer type	Chemical name	Affected molecule or pathway	(Refs.)
Liang <i>et al</i> , 2023	Leukemia	3-(1-((9H-purin-6-yl)amino)ethyl)-8-((4-methoxyphenyl) ethynyl)-2-phenylisoquinolin-1(2H)-one	PI3K-AKT↓ p-p38, p-ERK↑	(58)
Kim <i>et al</i> , 2021	Hematologic malignancies	(S)-2-(((7H-Purin-6-yl)amino)(cyclopropyl)methyl)-5-fluoro-3-phenylquinazolin-4(3H)-one	p-AKT, p-S6↓ 4EBP1↓	(59)
Wani <i>et al</i> , 2016	Colon cancer	3-(3-((E)-3-(4-hydroxy-3-methoxyphenyl)-2propenoyl)phenyl)-2-methyl-3,4-dihydro-4-quinazolinone	PI3K/AKT/mTOR signaling pathway; Bcl-2/Bax↓, Caspase-9,3↑, PARP-1↑	(60)
Madbouly <i>et al</i> , 2022	Epidermoid carcinoma, fibrosarcoma	(E)-2-((4-Cinnamoylphenoxy)methyl)-3-(4-fluorophenyl)-quinazolin-4(3H)-one	Caspase-3↑ PARP↓	(61)
Xie <i>et al</i> , 2023	Glioma	6,8-Dibromo-2-thio-3-(4-rhamnosylphenylmethyl)-2,3-dihydroquinazolin-4-one	Caspase-3↑ Bax/Bcl-2↑	(62)
Qiu <i>et al</i> , 2020	Lung cancer	2-(Benzylthio)-6-(3-(dimethylamino)propoxy)-3-(furan-2ylmethyl)quinazolin-4(3H)-one	Bad, Bax↑ Bcl-2, Bcl-xl↓	(63)
El-shafey <i>et al</i> , 2020	Breast cancer	3-(4-(((3-Benzyl-6-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)thio)methyl)-1H-1,2,3-triazol-1-yl)benzoic acid	ROS accumulation, Bax/Bcl-2↑ Caspase-6,7,9↑	(64)
Hour <i>et al</i> , 2023 and Chiang <i>et al</i> , 2013	Pancreatic cancer	2-(3'-Methoxyphenyl)-6-pyrrolidinyl-4-quinazolinone	p53/ATM signaling pathway; Fas/CD95 and death receptor-modulated extrinsic caspase signaling	(65,66)
Lu <i>et al</i> , 2012	Murine leukemia	6-Pyrrolidinyl-2-(2-hydroxyphenyl)-4-quinazolinone	Calpain 1, CHOP and p-eIF2α↑	(67)

p-S6, phospho-ribosomal protein S6; 4EBP1, eIF4E-binding protein 1; mTOR, mammalian target of rapamycin; Bax, BCL2-associated X protein; Caspase, cysteinyl aspartate specific proteinase; PARP, poly(ADP-ribose) polymerase 1; Bad, BCL2 associated agonist of cell death; ROS, reactive oxygen species; ATM, Ataxia-telangiectasia mutated proteins; FAS/CD95, factor-related apoptosis; CHOP, C/EBP homologous protein; eIF2α, phospho-eukaryotic translation initiation factor 2α.

derivative, inhibits tubulin polymerization. Hour *et al* (65) showed that HMJ-38 induces both autophagy and apoptosis in gemcitabine-resistant pancreatic cancer cells, with the recruitment of pro-caspase-9 to the apoptosome by the Apaf-1 complex activating caspase-9 auto-catalytically, thereby enhancing apoptosis through subsequent activation of caspase-3, caspase-6 and caspase-7. Chiang *et al* (66) reported that HMJ-38 induces apoptosis in human umbilical vein endothelial cells through ROS generation and activation of the Fas/death receptor-mediated caspase-8 pathway, regulated by p53/ATM signaling. In WEHI-3 cells, MJ-29 activates key markers of ER stress by increasing the protein levels of calpain 1 and C/EBP homologous protein (CHOP), playing an important role in regulating cell apoptosis (67).

Ferroptosis. Ferroptosis is a regulated form of cell death first identified in cancer cells with oncogenic Ras mutations. It is

characterized by iron-dependent lipid peroxidation (68,69). Unlike classical forms of cell death such as apoptosis and necrosis, ferroptosis involves intracellular iron accumulation and ROS generation. These processes lead to polyunsaturated fatty acid peroxidation in cell membranes, resulting in membrane damage and cell death (70). Ferroptosis is regulated by multiple metabolic pathways, including those involved in redox balance, iron metabolism, mitochondrial function, and amino acid, lipid and carbohydrate metabolism. Several disease-related signaling pathways also contribute to its regulation (71). The three primary pathways that control ferroptosis are the system Xc⁻/glutathione (GSH) peroxidase 4 (GPX4) axis, lipid metabolism and iron metabolism (72). In addition to small molecules and drugs, external stressors such as heat, cold, hypoxia and radiation can also induce ferroptosis (73) (Table II, Fig. 3).

Erastin, a piperazinyl-quinazolinone compound, is a well-known ferroptosis inducer (74). It inhibits the system

