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Fighting new wars with old Weapons: Repurposing of Anti-Malarial drug for Anticancer Therapy

Angela Samanta[a], Angshuman Sarkar*[a]

[a]*CMBL, Department of Biological Sciences, BITS Pilani K K Birla Goa Campus, Zuarinagar, Goa 403726, India*

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ABSTRACT

Background: Quinacrine (QC), an attractive anticancer drug, has been forwarded for clinical evaluation in various cancer types due to its tremendous safety data accumulated since World War II. Its shotgun nature makes it unmissable as a chemotherapy drug that traps and activates multiple pathways.

Results: Recently, QC has been shown to block malignancy by affecting pathways, including RHO signaling, G1/S arrest, ROS emission, and cell death through autophagy. In this review, we have extensively studied QC as an anticancer agent that affects various signaling pathways. We have documented activity via WNT, NOTCH, HEDGEHOG, MAPK, EGFR, P53, RHO, AKT, NF-k and TGF pathways and reformed the already established mode of action of QC.

Conclusion: QC's effects on multiple key signaling pathways, implicated in the malignant progression of numerous cancer types, make it an exciting candidate as a chemotherapeutic agent for new combination treatments and therapies.

INTRODUCTION

The most common cancer in 2019 was breast cancer, followed by lung and prostate cancer.[1] There are different types of cancer treatment including conventional single treatment or a combination of other treatments. The primary therapy includes surgery, radiation therapy, chemotherapy, immunotherapy, targeted therapy, hormone therapy, stem cell transplantation, or precision medicine.[2] The three main agents widely used to alter cancer development through signaling pathways are small molecules, nucleic acids and antibodies. However, small molecule inhibitors are widely studied but have drawbacks in terms of solubility, bioavailability, cellular targeting, and toxicity in normal cells.[3]

Most treatments result in high morbidity and reduced quality of life. Researchers are focusing on existing drugs and using them for cancer therapy because of their known profiles and high success rates. For the reuse of age-old used drugs, the clinical approval time is also shorter and the success rates are significant.[4] Small molecules face different challenges when acting in different pathways, particularly due to their complexity within the pathway. For example, Wnt (Wingless-related integration site), Notch (Neurogenic locus notch homolog protein)[1], and Hedgehog signaling pathways are interconnected and crossed downstream. These genes acts as a tumor promoter in one pathway and as a tumor suppressor in another.[3]

Much research has been conducted on the safety of quinacrine since US soldiers widely used it; About three million people were treated during World War II. For the identification of anticancer drugs, preference has been given to QC because it has low toxicity in normal cells and has no ff-target effects that might limit chemotherapy.[4]

QUINACRINE

Quinacrine (QC) (4-N-(6-Chloro-2-methoxyacridin-9-yl)-1-N,1-N-diethylpentane-1,4-diamine) is an FDA-approved antimalarial drug discovered in the

***Address for correspondence:**
Angushman Sarkar, Ph. D.,
CMBL, Department of Biological Sciences, BITS Pilani K K Birla Goa Campus, Zuarinagar, Goa 403726, India
Tel: +91-8322580261/+91-9503384704
Email: asarkar@goa.bits-pilani.ac.in

1920s.[5] QC is commonly used as mepacrine, quinacrine hydrochloride, quinacrine dihydrochloride and atabrine (registered name) to treat diseases other than malaria, giardiasis, tapeworm infection, refractory lupus erythematosus, rheumatoid arthritis and even as adjuvant cancer therapy. QC was rediscovered in a blind chemical library screen for small molecules that can activate p53 in tumor cells without causing genotoxicity. There is a need for a rationally designed drug that can act like a shotgun and be targeted in different or multiple pathways.[6] Its effects on several important signaling pathways involved in the malignant progression of numerous cancers make QC an exciting candidate as a chemotherapeutic agent for novel combination treatments.[7] QC has been shown to be a chemosensitizer that can enhance the chemotherapeutic effect on cancer cells, opening a new dimension for combination therapy.[8]