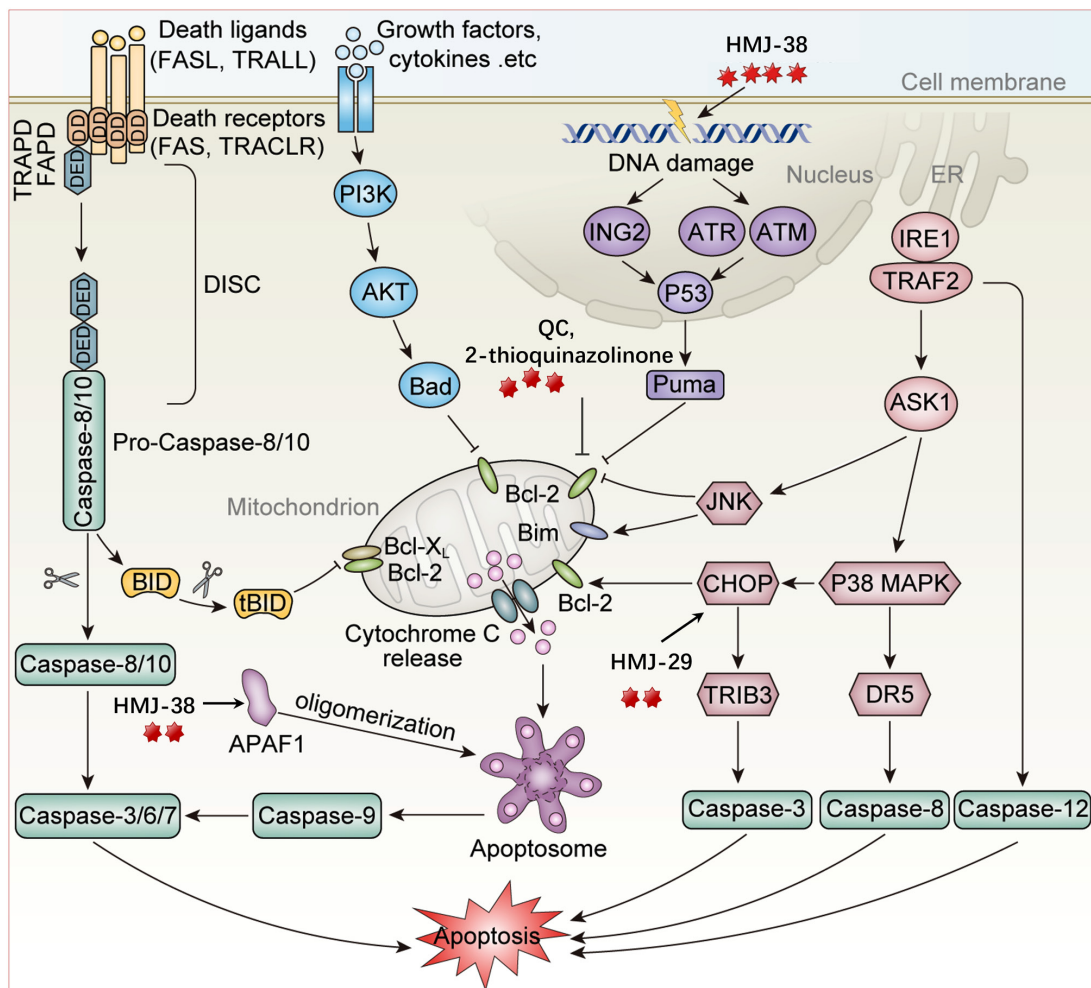


Figure 2. Mechanism of quazolinone compounds inducing cell death through apoptosis. i) In the extrinsic pathway, the death ligand-receptor interaction triggers apoptotic signaling and forms the DISC complex, activating the Caspase-8/-3 cascade, leading to cell apoptosis (HMJ-38 induces apoptosis through the Fas/Death receptor-Caspase-8 pathway and is regulated by p53/ATM signaling). ii) In the intrinsic pathway, quazolinones downregulate Bcl-2/Bcl-xL and upregulate Bax/Bad, thereby promoting cytochrome c release, Apaf-1 apoptosome formation and Caspase-9/Caspase-3 cascade activation (QC suppresses Bcl-2, promotes the translocation of Bax into the mitochondria, releases Cyt C and activates Caspase-9. MITC-12 upregulates the Bax/Bcl-2 ratio and increases Caspase-3 expression. The analogs synthesized by Madbouly *et al* (61) induce apoptosis by promoting Caspase-3 and PARP-1 cleavage (compound 5k increases Bad and Bax, reduces Bcl-2 and Bcl-xL and enhances pro-apoptotic signals). iii) In the DNA damage pathway, ATM/ATR/p53 signaling induces Puma expression to enhance mitochondrial apoptosis (one of the mechanisms of HMJ-38 is to induce the p53/ATM signaling pathway through DNA damage, thereby activating the death receptor pathway Caspase-8). iv) ER stress activates the IRE1-TRAF2-ASK1 signaling pathway, which in turn activates the JNK and p38 MAPK pathways, induces CHOP expression, promotes the upregulation of TRIB3 and DR5 and subsequently activates Caspase-3, Caspase-8 and Caspase-12, thereby inducing apoptosis (MJ-29 activates key markers of ER stress by increasing the protein levels of calpain 1 and CHOP). ER, endoplasmic reticulum; DISC, death-inducing signaling complex; DED, death effector domain; BID, BH3 interacting domain death agonist; APAF1, apoptotic peptidase activating factor 1; ING2, inhibitor of growth family member 2; Puma, P53 upregulated modulator of apoptosis; Bim, Bcl-2 interacting mediator of cell death; Bad, BCL2-associated agonist of cell death; JNK, c-Jun N-terminal kinase; IRE1, immunoglobulin-regulated enhancer 1; TRAF2, TNF receptor associated factor 2; ASK1, apoptosis signal-regulating kinase 1; CHOP, C/EBP homologous protein; TRIB3, Tribbles pseudokinase 3; DR5, death receptor 5; ATM, Ataxia-telangiectasia mutated proteins; ATR, Ataxia telangiectasia mutated and Rad3 related; caspase, cysteinyl aspartate specific proteinase.

Xc⁻, leading to reduced intracellular GSH levels and impaired GPX4 function. This results in increased lipid peroxidation, mitochondrial damage and other ferroptotic features (75). Erastin remains in the preclinical stage and is not yet marketed. Although it induces ferroptosis in various tumor cells, its therapeutic effect is limited by a feedback mechanism involving degradation of voltage-dependent anion channel (VDAC)2 and VDAC3. In melanoma cells, Erastin activates forkhead box M1, which transcriptionally upregulates NEDD4 E3 ubiquitin protein ligase, leading to VDAC2/3 ubiquitination and proteasomal degradation. This reduces intracellular ROS levels and modulates ferroptosis. Silencing Nedd4 restores VDAC2/3 levels and enhances cancer cell sensitivity to Erastin (76).

Furthermore, Erastin induces mitochondrial dysfunction and ROS accumulation in HGC-27 gastric cancer and endometrial stromal cells, thereby promoting ferroptosis and suppressing malignancy (77,78). This process is also marked by iron accumulation and decreased ferroportin expression. Huang *et al* (79) found that Erastin induces both ferroptosis and apoptosis in A549 lung cancer cells by increasing ROS and activating p53. Erastin may also enhance the therapeutic effects of programmed cell death 1/programmed cell death ligand 1 inhibitors by influencing tumor-associated macrophage polarization (80). In another study, aspirin induced ferroptosis in HepG2 and Huh7 cells, and its effect was enhanced by Erastin co-treatment (81,82).

Table II. Ferroptosis pathway changes following quinazolinone derivative treatment.

Authors, year	Cancer type	Chemical name	Affected molecule or pathway	(Refs.)
Yang <i>et al</i> , 2020	Melanoma	2-(1-(4-(2-(4-chlorophenoxy)acetyl)piperazin-1-yl)ethyl)-3-(2-ethoxyphenyl)quinazolin-4(3H)-one	FOXMI-Nedd4-VDAC2/3 negative feedback loop	(76)
Sun <i>et al</i> , 2020	Gastric cancer	2-(1-(4-(2-(4-chlorophenoxy)acetyl)piperazin-1-yl)ethyl)-3-(2-ethoxyphenyl)quinazolin-4(3H)-one	System Xc ⁻ ↓ Block of the uptake of cystine, resulting in the accumulation of ROS	(77)
Li <i>et al</i> , 2021	Endometrial cancer	2-(1-(4-(2-(4-chlorophenoxy)acetyl)piperazin-1-yl)ethyl)-3-(2-ethoxyphenyl)quinazolin-4(3H)-one	ROS↑, FPN↓	(78)
Huang <i>et al</i> , 2018	Lung cancer	2-(1-(4-(2-(4-chlorophenoxy)acetyl)piperazin-1-yl)ethyl)-3-(2-ethoxyphenyl)quinazolin-4(3H)-one	ROS↑, p53↑, p-p53↑, p21, Bax↑, SLC7A11↓	(79)
Zhao <i>et al</i> , 2024	Liver cancer	N-(2-(4-(((2-(7-(diethylamino)-2-oxo-2H-chromen-3-yl)-4-oxo-3,4-dihydroquinazolin-6-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)ethyl)-4-methylbenzenesulfonamide	Gpx4↓, Nrf2↑, Keap1↓	(83)
Xing <i>et al</i> , 2024	Melanoma	(E)-2-(4-(diphenylamino)styryl)-6-fluoro-6-methyl-5λ ⁴ ,6λ ⁴ -pyrido(1',2':1,5) (1,3,2) diazaborolo(4,3-b)quinazolin-8(6H)-one	GPX4-GSH-cysteine axis	(84)
Huang <i>et al</i> , 2023	Liver damage	3-(2,4-Dichloro-5-methoxyphenyl)-2,3-dihydro-2-thioxo-4(1H)-quinazolinone	p-Drp1↓, MDA↓, GSH, GPX4↑	(85)
Nakamura <i>et al</i> , 2023	Liver disease	N-(4-(2-methyl-4-oxoquinazolin-3(4H)-yl)phenyl)-2-(3,4,5-trimethoxyphenyl)acetamide	FSP1↑, combination with iron death inducers promotes apoptosis	(87)
Hu <i>et al</i> , 2020	Pancreatic cancer	6-(4-(4-Methylpiperazin-1-yl)phenylamino)quinazoline-5,8-dione	ROS↑, GSH/GSSG↓ lipid peroxidation↑	(90)

FOXMI, forkhead box M1; Nedd4, neural precursor cell expressed developmentally downregulated 4; VDAC, voltage-dependent anion channel; system Xc⁻, cystine/glutamate antiporter system; ROS, reactive oxygen species; FPN, ferroportin; Bax, Bcl2-associated X protein; SLC7A11, solute carrier family 7 member 11; GPX4, glutathione peroxidase 4; Nrf2, nuclear factor erythroid 2-related factor 2; Keap1, Kelch-like ECH-associated protein 1; GSH, glutathione; p-DRP1, phospho-dynamain-related protein 1; MDA, malondialdehyde; FSP1, ferroptosis suppressor protein 1; GSSG, oxidized glutathione.

Organelle-targeted photosensitizers (PSs) are promising in enhancing photodynamic therapy, as they generate ROS under light exposure in the presence of oxygen. Zhao *et al* (83) developed a series of PSs based on the coumarin-quinazolinone (CQ) structure. The mitochondria-targeted CQ-Mito compound inhibits GPX4 upon light exposure, induces lipid peroxidation and activates Nrf2 while reducing Keap1 expression, which normally deubiquitinates Nrf2. Treatment with the ferroptosis inhibitor Fer-1 restores ferroptosis-related protein expression, confirming the light-induced ferroptotic effect of CQ-Mito (83). Additionally, BODIQPy-triphenylamine (BODIQPy-TPA), a lipophilic quinazolinone-based probe, can directly induce lipid peroxidation upon light exposure. In B16 and HepG2 cells, BODIQPy-TPA triggers ferroptosis by inhibiting GPX4, depleting GSH, and promoting cystine starvation, thereby activating the GPX4-GSH-cysteine axis (84). It also emits strong near-infrared fluorescence in live cells,

making it useful for real-time imaging of the ferroptosis process.

3-(2,4-Dichloro-5-methoxyphenyl)-2,3-dihydro-2-thioxo-4(1H)-quinazolinone (Mdivi-1) is a quinazolinone derivative and a selective inhibitor of dynamain-related protein 1 (Drp1). In cold stress-induced liver injury, Mdivi-1 reduces malondialdehyde levels, increases GSH and GPX4 levels, inhibits mitochondrial fission and effectively mitigates ferroptosis (85). It also decreases ferrous ion and lipid peroxide levels. In models of PM2.5 exposure, Mdivi-1 significantly reduces the expression of acyl-CoA synthetase long chain family member 4, ferritin, ferritin heavy chain 1 and ferritin light chain 1, while increasing GPX4 protein levels, thereby inhibiting ferroptosis (86).

Ferroptosis suppressor protein 1 (FSP1), in conjunction with mitochondrial-derived ubiquinone, exogenous vitamin K and NAD(P)H/H⁺ as electron donors, has been identified as

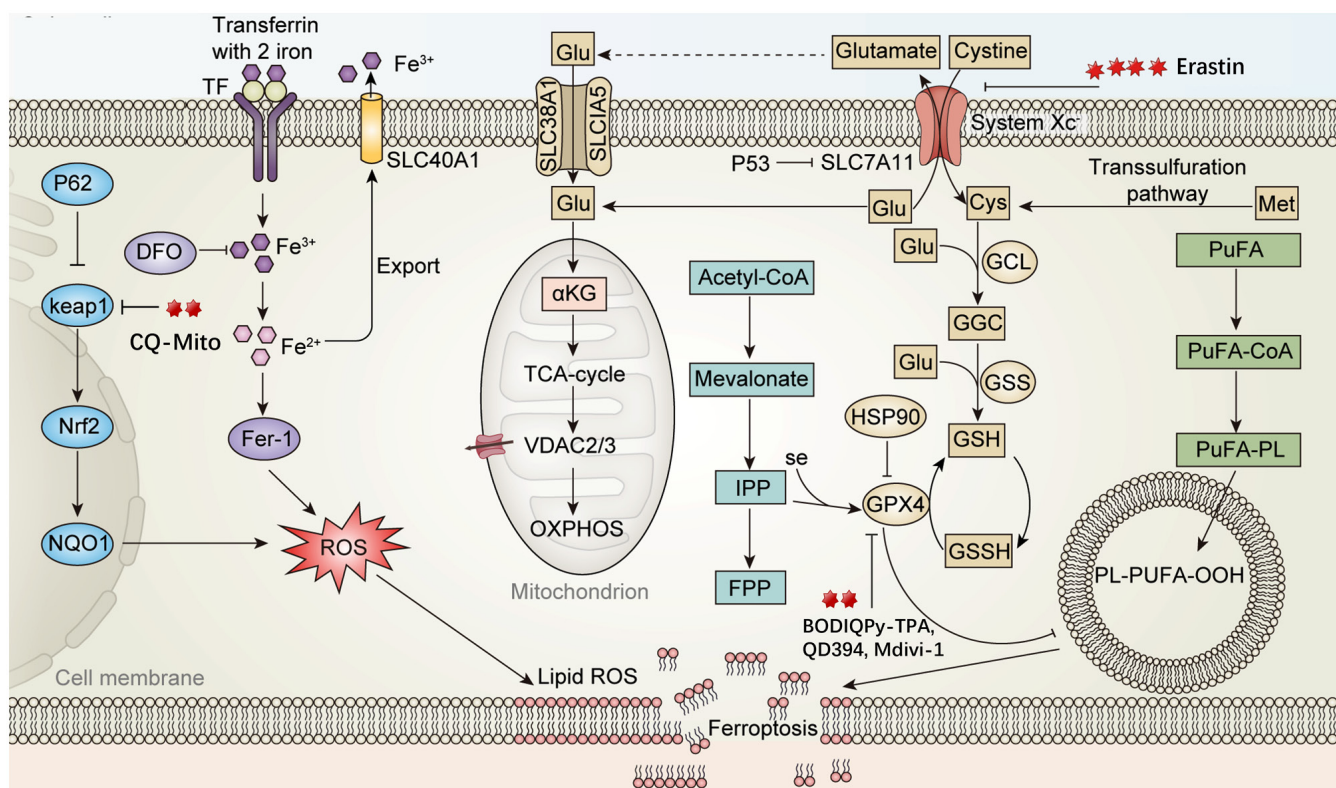


Figure 3. Mechanism of quazolinone compounds inducing cell death through ferroptosis. i) System Xc⁻ is responsible for importing extracellular cysteine into cells for GSH synthesis, maintaining GPX4 activity to clear lipid peroxides PL-PUFA-OOH. When cysteine uptake is blocked or GSH is depleted, GPX4 becomes inactive, leading to the accumulation of lipid peroxides and triggering ferroptosis (Erastin inhibits SLC7A11, prevents Cys entry, reduces GSH synthesis, weakens GPX4 activity and enhances lipid peroxidation, thereby inducing ferroptosis; BODIPY-TPA directly acts on the GPX4/GSH axis, inhibits GPX4, depletes GSH, blocks lipid peroxide clearance and promotes ferroptosis). ii) After transferrin-bound Fe³⁺ enters the cell, it is reduced to Fe²⁺, promoting ROS generation and inducing lipid peroxidation. The Keap1-Nrf2 signaling axis regulates the downstream antioxidant gene NQO1, which helps buffer ferroptosis stress to a certain extent (CQ-Mito generates ROS under light, inhibits GPX4, reduces Keap1 and activates the Nrf2 antioxidant pathway). iii) PUFA is acylated to form PuFA-CoA, and under the influence of iron and ROS, lipid peroxides PL-PUFA-OOH are generated, which are direct molecular effectors of ferroptosis. ROS, reactive oxygen species; GSH, glutathione; TF, transcription factors; GCL, glutamate cysteine ligase; GGC, gamma-glutamylcysteine; GSS, glutathione synthetase; SLC40A1, solute carrier family 40 member 1; system Xc⁻, cystine/glutamate antiporter system; αKG, α-ketoglutaric acid; TCA-cycle, tricarboxylic acid cycle; VDAC, voltage-dependent anion channel; OXPHOS, oxidative phosphorylation; PuFA, polyunsaturated fatty acid; CoA, coenzyme A; Cys, cysteine; Met, methionine; PuFA-PL, polyunsaturated-fatty-acid-containing phospholipids; IPP, Isopentenyl pyrophosphate; FPP, farnesyl pyrophosphate; HSP90, heat shock protein 90; GPX4, glutathione peroxidase 4; DFO, deferoxamine; Keap1, Kelch-like ECH-associated protein 1; Nrf2, nuclear factor erythroid 2-related factor 2; NQO1, quinone oxidoreductase.

a second ferroptosis-suppressing system (87). A recent study indicated that 3-phenyl-quinazolinone, an FSP1 inhibitor, promotes FSP1 aggregation in tumors. This aggregation synergizes with ferroptosis inducers to enhance iron-dependent cell death and suppress tumor progression *in vivo* (88).

In the search for new therapies for uveal melanoma, coumarin-quinazolinone-phenylboronic acid has been developed as a prodrug to induce ferroptosis by targeting elevated ROS and tyrosinase levels in melanoma cells (89). QD394, a quinazolinone-dione compound, promotes lipid peroxidation and destabilizes GPX4 protein, thereby triggering GPX4-mediated ferroptosis (90).

Autophagy. Autophagy is a conserved cellular process that plays an essential role in maintaining homeostasis by degrading damaged or unnecessary organelles and proteins (91). It begins with the formation of autophagosomes, which enclose the targeted materials and deliver them to lysosomes for degradation. The term 'autophagy-dependent cell death (ADCD)' was introduced in 2018 by the Nomenclature Committee on Cell Death (92). ADCD is a regulated form of cell death

characterized by the activation of autophagy markers, such as enhanced degradation of autophagosomal substrates and lipidation of microtubule-associated-protein-light-chain-3 (LC3) (93). During autophagy, LC3 is converted from the cytoplasmic form LC3-I to the membrane-associated form LC3-II, and the LC3-II/LC3-I ratio is widely used as a marker of autophagy activity (94). Autophagy and apoptosis may act interchangeably under certain conditions. Excessive autophagy, referred to as 'autophagic death', can lead to cell death resembling apoptosis. These two processes are regulated by overlapping signaling pathways, including mTOR, Bcl-2 and Beclin-1 (95). Quinazolinone compounds modulate the initiation and progression of cell autophagy (Table III, Fig. 4).