QC ACTIVATES APC (Adenomatous polyposis coli) IN WNT SIGNALING PATHWAY

WNT signaling can be broadly categorized as canonical and non-canonical pathways, with canonical or B-catenin pathways playing critical roles in cancer progression. Much work has been done in recent years to provide a detailed insight into the function and regulation of each stage of the canonical path, which has proved complicated.[9] APC and β-catenin play critical roles in proliferation, differentiation, and migration associated with multiple proteins in signaling pathways involved in attachment and cell cycle signaling.[10] Research shows that QC exposed breast cancer cells activate apoptosis by APC in the WNT-TCF pathway. Upregulation of APC with significant downregulation of GSK-3 (Glycogen synthase kinase-3) and Axin has been noted. APC, a multidomain protein, forms an Armadillo repeat domain, 15 residues, 20 residue domains and SAMP repeats, and a primary domain of which 15 amino acid repeats and 20 amino acid repeats are residues. This is essential to negatively regulate canonical signaling by binding to CTBP1 and CTBP2. Both of these transcriptional co-repressors block β-catenin and stimulate APC oligomerization.[11] APC also regulates microtubule stabilization, kinetochore function, and chromosomal segregation through basic and C-terminal domains (Zhang and Shay 2017), thereby inhibiting PARP and disassembling the BER complex. In the presence of QCABT 888, a PARP inhibitor has also shown increased DNA damage-inducing apoptosis in breast cancer cell lines.[12] An increase in cytotoxicity leading to apoptosis has been identified through DNA damage, cell cycle arrest and topoisomerase activity via the WNT-Tcf pathway.[13]

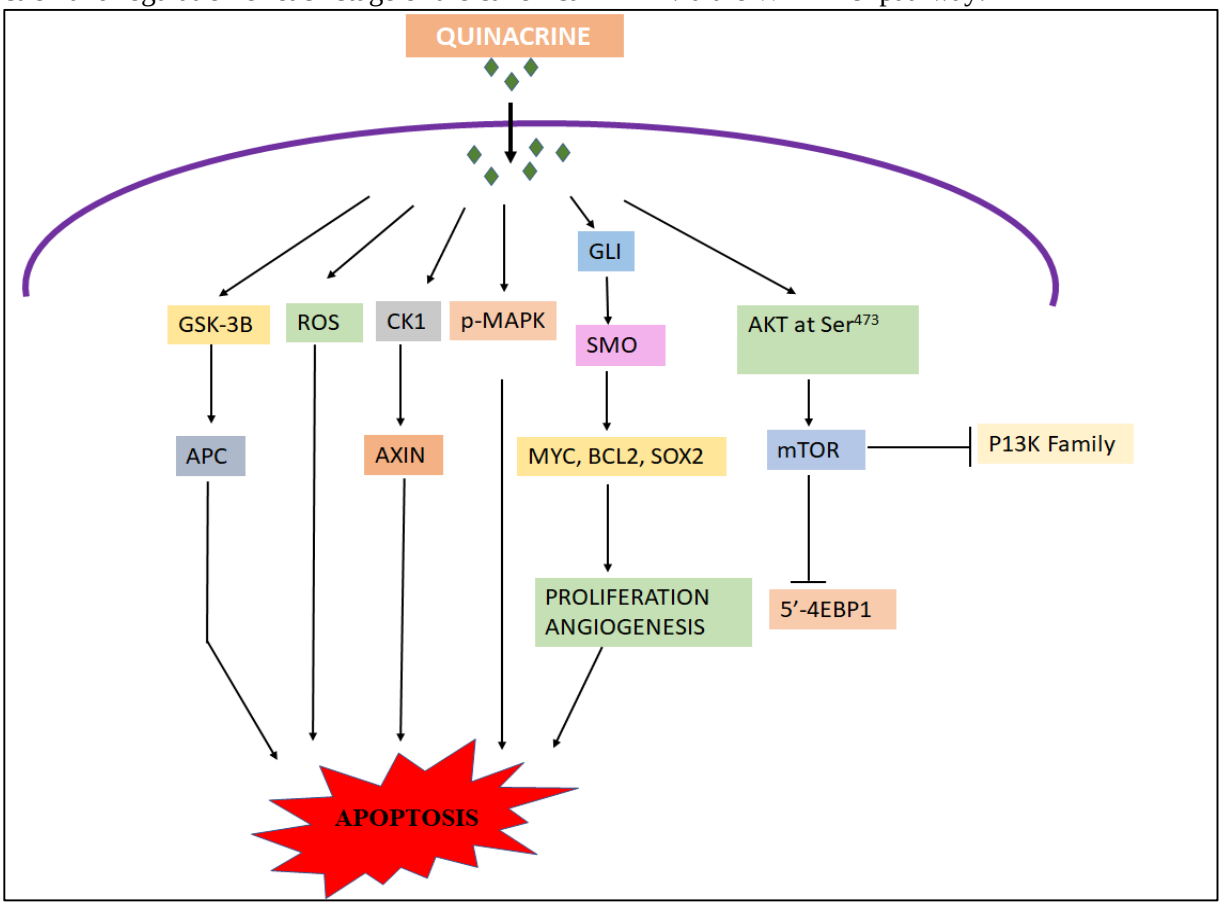

Figure 1. Graphical representation of the mode of action of Quinacrine. Flowchart representation of QC influencing the interplay between genes leading to cell death or apoptosis.