Kumar *et al* (96) investigated a novel quinazolinone derivative, 2,3-dihydro-2-(quinoline-5-yl)quinazolin-4(1H)-one (DQQ). DQQ induced the formation of acidic vacuolar organelles (AVOs) in MOLT-4 cells and significantly increased the expression of autophagy-related proteins, including LC3-II, autophagy-related 7 (ATG7), ATG5 and Beclin-1 (96). Another study showed that a fused quinazolinone compound [compound 6, based on 7,8,9,10-tetrahydroazepino (2,1-b)

Table III. Autophagy pathway changes following quinazolinone derivative treatment.

Authors, year	Cancer type	Chemical name	Affected molecule or pathway	(Refs.)
Kumar <i>et al</i> , 2014	Leukemia	2,3-Dihydro-2-(quinoline-5-yl)quinazolin-4(1H)-one	AVOs $\uparrow$, beclin1 $\uparrow$, ATG7 $\uparrow$, ATG5 $\uparrow$, LC3-II $\uparrow$	(96)
Sharma <i>et al</i> , 2022	Lung cancer	7,8,9,10-Tetrahydroazepino (2,1-b)quinazolin-12 (6H)-one	AVOs $\uparrow$	(97)
Xia <i>et al</i> , 2017	Breast cancer	7-bromo-6-chloro-3-(3-(3-hydroxypiperidin-2-yl)propyl)quinazolin-4(3H)-one	LC3 $\uparrow$, ATG5-ATG12 complex $\uparrow$, SQSTM1 $\downarrow$, STMN1 $\downarrow$, p53 $\downarrow$	(98)
Ha <i>et al</i> , 2021	Colorectal cancer	2-(3-Ethoxyphenyl)-6-pyrrolidinylquinazolinone	ATG5, ATG7, ATG12, ATG16 $\uparrow$ p62 $\uparrow$, LC3/LC3-II $\downarrow$	(99)
ElZahabi <i>et al</i> , 2021	Breast cancer	3-Amino-6,8-dibromo-2-methylquinazolin-4(3H)-one	EGFR $\downarrow$, PI3K, AKT, mTOR $\downarrow$	(100)

AVOs, acidic vacuolar organelles; ATG, autophagy-related gene; LC3, microtubule-associated-proteinlight-chain-3; SQSTM1, sequestosome 1; STMN1, stathmin 1; mTOR, mammalian target of rapamycin.

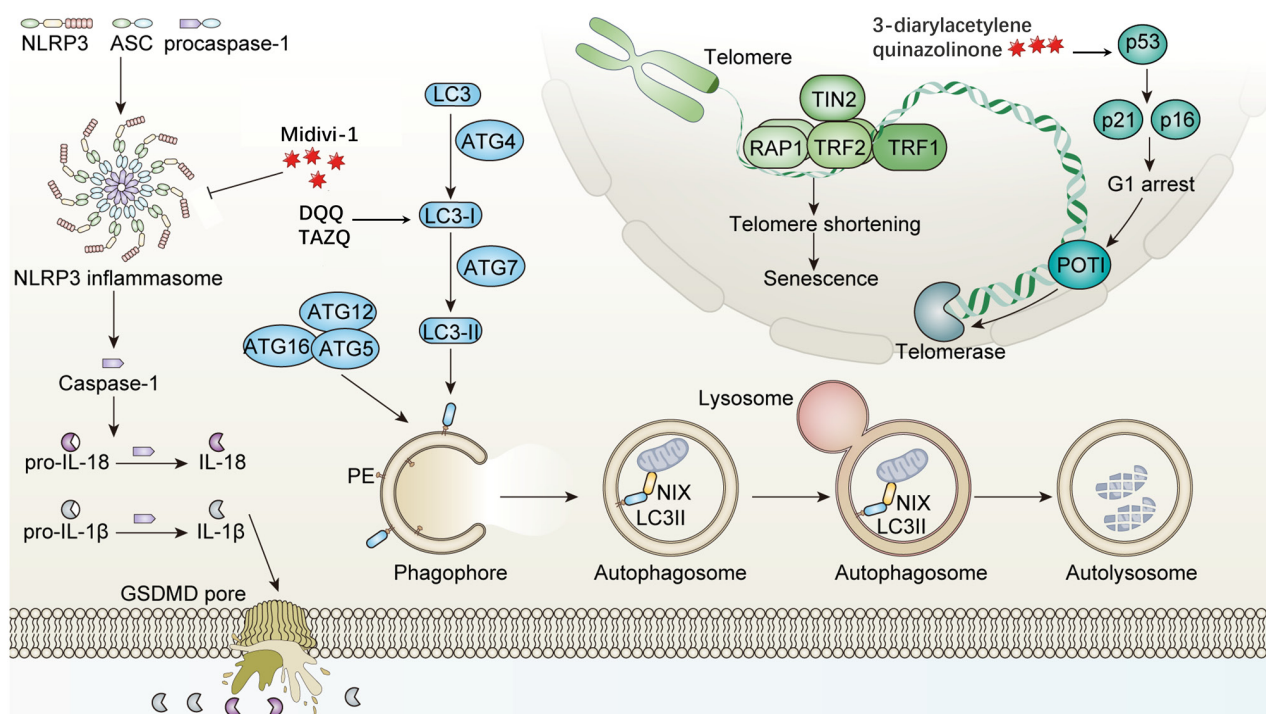


Figure 4. Mechanism of action of Quinazolinone compounds in pyroptosis, autophagy and cellular senescence pathways. i) In the senescence pathway, telomere shortening and limited telomerase function activate the p53/p21/p16 pathway, causing G1 phase arrest and cellular senescence [3-(2-(hydroxymethyl)phenyl)-2-methylquinazolin-4(3H)-ones upregulate the expression of TRF1, POT1 and p53/p21/p16, and inhibit telomerase, inducing cells to enter a senescence phenotype]. ii) In the pyroptosis pathway, NLRP3 assembles with ASC and procaspase-1 to form the inflammasome, activating caspase-1, which mediates the maturation of IL-1 β and IL-18, and induces pyroptosis through GSDMD, forming membrane pores. Quinazolinone derivatives can inhibit this process by blocking NLRP3 inflammasome activation and the release of inflammatory factors (Mdivi-1 inhibits NLRP3 inflammasome activation, reduces the activation of NLRP3, ASC, Caspase-1 and the level of GSDMD-NT, and decreases the release of IL-1 β and IL-18). iii) In the autophagy pathway, ATG family proteins mediate phagophore nucleation and extension. LC3 is modified by ATG4 and ATG7, transforming into LC3-II, which promotes autophagosome formation and fusion with lysosomes for substrate degradation (DQD and HF promote LC3-II generation, enhance ATG5-ATG12 complex formation and promote autophagy). MJ-33 initiates autophagy by activating ATG proteins during vesicle nucleation but reduces the LC3/LC3-II ratio and increases p62 levels, inhibiting autophagy). NLRP3, NOD-like receptor thermal protein domain associated protein 3; ASC, apoptosis-associated speck-like protein containing a CARD; GSDMD, gasdermin D; ATG, autophagy related gene; LC3, microtubule-associated-proteinlight-chain-3; NIX, NIP3-like protein X; TIN2, Terf1 interacting nuclear factor 2; RAP1, Ras-proximate-1; TRF1, telomeric repeat binding factor 2; POT1, protection of telomeres 1.

quinazolin-12(6H)-one] increased AVO formation, as detected by acridine orange staining, indicating enhanced autophagic

flux (97). Halofuginone (HF), a quinazolinone alkaloid derived from *Dichroa febrifuga*, promoted autophagy while inhibiting

Table IV. Senescence, necrosis and pyroptosis pathway changes following quinazolinone derivative treatment.

Authors, year	Cancer type	Chemical name	Affected molecule or pathway	(Refs.)
Kamal <i>et al</i> , 2013	Breast cancer, non-small cell lung cancer, pancreatic cancer, colorectal cancer	A series of 3-diarylethyne quinazolinone compounds	p53, p21, p16↑ TRF1, POT1↑ SKP2, TRF2 and tankyrase protein levels↓	(106)
Venkatesh <i>et al</i> , 2015	Cervical cancer	2-Methyl-3-(2-((4-phenyl-1H-1,2,3-Triazol-1-yl)methyl)phenyl)quinazolin-4(3H)-one	p53, p21↑ HDAC-1,2,3,4↓	(107)
Shams <i>et al</i> , 2011	Kidney damage	4(3H)-Quinazolinone-2-propyl-2-phenylethyl and 4(3H)quinazolinone-2-ethyl-2-phenylethyl	By metabolization and production of active metabolites and free oxygen radicals, cell membrane and organelles such as mitochondria and peroxisome are damaged and necrosis appears in renal tubule cells	(112)
Piamsiri <i>et al</i> , 2024	Acute myocardial infarction	3-(2,4-Dichloro-5-methoxyphenyl)-2,3-dihydro-2-thioxo-4(1H)-quinazolinone	NLRP3, GSDMD-NT↑	(113)
Li <i>et al</i> , 2021	Atopic dermatitis	3-(2,4-Dichloro-5-methoxyphenyl)-2,3-dihydro-2-thioxo-4(1H)-quinazolinone	NLRP3, ASC↓ Cleavage of Caspase-1↓ GSDMD-NT↓ IL-1β, IL-18↓	(114)
Liu <i>et al</i> , 2020	Acute kidney injury	3-(2,4-Dichloro-5-methoxyphenyl)-2,3-dihydro-2-thioxo-4(1H)-quinazolinone	NLRP3↓ IL-1β, IL-18↓	(116)

TRF1, telomeric repeat binding factor 1; POT1, protection of telomeres 1; SKP2, S-phase kinase-associated protein 2; HDAC, histone deacetylase; NLRP3, NOD-like receptor thermal protein domain associated protein 3; GSDMD-NT, gasdermin D N terminus; ASC, apoptosis-associated speck-like protein containing a CARD; Caspase, cysteinyl aspartate specific proteinase.

stathmin 1 and p53 expression and activity. HF increased LC3 expression, promoted ATG5-ATG12 complex formation and reduced sequestosome 1 expression in MCF-7 cells (98).

Certain quinazolinone derivatives can also inhibit autophagy. For instance, MJ-33 initiates autophagy at the vesicle nucleation stage by activating ATG proteins but decreases the LC3/LC3-II ratio and increases p62 levels, suggesting suppression of autophagic flux. In HT-29/5FUR cells, this suppression enhances MJ-33-induced apoptosis (99). ElZahabi *et al* (100) designed a series of quinazolin-4-one derivatives, among which compound 7 reduced autophagy, leading to increased apoptosis and cancer cell death.

Senescence. Cellular senescence is generally an irreversible arrest of cell proliferation in damaged normal cells that have exited the cell cycle. It is associated with widespread macromolecular alterations and a secretory phenotype linked to chronic inflammation (101). Senescent cells show characteristic morphological changes, including flattened cell shape, vacuolization, cytoplasmic granularity and organelle abnormalities (102). Key features of senescence include persistent cell cycle arrest, altered transcriptional activity,

a pro-inflammatory secretome, accumulated macromolecular damage and metabolic dysregulation (103). Increasing evidence indicates a complex relationship between aging and cancer (Table IV, Fig. 4). Initially, senescence functions as a protective mechanism by limiting abnormal cell proliferation and reducing cancer risk. However, with aging, immune decline and accumulated DNA damage may contribute to cancer development (104,105).

Kamal *et al* (106) developed a series of 3-diarylacetylene quinazolinone compounds that activate p53, p21, p16, telomeric repeat binding factor 1 (TRF1) and protection of telomeres 1 (POT1) proteins. These compounds exhibited significant telomerase inhibitory activity, suggesting their potential as senescence inducers. Similarly, certain 3-(2-(hydroxymethyl)phenyl)-2-methylquinazolin-4(3H)-ones induced a senescence phenotype in HeLa cells (107). The application of quinazolinone and its derivatives in aging and cancer therapy remains an area of active investigation.

Necrosis and pyroptosis. Necrosis is an abnormal form of cell or tissue death caused by external factors such as trauma, hypoxia, infection or injury. Receptor-interacting protein

kinase 1 has been identified as a key regulator of necroptosis, a programmed form of necrosis activated by stimuli such as TNF, TNF superfamily member 10 (also known as TRAIL), lipopolysaccharide, oxidative stress or DNA damage (108). During necrosis, membrane breakdown leads to the release of cytoplasmic contents into the extracellular environment (109).

Pyroptosis is a regulated form of cell death mediated by gasdermins and characterized by continuous cell swelling, plasma membrane rupture and the release of intracellular contents that trigger inflammatory and immune responses (110). It is initiated by inflammasome activation in response to various triggers (111). Pyroptosis is involved in cancer, neurodegenerative diseases and ischemia-reperfusion injury. Research on the effects of quinazolinone derivatives in necrosis and pyroptosis is still at an early stage and the specific mechanisms remain elusive. The available literature is limited. Quinazolinone compounds can induce cell death through necrosis and pyroptosis (Table IV, Fig. 4).

In BALB/c mice, administration of two new quinazolinone compounds, 4(3H)-quinazolinone-2-propyl-2-phenylethyl and 4(3H)-quinazolinone-2-ethyl-2-phenylethyl, caused abnormal kidney function. Quinazolinones can affect sulfhydryl groups, disrupt protein structures, generate reactive metabolites and free radicals, and damage organelles such as tubular membranes, mitochondria and peroxisomes, ultimately leading to cell necrosis (112).

Mdivi-1, a quinazolinone-derived compound, has been shown to reduce necroptosis- and pyroptosis-related protein expression, including NLR family pyrin domain containing 3 (NLRP3) and gasdermin D N-terminus (GSDMD-NT), in cardiomyocytes of rats with myocardial infarction, thereby improving cardiac function in post-MI rats (113). Li *et al* (114) were the first to study the effect of Mdivi-1 on primary human keratinocytes in an *in vitro* model of atopic dermatitis-related inflammation induced by an inflammatory cocktail. Their results showed that Mdivi-1 inhibited NLRP3 inflammasome activation and pyroptosis, as indicated by reduced levels of NLRP3, apoptosis-associated speck-like protein containing a CARD, cleaved caspase-1, GSDMD-NT, and mature interleukins IL-1 β and IL-18 in keratinocytes. In cellular and animal models of septic acute kidney injury, Mdivi-1 suppressed NLRP3-driven pyroptosis and improved mitochondrial function (115,116). Further research is needed to fully understand the roles and mechanisms of quinazolinone and its derivatives in necrosis and pyroptosis.

3. Application of quinazolinone derivatives in cancer therapy

Quinazolinone and its derivatives have attracted considerable attention in recent years for their ability to induce cell death in various cancer types, representing a promising therapeutic approach. As single agents, these compounds act through multiple mechanisms, including apoptosis, autophagy and ferroptosis. To enhance therapeutic efficacy and address challenges such as drug resistance and toxicity, increasing efforts have focused on combining quinazolinone derivatives with other pharmacological agents. This strategy not only amplifies their anti-tumor effects but also enables more targeted interventions, potentially reducing adverse

effects. The following section discusses the clinical prospectss of quinazolinone and its derivatives in combination therapy, emphasizing their synergistic effects when used with conventional chemotherapeutic agents and molecular targeted therapies.

Combination with platinum-based drugs. Studies have shown that co-treatment with cisplatin and Mdivi-1 synergistically enhances apoptotic cell death in both intrinsically and acquired cisplatin-resistant tumor cells, including MDA-MB-231 breast cancer, H1299 non-small cell lung cancer, glioblastoma, melanoma, cholangiocarcinoma and A2780cis cisplatin-resistant ovarian cancer cells (117,118). In A2780cis cells, Mdivi-1 enhances cisplatin sensitivity through a Drp1-independent pathway. The combination increases DNA damage, upregulates phorbol-12-myristate-13-acetate-induced protein 1 and disrupts mitochondrial function, ultimately triggering Bax- and Bak-independent mitochondrial outer membrane permeabilization and activating the mitochondrial apoptotic pathway (117). Tuskorn *et al* (118) demonstrated that Mdivi-1 increases the sensitivity of cholangiocarcinoma cells to cisplatin by promoting oxidative stress and autophagosome formation, thereby inducing cell death through mitochondrial pathways. Furthermore, Mdivi-1 protects against cisplatin-induced hair cell death in zebrafish by modulating mitochondrial dynamics, suggesting its potential for reducing ototoxicity. Further studies in mammalian models are required to clarify the underlying protective mechanisms (119).