QC ALTERS HEDGEHOG SIGNALING PATHWAY THROUGH SMO (Smoothened, Frizzled Class Receptor) INACTIVATION

Hedgehog signaling can be activated classically or non-classically, both of which require the involvement of GLI. Although the end result of this pathway is proliferation and differentiation, different cancer type activation pathways are observed to alter their mode of action.[14] Since metastasis and drug resistance are the major barriers to curing cancer, most drugs are observed to have the potential to stop cancer metastasis by blocking the hedgehog GLI axis.[15] SMO, a GPCR-like protein, is activated by PTCH1 and translocated to the ciliary membrane after launch, which is essential for GLI activation. GLI, an oncogene activation, has also been shown to induce the modulation of Wnt signaling.[16] Recently, it was confirmed that QC significantly reduces the expression of SMO in triple-negative breast cancer while there is no significant toxic effect on normal breast cells.[17]

A 2016 study proved that NQC (Nano Quinacrine) is more potent and has the potential to induce cytotoxicity and, therefore, apoptosis than QC. Recent research has showed that there was downregulation of GLI, c-Myc, and Cyclin D and no changes in the sub-G1 population. GSK-3, a negative regulator of HH-GLI, has shown upregulation of protein expression after NQC exposure. Because QC is an intercalating agent, it inserts itself between the GLI-DNA bond, thus destabilizing the complex. The GLI-DNA complex is an essential phenomenon for downstream activation and GLI-dependent cell survival. NQC binds between two GC base pairs and thus damages DNA.[15]

QC SUPPRESS MS12 IN NOTCH/NUMB SIGNALING PATHWAY

Notch pathways play important roles in cancer metabolism, cell survival and also maintenance of cancer stem cells from cancer. It is also through this pathway cancer cells shifts from epithelial to mesenchymal transition to mesenchymal to epithelial cells and viceversa[18]. The Notch pathway is mostly considered non-functional in cancer, but it also depends on the type of cancer. It could serve as a tumor suppressor, while it has been shown to be oncogenic when upregulated.[3] Kundu *et al.* have mentioned that no commendable changes in the expression of cleaved NOTCH 1, an activator of the NOTCH cascade, were observed.[15] In 2019, they observed that NQC exposure induced nuclear translocation of nectin-4 and downregulated ADAM-17 expression. In combination treatment with 5-FU and NQC, the expression of nectin 4 was downregulated and there were no other changes in the NOTCH pathway.[19]

Musashi proteins are RNA-binding proteins encoded by MSI1 and MSI2 that regulate transcription events and cellular regulation. These relate to the prognosis of glioma, brain tumor, breast cancer and colon cancer. In contrast, when overexpressed, Numb inhibits cell proliferation, migration, and invasion due to downregulation of cyclin D1 or MMP-9 expression.[20,21] QC has been shown to downregulate MSI2, induce expression of Numb, which inhibits cell cycle progression at G0/G1 phase, repress c-Myc, and downregulate CDK4 and CDK6 expression. This study demonstrated that QC mode of action in DLBCL (diffuse large B cell lymphoma) is heterogeneous and mediates through the MSI2-NUMB pathway.[20]

QC INDUCE P38 AND INACTIVATE ERK IN MAPK SIGNALING PATHWAY

The JNK signaling pathway includes an important MAPK signaling pathway that controls proliferation, migration, development, and apoptosis. There are 13 different MAPK signals that can be activated by the JNK pathway, each inducing a different cellular function, metabolism, inflammation, and cytokine production. Once started, this pathway can lead to apoptosis by two different mechanisms. The c-Jun/Ap1-dependent pathway involves BAX/BCL2, cytochrome-c and Apaf-1, and the other involves Smac/Diablo through caspase8 activation.[22]