Combination with 5-fluorouracil (5-FU). MJ-33, a quinazolinone derivative, exhibits anti-tumor activity by reducing the viability of 5-FU-resistant HT-29 colon cancer cells. It induces apoptosis and autophagy through the AKT/mTOR signaling pathway, offering potential therapeutic value in 5-FU-resistant colorectal cancer (CRC) (76).

Lai *et al* (120) reported that 2-(3-fluorophenyl)-6-morpholinoquinazolin-4(3H)-one induces mitotic arrest, subsequently leading to apoptosis. This compound also synergizes with 5-FU to enhance cytotoxic effects against oral squamous cell carcinoma (OSCC).

Combination with gemcitabine. HMJ-38 promotes both autophagy and apoptosis in MIA-RG100 pancreatic cancer cells and demonstrates cytotoxic effects against gemcitabine-resistant cells. The mechanism involves activation of the EGFR-AKT-mTOR signaling pathway, which induces autophagy, and the mitochondrial pathway, which facilitates apoptosis (65). These findings provide new perspectives for overcoming gemcitabine resistance in pancreatic cancer. Another quinazolinone derivative, QD232, suppresses the growth of gemcitabine-resistant MIA PaCa-2 cells by inhibiting STAT3 and Src phosphorylation, offering a potential strategy for treating drug-resistant pancreatic cancer associated with STAT3 activation (121).

Combination with temozolomide. Targeting the catalytic domain of PARP-1, a series of quinazolin-2,4(1H,3H)-dione derivatives have been synthesized as PARP-1 inhibitors. Zhou *et al* (122) developed novel compounds containing a 3-amino-pyrrolidine group, which enhanced the cytotoxic

effects of temozolomide in the MX-1 xenograft breast cancer model. Similarly, 1-substituted benzyl quinazoline-2,4(1H,3H)-dione derivatives demonstrated comparable efficacy (123). Another study confirmed that the 2-propionyl-3H-quinazoline-4-one scaffold acts as a novel PARP-1 inhibitor, exhibiting synergistic effects with temozolomide in MX1 cells (124).

Combination with paclitaxel. Ucleotide binding oligomerization domain containing 1 (NOD1) and NOD2 receptors, which contain nucleotide-binding oligomerization domains, are emerging as potential immune checkpoints. In a study by Ma *et al* (125), a quinazolinone derivative [6-(3-chlorophenyl)-3-(2-(3,3-difluoropiperidin-1-yl)-2-oxoethyl)-4-oxo-N-(3-(4-(trifluoromethyl)phenoxy)propyl)-3,4-dihydroquinazoline-7-carboxamide] was designed as a dual antagonist of NOD1/2. By inhibiting NOD1/2-mediated NF- κ B and MAPK signaling pathways, this compound enhanced the response of B16 melanoma-bearing mice to paclitaxel therapy (125).

4. Quinazolinone derivatives approved by the FDA or under clinical investigation

Idelalisib. Idelalisib (ZydeligTM; CAL-101; Gilead Sciences), with the chemical name 5-fluoro-3-phenyl-2-((1S)-1-(9H-purin-6-yl-amino)propyl)quinazolin-4(3H)-one, has the molecular formula $C_{22}H_{18}FN_7O$ and functions as a lipid kinase inhibitor, specifically targeting the p110 δ isoform of class I phosphatidylinositol-3 kinase (PI3K δ) (126). Idelalisib inhibits PI3K δ by competitively binding to the ATP-binding site of the p110 δ subunit. This inhibition disrupts key PI3K δ signaling functions, including chemokine secretion, cell migration and receptor-driven kinase phosphorylation, ultimately reducing cell survival and promoting apoptosis (127,128).

Idelalisib has shown clinical efficacy in indolent B-cell non-Hodgkin lymphoma and was approved by the FDA in 2014 for monotherapy in patients with chronic lymphocytic leukemia (CLL), follicular lymphoma and small lymphocytic lymphoma. It is also approved in combination with rituximab for the treatment of CLL (129,130). In patients with previously treated indolent non-Hodgkin lymphoma, idelalisib as monotherapy achieved an objective response rate (ORR) of 57%, with a median duration of response (mDOR) of 12.5 months and a median progression-free survival (PFS) of 20.3 months (131,132). When combined with rituximab, idelalisib further improved overall response rates and 12-month overall survival (OS) in patients with CLL (133).

Despite its clinical benefits, idelalisib carries a black box warning from the FDA due to the risk of severe or fatal adverse events, including hepatotoxicity, diarrhea, colitis, pneumonia and intestinal perforation (134). Patients who developed colitis or transaminitis after idelalisib treatment exhibited elevated plasma chemokine levels and reduced T-regulatory cell (Treg) populations, suggesting that Treg depletion may contribute to the adverse effects of p110 δ inhibition by releasing the suppression of cytotoxic T cells (135). In a Phase III clinical trial, the combination of idelalisib and rituximab improved PFS in patients with relapsed/refractory CLL from 11.1 to 20.8 months; however, long-term follow-up revealed a 5-year overall survival rate of only 40%, indicating disease progression

in certain patients and suggesting the development of resistance (136,137). In CLL, resistance to idelalisib is closely associated with the activation of insulin-like growth factor 1 receptor (IGF1R). Specifically, the upregulation of IGF1R enhances the MAPK signaling pathway, bypassing PI3K δ inhibition and thereby promoting tumor cell survival (138). To overcome Idelalisib resistance, researchers have explored various combination therapy strategies. For instance, idelalisib combined with bortezomib blocks drug resistance properties of Epstein-Barr virus-related B-cell origin cancer cells via regulation of NF- κ B (139). Nevertheless, further investigation into the molecular mechanisms of resistance is necessary to develop more precise therapeutic strategies.

Ispinesib. Ispinesib, a quinazolinone-derived compound, is a selective inhibitor of kinesin spindle protein (KSP) and functions as an allosteric modulator of KSP motor ATPase activity. By inhibiting KSP, ispinesib disrupts mitotic spindle formation, leading to cell cycle arrest and apoptosis (140). Developed by Cytokinetics, ispinesib entered clinical trials in 2004 for multiple indications, becoming the first potent and selective KSP inhibitor to undergo clinical testing in human diseases (20). According to data from the National Institutes of Health, ispinesib has been evaluated as monotherapy in 13 Phase I/II clinical trials for various cancer types, including relapsed renal cell cancer (RCC), breast cancer, recurrent or metastatic head and neck squamous cell carcinoma (HNSCC), ovarian cancer (OC), hepatocellular carcinoma (HCC) and CRC, with the best responses observed in breast cancer and OC (141,142). As a combination therapy, ispinesib has been tested in three clinical trials: With docetaxel for HCC, with capecitabine for HNSCC and with carboplatin for metastatic or recurrent malignant melanoma (142,143).

In clinical studies of breast cancer, Ispinesib has shown some antitumor activity, with an ORR of 9% (144). However, its ORR was relatively poor in other tumor types. In a phase II clinical trial for advanced RCC, no complete responses or partial responses were observed, and only 6 patients had stable disease (145). A phase II trial of Ispinesib was conducted in patients with advanced HCC who had not undergone chemotherapy. At the 8-week evaluation, 46% of patients had stable disease as the best response, with an mDOR of 3.9 months and a median time to tumor progression of 1.61 months (146). No significant objective response was achieved. The most common adverse reactions associated with ispinesib treatment include neutropenia, anemia, elevated alanine aminotransferase and aspartate aminotransferase, and diarrhea, while no neuropathy, mucositis or alopecia have been observed (147).

In glioblastoma, resistance to ispinesib is closely associated with the activation of STAT3. STAT3 mediates anti-apoptotic and metabolic effects through dual phosphorylation by Src and EGFR, thereby promoting drug resistance that can be reversed by simultaneously inhibiting Src and EGFR (148). In addition, drug efflux mediated by P-glycoprotein (P-gp) can pump ispinesib out of the cells, reducing its intracellular concentration and leading to drug resistance, which can be overcome by inhibiting P-gp activity to enhance the cytotoxicity of ispinesib (149). Clinical trials have reported a favorable safety profile, with no significant neurotoxicity, alopecia or gastrointestinal toxicity. The most common adverse event was

reversible neutropenia (150). Ispinesib is currently in Phase I/II clinical development and further studies on its mechanisms and optimized clinical protocols may establish it as an effective anti-tumor therapy.

Nolatrexed. Nolatrexed [2-amino-6-methyl-5-(4-pyridylthio)-4(3H)-quinazolinone] is a thymidylate synthase inhibitor primarily developed for the treatment of HCC. In patients with unresectable HCC, nolatrexed achieved a median overall survival of 22.3 weeks, with an ORR of 1.4% and a median PFS of 12 weeks (151). Initially developed by Agouron Pharmaceuticals in the US, nolatrexed advanced to Phase II/III trials for liver cancer and head and neck tumors through a partnership with Roche. In 1999, Agouron transferred global oncology rights for nolatrexed to Eximias Pharmaceutical Company, which currently leads global development of nolatrexed. Ongoing Phase II clinical trials are being conducted for CRC, HNSCC, prostate cancer (PCA), pancreatic cancer and lung cancer in countries including the US, UK, Canada, Italy and South Africa. Phase III trials for liver cancer are also in progress (152,153).

Nolatrexed, a 4(3H)-quinazolinone derivative, has shown promising efficacy in clinical trials, exhibiting typical antimetabolite-related side effects such as short duration of action and low toxicity, along with mucositis, vomiting, diarrhea and thrombocytopenia (151). Thymidylate synthase (TS) is the primary target of nolatrexed and its overexpression is one of the key mechanisms of resistance. In CRC cells with p53 mutations, both TS mRNA and protein expression levels are significantly elevated, thereby increasing the cells' resistance to nolatrexed (154). Furthermore, being lipophilic, nolatrexed passively diffuses into cells without the need for specific membrane transport proteins. Since inhibition of transporter-mediated uptake is a mechanism of tumor cell resistance, this property may allow nolatrexed to be effective against drug-resistant tumors and reduce the likelihood of resistance development (155). Although granted orphan drug status by the European Medicines Agency, it was not approved by the FDA in 2005 (20).

Halofuginone. Halofuginone is a synthetic derivative of a quinazolinone alkaloid with the chemical name 7-bromo-6-chloro-3-(3-(3-hydroxy-2-piperidiny)-2-oxopropyl)-4(3H)-quinazolinone (156). It was developed by Collgard Biopharmaceuticals and received FDA approval in 2000 as an orphan drug for the treatment of scleroderma (20). Halofuginone inhibits epithelial-to-mesenchymal transition in tumor cells, reducing migration and invasiveness. It also selectively suppresses Th17 cell differentiation and inhibits Smad3 phosphorylation, a key downstream mediator of the TGF- β pathway. These effects reduce tumor-associated fibrosis and enhance immune surveillance (157,158). As a broad-spectrum anti-tumor agent, it has demonstrated efficacy against Pancreatic adenocarcinoma, CRC, breast cancer and lung cancer (159). Halofuginone has demonstrated promising results in a Phase II study for recurrent superficial transitional cell carcinoma of the bladder. In addition, a sustained-release formulation of fluoroferin is under Phase II evaluation for safety, tolerability and pharmacokinetics in patients with Duchenne muscular dystrophy (20).

Up to date, clinical investigations of halofuginone have primarily focused on exploring its safety and tolerability rather than establishing overall therapeutic efficacy, and no specific data on ORR, PFS or DOR have yet been reported. Nonetheless, its antitumor potential has been demonstrated in several experimental models. For instance, in anaplastic thyroid carcinoma (ATC), halofuginone significantly suppresses ATC cell proliferation and tumor growth by inhibiting the enzyme-prolyl-tRNA synthetase-activating transcription factor 4-collagen type I signaling axis (160). In OSCC, halofuginone suppressed collagen synthesis and myofibroblast activation, thereby attenuating tumor invasiveness and growth (161). Common adverse effects include nausea, vomiting, a possible increased risk of bleeding, and decreased red and white blood cell counts (162). A study suggested that halofuginone can overcome drug resistance in cancer therapy with a relatively low risk of inducing resistance. For instance, it restores sensitivity to EGFR-tyrosine kinase inhibitors by targeting phosphoserine aminotransferase 1 down-regulation (163), reverses paclitaxel resistance in basal-like breast cancer by modulating the BRCA1/TGF- β signaling axis (164) and serves as a potential therapeutic agent for 5-FU-resistant CRC by targeting microRNA-132-3p *in vitro* (165).

Febrifugine. Febrifugine is the active antimalarial compound isolated from the traditional Chinese herb Chang Shan, which has been used for centuries to treat malaria-induced fevers (166). Febrifugine also demonstrates anti-tumor activity and has shown potential therapeutic effects of PCA and bladder cancer (BLCA), likely through inhibition of focal adhesion kinase (167-169). It also suppresses steroidogenesis and promotes apoptosis, contributing to its anti-tumor effects by inhibiting DNA synthesis (170). The effectiveness of febrifugine in clinical treatment is currently focused on basic research and animal models, with no specific data reported directly on clinical patients. A related study revealed its anticancer efficacy. In the BLCA model, febrifugine effectively inhibited the proliferation of T24 and SW780 BLCA cells, with IC₅₀ values of 0.02 and 0.018 μ M, respectively, and demonstrated good anticancer effects by reducing steroidogenesis and promoting apoptosis (168). It was also shown to enhance the anticancer effects of cisplatin *in vivo* (171). Due to significant side effects, there has been no further research on febrifugine for a long period of time and there is limited literature or clinical data that discuss its resistance in different cancer types in detail. Some potential mechanisms of resistance may include cancer cells rejecting febrifugine, mutations in target genes or cancer cells altering their sensitivity to the drug through metabolic pathways. The specific mechanisms of resistance may be gradually revealed in future studies. Common adverse effects include dizziness, dry mouth and persistent vomiting (172,173). A summary of the aforementioned quinazolinone derivatives is presented in Table V.

5. SAR of anticancer quinazolinone compounds

SAR studies of quinazolinone derivatives reveal a close association between molecular structure and biological activity. Structural optimization and the introduction of various substituents can effectively modulate anti-tumor activity, pharmacokinetic stability and targeting specificity. The substitution sites of quinazolinone are shown in Fig. 1.

Table V. Quinazolinone derivatives approved or under clinical investigation in cancer therapy.

Drug	Chemical structure	Clinical use/treatment	Clinical analysis	Clinical development state
Idelalisib		Clinical use: Antitumor agent and PI3K inhibitor Treatment: iNHL, CLL, FL, SLL	Clinical metrics: For the treatment of iNHL, the ORR is 57%, DOR is 12.5 months and PFS is 20.3 months Adverse effects: Hepatotoxicity, diarrhea, colitis, pneumonia and intestinal perforation	FDA approved
Ispinesib		Clinical use: KSP inhibitor Treatment: RCC, BC, HNSCC, OC, HCC, CRC	Clinical metrics: For the treatment of breast cancer, the ORR is 9%. For the treatment of HCC, the mDOR is 3.9 months and mTTP is 1.61 months Adverse effects: Neutropenia, elevated ALT, elevated AST, anemia and diarrhea	Phase-I and II clinical trial
Nolatrexed		Clinical use: Thymidylate synthase inhibitors Treatment: CRC, HNSCC, PC and pancreatic cancer	Clinical metrics: For the treatment of HCC, the ORR is 1.4%, the median OS is 22.3 weeks and PFS is 12 weeks Adverse effects: Typical antimetabolite-related side effects, mucositis, vomiting, diarrhea and thrombocytopenia	Phase-II and III clinical trial
Halofuginone		Clinical use: Epithelial-mesenchymal transition inhibitor Treatment: CRC, ATC, breast cancer, pancreatic cancer, lung cancer and transitional cell carcinoma of the bladder	Clinical metrics: Have not been systematically reported Adverse effects: Nausea, vomiting, potential increase in the risk of bleeding, a risk of reduced red and white blood cell counts	Phase-I and II clinical trial
Febrifugine		Clinical use: Inhibition of tumor metastasis, invasion and epithelial-to-mesenchymal transition Treatment: PCA, BLCA	Clinical metrics: Have not been systematically reported Adverse effects: Dizziness, dry mouth and persistent vomiting	Phase-I and II clinical trial

The chemical structures were retrieved from PubChem (<https://pubchem.ncbi.nlm.nih.gov/>) and drawn using ChemDraw 23.1.1 software (PerkinElmer Informatics). ORR, objective response rate; mDOR, median duration of response; PFS, progression-free survival; mTTP, median time to tumour progression; OS, overall survival; iNHL, indolent non-Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; FL, follicular lymphoma; SLL, small lymphocytic lymphoma; RCC, relapsed renal cell cancer; BC, breast cancer; HNSCC, head and neck squamous cell carcinoma; OC, ovarian cancer; HCC, hepatocellular carcinoma; CRC, colorectal cancer; PC, pancreatic cancer; ATC, anaplastic thyroid carcinoma; PCA, prostate cancer; BLCA, bladder cancer.