Quinacrine induces ROS generation in various cancers, ultimately leading to apoptosis. ROS has been shown to phosphorylate the MAPK pathway QC does not alter JNK phosphorylation in K562 cells although phosphorus-ERK is reduced. QC acts by inducing p38 phosphorylation and inactivating ERK, independently. Apoptosis is also activated by repression of BCL2, BCL2L1 and translocation of BAX in the nucleus when QC is exposed, which depends on p38 and p-ERK regulation. Reducing ERK has proved to involve HSP70 folding and mitigating cancer promotion.[91] BCL2 is regulated by AP1, which consists of homodimers and heterodimers of c-Jun, c-Fos, and ATF-2. QC induces the ERK pathway by downregulating phospho-c-Jun and phospho-c-Fos without altering ATF-2 and MCL1 expression. All of these steps cumulatively lead to apoptosis by releasing cytochrome c and activating caspase 9 and caspase 3.[23] Furthermore, the elimination of Mcl-1 has been shown to be a critical point in inducing apoptosis, and in the presence of a low dose of QC, down-regulation of MCL1 is promising.[24] Janie *et al.* demonstrated that BCL2 can also be induced by the QC-activated NF-k pathway in

colon cancer cells[25], indicating that apoptosis induction by QC is cancer- and cell-origin dependent.

JNK regulates various cellular processes including proliferation, differentiation, apoptosis, and DNA repair, and its activity depends on GSTA1 expression. GST upregulation, arrest of apoptosis, abnormal cell growth and the JNK signaling pathway are observed to be linked and interdependent.[26] QC inhibits GSTA1 by binding to the G site and tyrosine 9 through hydrogen bonding, which is the catalytic subunit of GSTA1. An increase in ROS generation due to inhibition of GSTs has been studied, resulting in blockage of phosphorylation of eIF2a.[27]

PLA2 has a significant association with prognosis in multiple tumors by modulating signaling pathways including proliferation, tumorigenesis and metastasis.[28] The cytosolic PLA2 enzyme has been shown to be activated and phosphorylated by MAP kinase. QC inhibits the action of PLA2 by downregulating it.[29]

QC INDERS EGFR EXPRESSION IN EGFR SIGNALING PATHWAY

EGFR, a proto-oncogene, plays an important role in cell proliferation and cell survival. Small aberrations in this gene can cause changes in cyclin/CDK 4-6, causing oncogenesis.[30] EGFR activation involves a number of activations of different signaling pathways, including P13K, AKT, ERK and signaling pathways leading to apoptosis and migration.[31] KRAS mutant lung cancer cells suppress autophagy upon exposure to QC, while inhibition of autophagy does not induce apoptosis in KRAS mutant cells. Additionally, inhibition of oxPPP (an oxidative arm of the pentose phosphate pathway) has been shown to promote autophagy inhibition while increasing cytotoxicity in cells. This study focuses primarily on PDAC and NSCLC cancer types, most of which have KRAS mutant cells. Nevertheless, QC has been found to block autophagy and oxPPP and stimulate cytotoxicity and hence cell death regardless of status.[32]

FER tyrosine kinase is a non-receptor tyrosine kinase that is activated downstream of EGFR, regulates cell adhesion and sends signals from the cell surface to the cytoskeleton. It is observed to be overexpressed in malignant cells compared to its standard counterpart, but its relevance depends on the type of cell and the stimulus.[13,33] Once overexpressed, FER increases phosphorylation of EGFR, ERK, and NF-k in the presence of QC EGFR binds directly to the SH2 domain of FER with phosphotyrosine residues of EGFR, thereby activating ERK and NF-k signaling pathways. QC exposed cells are more effective in the average number of EGFR and FER expressed cells. While overexpression of these proteins will terminate the effects of QC, resulting in better potency, the ERK inhibitor will support exposure.[33]

SMALL GTPASES SIGNALING PATHWAY ALTERATION ON QC EXPOSURE

The Rho signaling pathway plays a crucial role in cancer progression in (i) cell cycle, (ii) morphogenesis and (iii) migration.[34] In our laboratory, we observed different types of modulations of the cytoskeleton, such as B. lamellipodial protrusions and the formation of filopodial structures leading to the expression of Rac1, RhoA and Cdc42. Our study sheds light on the activation of Rac1 and Cdc42 after QC exposure to show a decrease in RhoA expression. QC was able to downregulate the master gene for modulation of the cell cytoskeleton, which is RhoA, since RhoA plays a role in tumor cell proliferation, cell survival and stimulation of transformation.[35] During motility, previous investigators observed that Rac activation at the front and Rho activation at the back promote migration.[34,36] The lack of migratory ability with QC concentration could also be attributed to the down-regulation of RhoA.