The 2- and 3-positions are key sites for SAR studies, as they directly influence selectivity, potency and cellular activity. In anticancer compounds, substituents at positions 2 and 3 are predominantly sulfur ethers and aryl ketones, as seen in the investigational drug ispiresib. Electron-withdrawing groups at the meta position, such as halogens and trifluoromethyl,

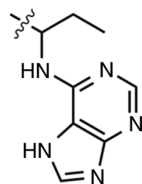
generally enhance inhibitory activity against EGFR, as exemplified by the quinazoline-based drugs gefitinib and erlotinib, which contain -Cl and -CF₃ groups (174).

Substituents at the 6- and 7-positions typically target the solvent-exposed regions or entry channels of the ATP-binding pocket (175). Modifications at these positions

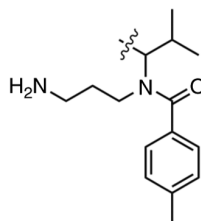
Table VI. Substitution at different positions of several common quinazolinone compounds.

Drug	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	R ₇
Idelalisib	H	C ₈ H ₁₀ N ₅	Benzene	H	F	H	H
Ispinesib	H	C ₁₅ H ₂₃ N ₂ O	Benzene	H	H	H	Cl
Nolatrexed	H	NH ₂	H	H	C ₅ H ₄ NS	H	H
Halofuginone	H	H	C ₈ H ₁₆ NO	H	H	Cl	Br
Febrifugine	H	H	C ₈ H ₁₄ NO ₂	H	H	H	H
Mdivi-1	H	S	C ₇ H ₅ Cl ₂ O	H	H	H	H
Erastin	H	C ₁₄ H ₁₈ ClN ₂ O ₂	Ethoxybenzene	H	H	H	H
HMJ-38	H	C ₇ H ₇ O	H	H	H	Pyrrolidine	H
MJ-33	H	C ₈ H ₉ O	H	H	H	Pyrrolidine	H

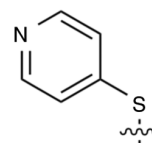
Each row corresponds to a specific compound, with the columns specifying the chemical moieties or atoms occupying the respective substitution sites.



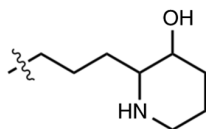
Substituent at Idelalisib position 2



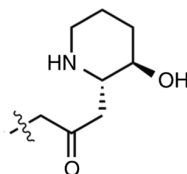
Substituent at Ispinesib position 2



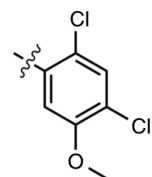
Substituent at Nolatrexed position 5



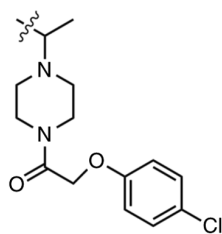
Substituent at Halofuginone position 3



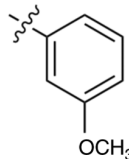
Substituent at Febrifugine position 3



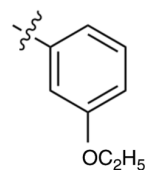
Substituent at Mdivi-1 position 3



Substituent at Erastin position 2



Substituent at HMJ-38 position 2



Substituent at MJ-33 position 2

Figure 5. Structures of substituents in common quinazolinone derivatives.

significantly affect solubility, membrane permeability and pharmacokinetics. Halogen atoms are frequently introduced at these positions to increase lipophilicity and stability, thereby improving membrane penetration and bioactivity, as observed with -Cl and -Br in halofuginone (176). However, methoxy groups generally have the opposite effect, reducing the reactivity of the ring toward various reactions (50). The 6,7-dimethoxyquinazolinone derivative forms an additional hydrogen bond with Thr918 of VEGFR2 via the oxygen atom of the methoxy group. A molecular docking study

showed that it can strongly bind to the hydrophobic site of VEGFR2 kinase, making it a potent VEGFR2 inhibitor (174). Furthermore, Kurogi *et al* (177) found from structure-activity relationship studies that introducing methoxy groups at the 6- and 7-positions of quinazolinone enhanced its hypolipidemic activity. Therefore, the addition or removal of such groups *in vivo* can serve as a tool for modulating the toxicity of quinazolinone derivatives.

Substitution at the 5-position is relatively uncommon, as introducing substituents at this site may increase steric

hindrance. However, it shows specificity for cytotoxic agents, such as the protein kinase inhibitor idelalisib and the dihydrofolate reductase inhibitor nolatrexed (20). These positions can also serve as linkers for synthesizing dual-target inhibitors. In the study on RAF kinase inhibitors, Huestis *et al* (178) designed the 5-fluoro-substituted quinazolinone compound GNE-0749. By masking the adjacent polar NH group, they enhanced the molecule's interaction with RAF kinase and significantly improved its solubility and permeability, thereby endowing it with properties suitable for oral administration (178). Table VI summarizes the SAR of several common quinazolinone derivatives. Fig. 5 shows the specific structure of these substituents.

6. Discussion

This review examined the structure, applications and mechanisms of cell death induced by quinazolinone and its derivatives. Quinazolinone is a multifunctional heterocyclic compound that has attracted considerable attention for its promising biological activity (179). Quinazolinone derivatives act through multiple cell death pathways, including classical apoptosis, autophagy and ferroptosis associated with metabolic stress and damage, as well as inflammatory responses triggered by senescence, necrosis and pyroptosis. Importantly, quinazolinone and its derivatives offer distinct advantages in overcoming tumor resistance and immune evasion. Cancer cells often develop resistance to chemotherapy through mechanisms such as drug efflux and altered drug metabolism (180,181). Quinazolinone derivatives have demonstrated the ability to counteract some of these mechanisms by sensitizing cancer cells to chemotherapeutic agents. Several quinazolinone-based compounds have received FDA approval for cancer treatment, while others have shown encouraging efficacy in preclinical studies and in Phase I and II clinical trials (182). Despite these advances, further rigorous clinical studies are needed to fully evaluate the safety, efficacy and optimal dosing strategies of quinazolinone derivatives.

Although quinazolinone and its derivatives show considerable potential in cancer therapy, several challenges and unresolved issues remain. First, the chemical synthesis of quinazolinones still relies heavily on high temperatures and harsh reaction conditions, and generates numerous by-products (183). A team from South China Normal University developed a covalent organic framework, TAPP-Cu-An, which enables efficient dehydrogenative cross-coupling reactions under mild conditions (room temperature and light exposure), facilitating the photochemical synthesis of 4-quinazolinone (184). Furthermore, a team from Guilin University of Technology developed a 4-DPAIPN catalyst, using acetonitrile as the solvent and blue LED light irradiation, achieving a metal-free synthesis of tetracyclic quinazolinones and avoiding the use of precious metals (185). Second, although it is established that these compounds act through multiple cell death pathways, the interactions and regulatory mechanisms among these pathways are not yet fully understood. Future research should investigate the crosstalk between these pathways and determine how quinazolinone modulates them in different cancer types to optimize its anti-tumor effects. Most current studies have examined combinations of quinazolinone derivatives

with chemotherapy agents; however, their synergistic potential with immunotherapy also warrants exploration (4,186). Finally, most quinazolinone derivatives suffer from poor water solubility, low oral bioavailability and short half-life, which limit their therapeutic efficacy *in vivo* (187). Future research should consider the use of nanocarriers (such as nanoparticles, liposomes and polymeric microparticles) to encapsulate the drug, improve solubility in aqueous solutions and enable targeted delivery, thereby maximizing therapeutic potential (188). Additionally, prodrug strategies can be employed, incorporating solubilizing moieties such as phosphate esters or polyethylene glycol (PEG) groups, such as PEG-400, to improve bioavailability (189).

Quinazolinone molecules can interact with fluorescent dyes through covalent coupling, electrostatic adsorption, or coordination bonding. These interactions allow real-time tracking of drug delivery *in vivo*, enable observation of drug absorption, transport and dynamic changes at the cellular level, and can be applied in fluorescent imaging of tumors (190). With advances in synthetic chemistry and drug design, structural modifications of quinazolinone compounds could further enhance specificity, selectivity and therapeutic efficacy. Designing new quinazolinone derivatives and investigating their roles in cancer treatment will be critical for advancing this field. By optimizing molecular structures to improve selectivity and cytotoxicity toward cancer cells, significant progress in therapeutic outcomes may be achieved.

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Availability of data and materials

Not applicable.

Authors' contributions

JL and YuY wrote the manuscript. YuY conceived and supervised the study. XK and YaY revised the manuscript. LW and QL finalized the figures and checked the grammar of the text. All authors contributed to the article and approved the submitted version. Data authentication is not applicable. All authors have read and agreed to the submitted version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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