EFFECT OF QC ON AKT SIGNALING PATHWAY

The AKT pathway is an essential pathway related to the stimulation of growth factors and other cell functions such as cell growth, apoptosis, and cell survival. Most studies have proven that tumor aggressiveness is the result of the malfunction of the AKT pathway and its proteins namely Eif4E, periostin, both the p110 and p85 subunits of PI3K. The mTOR-activated pathway negatively regulates autophagy, making it an unavoidable target for targeting PI3K/Akt/mTOR pathways and thus reducing angiogenesis.[37] 9AA or QC blocks AKT phosphorylation at Ser473 and thus inhibits AKT and mTOR function, since mTOR is the essential component of TORC2 that phosphorylates Ser473.[38] mTOR is also a component of mTORC1, which has its effect on 5cap-dependent Mrna translation by 4EBP1. mTOR phosphorylates 4EBP1 and releases Eif4E, which initiates translation.[39] QC inhibits mTOR and mTOR-mediated translation, which in turn downregulates p110 protein. Since p110 is the class IB catalytic subunit of the P13K family, the pathway is also blocked by QC exposure. P13K induction is required for phosphorylation and activation of the AKT pathway, which sequentially activates THE NF-k pathway by phosphorylation of p65 and Mdm2 to start the p53 pathway.[38]

When a hybrid of the QC and the [1,3]thiazinan-4-one group was prepared, the anticancer effects were

enhanced. The hybrid affected mTOR-4E-BP1 directly without downregulating the AKT pathway, unlike QC. The compound is also successful in downregulating all genes affecting the mTOR pathway downstream.[40]

QC ACTIVATES THE P53 SIGNALING PATHWAY TO CELL DEATH

Cell metabolism and reprogramming are critical to cell sustenance, growth, and proliferation. This cellular metabolism is the connecting link between cell signaling and maintains the microenvironment and thus critical points of cancer, which is mainly influenced by p53.[41] QC increased p21 and MDM2 protein levels and also induced stabilization and accumulation of p53 protein. In addition to acting as a DNA damaging agent, QC also activates p53 and its transcription which is dose and time dependent, and also restores the wild-type p53 in UM-SCC-HNSCC cell lines by altering the TP53 mRNA and protein expression induced.[4] 9AA was found to be less apoptotic in renal cell carcinoma in the presence of null p53. It is noted that the QC mode of anticancer action and dependence on p53 makes it different from traditional anticancer agents, e.g. B. camptothecin, doxorubicin, taxol and vinblastine. QC does not phosphorylate p53, but Ser-392 of the protein kinase CK2.[42]

P53 plays a critical role in tumor cell susceptibility to TRAIL, particularly when TRAIL is combined with DNA-damaging chemotherapy or radiation to treat wild-type p53-expressing tumors. QC has been shown to enhance TRAIL-DR5 interaction, which ultimately increases cellular apoptosis.[25,43] When QC and TRAIL were administered, ROS production, BAX and caspase activation increased synergistically, leading to apoptosis by damaging mitochondria through the intrinsic pathway of apoptosis.[44,45] QC enhances the binding affinity of TRAIL-DR5, resulting in TRAIL binding to the ectodomain of DR5. Subsequently, FADD is recruited, which recruits the procaspase 8 for the activation of caspase8. FADD and caspase8 together form DISC, the death-triggering complex, hence apoptosis.[44] QC has been shown to increase the half-life of DR5 in the ovarian cancer cell line, leading to the accumulation of DR5 and altering its subcellular localization in lysosomes.[46]

The main regulatory factor that controls cell survival and apoptosis occurs through cell cycle regulation, mainly through one of the phases G0/G1, S or G2/M. QC has been shown to enrich cells in the S phase of the cell cycle and thus inhibit proliferation in the gastric cancer cell line. P53 was strongly upregulated upon drug exposure, confirming apoptosis. In the gastric cancer cell line, QC upregulated Bax and downregulated Bcl-2, releasing cytochrome c and activating caspase 3, resulting in the intrinsic pathway of apoptosis.[47]

Cell death can be divided into three types: apoptosis, autophagy and necrosis. Many anticancer drugs induce cell death through autophagy other than apoptosis, suggesting that it plays a critical role in tumor cell growth and differentiation.[48] First and foremost, QC, an anticancer agent, has been shown to act in the late stages of autophagy inhibitor.[32] It was later found to stimulate autophagy in various cancer cell lines. The mode of action turns out to be an excessive accumulation of autophagic vacuoles and their inability to degrade vacuoles and an increased expression of LCB3. Weak base QC traps itself in the lysosome, leading to increased pH and thus cell death via the p53 and p21 pathways.[49] One study confirmed that there is a dramatic increase in LC3-II expression upon exposure to QC and hypothesized that QC drives cells to autophagy, increasing stress within cells and thus inducing apoptosis.[4] In the breast cancer cell line, QC caused apoptosis by upregulating expression of both p53 and p21 genes and inhibiting topoisomerase activity. QC supercoils the DNA, resulting in the inhibition of replication; therefore, cells in S phase aggregate to cell death(50). This cessation of apoptosis or autophagy is decided by exposure to QC, and TRAIL is decided by activating two processes, p21 or DR5, in different breast cancer cell lines. Upregulation of these key proteins is the main feature of QC and TRAIL's synergistic effect with downregulation of other pathway proteins mTOR/P13K/AKT.[51]

Hsp70 prevents cell death by interfering with the ability of cytochrome c and Apaf-1 to recruit procaspase9. Hsp70 can block the release and activation of procaspase 9, which is functional for cell survival relative to cell death. Our study implies that QC increases Hsp70 downregulating Caspase9 expressions. It is evident that Hsp70, the anti-apoptotic gene, probably blocks expression of the apoptosome by caspase9 and therefore does not lead to apoptosis via the intrinsic pathway.[35] Colon cancer cells normally undergo the intrinsic pathway of apoptosis in the presence of QC, but as the cytotoxicity of the cells increases (QC dose increases), the cells tend to reach apoptosis via the extrinsic pathway of apoptosis.[35,52]

QC EXPOSURE INHIBITS NF-kβ SIGNALING PATHWAY

NF-k, a family of five transcription factors that regulate cellular processes, plays important roles in cancer initiation, development, metastasis, inflammatory microenvironmental activity, and exceptional resistance to cancer treatments. This

pathway is activated by multiple stimuli, namely cytokines, growth factors, bacterial, viral products, UV or ionizing radiation, ROS, DNA damage, and oncogenic stress.[53] QC has been shown to induce p53 and inhibit NF-kβ in renal cell carcinoma. In highly expressed NF-kβ cell lines, they are sensitive to QC, ignore p53 status and vice versa. Once activated, NF-kβ induces TRAIL and L-OHP in the cell lines mentioned; decreases c-FLIP and Mcl-1 without affecting NF-kβ dependent proteins. NF-kβ, in the presence of QC, binds to the promoter region of c-FLIP and MCL-1 and shortens their half-life, demonstrating that these two genes are key factors in NF-kβ regulation.[25]

The suppression of NF-kβ by TNF induction proved to be another function of this pathway. QC induced nuclear translocation, accumulation of NF-kβ and also increased its presence in nuclei.[42]

Heat shock response signaling is important for tumor survival and pyogenesis; QC represses Hsp70 synthesis by reducing HSF-1 dependent transcription.[8]

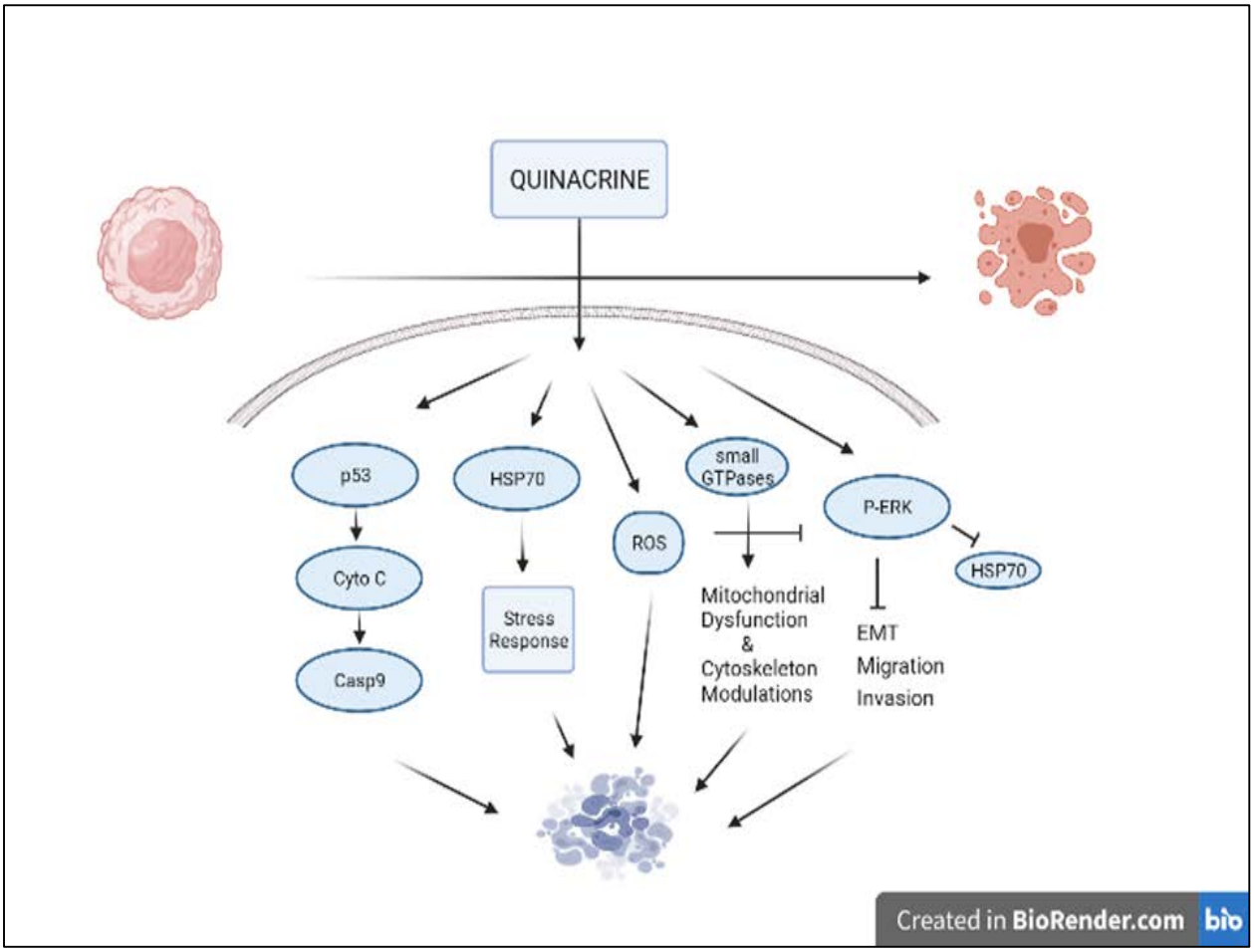

Figure 2. Graphical representation of the mode of action of Quinacrine. QC upregulates p53 and leads to caspase-mediated apoptosis. HSP70 was upregulated, resulting in a stress response and thus cell death. At a higher time point of QC exposure, the HSP70 fold was blocked by P-ERK downregulation. Once P-ERK is downregulated, the classic properties of cancer cells are disrupted, epithelial-to-mesenchymal transition (EMT), migratory ability, and invasiveness are disrupted. QC directly affects cytoskeletal modulations by acting on small GTPases, namely Rac1, RhoA and Cdc42. ROS production increases due to QC exposure and various stress responses, leading to cell death through apoptosis.

QC EXPOSURE TO TGF-β SIGNALING PATHWAY

BMPs (Bone Morphogenesis Protein) are multifunctional cytokines belonging to the TGF family that modulate tumor growth, differentiation, and apoptosis in various cancers. Depending on the type of cancer tissue and its epigenetics, BMPs can act as tumor suppressors or promoters. They have been shown to activate numerous essential proteins downstream, such as SMAD, which regulate p38, JNK, Akt, LIMK, Rho, Rock proteins.[54] QC has been shown to induce the expression of the BMP signaling genes BMP-2 and BMP-4, four times higher than average, and upregulates TGF-1 to induce TGF-β.[55]

Table 1. Genes associated with anticancer properties of Quinacrine

Signaling Pathway	Genes Involved	Gene Description
	APC	Gene responsible for tumor progression and malignant transformation[59]
	GSK-3	A therapeutic target for neurological diseases, diabetes mellitus, inflammation, and a wide variety of tumors[60]
WNT SIGNALING PATHWAY	AXIN	A single point mutation in Axin protein forms an oligomeric core with disoriented tentacles in cancer cells[61]
	CK1α	CK1α suppresses tumor growth and induces autophagy and regulating PTEN/ AKT/FOXO3a/Atg7 in NSCLC[62]
	SMO	Has been proved to play a role in different types of cancer, and its inhibitors can suppress proliferation, trigger apoptosis and cancer stem cell activity[63]
HEDGEHOG SIGNALING PATHWAY	GLI	GLI1 is a crucial target for the treatment of multiple cancer types[63]
	c-Myc	MYC induces tumorigenesis by evading checkpoints, which includes proliferation, cell death[64]
	Cyclin D	Responsible for cellular migration, DNA damage, response, and repair[65]
	NOTCH-1	The notch can be involved in tumor suppression or progression depending on the tissue or cell involved[66]
NOTCH SIGNALING PATHWAY	ADAM-17	Known to play a crucial role in cell invasion, proliferation, angiogenesis, apoptosis and metastasis[67]
	MSI2	Gene involved in the advanced clinical stage of several cancer progression with important roles in EMT[68]
	p38	A tumor suppressor regulating proliferation, invasion, transformation, and cell death[69]
	ERK	ERK is a subject of intense research leading to the development of inhibitors for the treatment of cancer[70,91]
MAPK SIGNALING PATHWAY	c-Jun	Gene plays a vital role in carcinogenesis and cancer progression[71]
	c-FOS	A protooncogene inducing stem-cell-like properties in cancer cells[72]
	ATF2	Factors induce the cancer progression and metastasis[73]
	MCL1	Protein is associated with tumorigenesis, and drug resistance and thus a crucial target for cancer therapeutics[74]
	GST	Protein takes an active part in tumor cell survival, cell proliferation, and drug resistance[75]
	PLA2	Regulates multiple cellular processes that can promote tumorigenesis, including proliferation, migration, invasion, and angiogenesis[76]
	SOX2	An anticancer target promoting proliferation, survival, invasion/metastasis, cancer stemness, and drug resistance[77]
EGFR SIGNALING PATHWAY	FER	It regulates cell migration, invasion, and anoikis resistance in breast cancer cells[78]
	Rac1	The Raf-MEK-ERK pathway is a crucial downstream effector of the Ras small GTPase, the most frequently mutated oncogene in human cancers[70]
small-GTPases	RHOA	A frequently modified gene in all types of human cancer, playing key roles in the actin-microtubule cytoskeleton and gene transcription[79]
	mTOR	Proved to have interesting mechanisms as a potential benefit for developing anticancer drugs[80]
AKT SIGNALING PATHWAY	4E-BP1	Has pro-tumorigenic activity and is mainly found inactive in different types of cancer[81]
	p21	A tumor suppressor gene stimulated in the presence and independent of p53[82]
p53 SIGNALING PATHWAY	MDM2	An attractive treatment for cancers and wild-type p53[83]
	TRAIL	A stimulator of apoptosis and diverse intracellular signaling pathway in cancer[84]
	BAX & BCL2	The ratio profoundly defines the resistance or submission to apoptosis in cancer[85]
	Hsp70	It helps the proliferation of cancer by suppressing multiple apoptotic pathways, regulating necrosis, bypassing cellular senescence program, interfering with tumor immunity, promoting angiogenesis, and supporting metastasis[86]
	TNF	An inflammatory cytokine having elevated expression in a variety of cancer cells[87]
NF-kβ SIGNALING PATHWAY	NF-kβ	Dominates critical roles in cancer progression like inflammation, cancer cell proliferation, and survival, EMT, invasive behavior, angiogenesis and metastasis, genetic and epigenetic alterations, and cancer stem cell formation[88]
TGF-β SIGNALING PATHWAY	BMP-2	Elevated levels of BMP2 promote liver cancer[89]
	BMP-4	Expression levels are commonly altered in tumors, and it is linked to patient prognosis[90]

CONCLUSION

Currently, there is a need for a rationally designed drug that can act as a shotgun and target different or several pathways.[6] QC affects multiple keys signaling pathways, implicated in the malignant progression of numerous cancer types, making it an exciting candidate as a chemotherapeutic agent for new kinds of combination treatments[7]. QC has been proved to be a chemosensitizer that can enhance chemotherapeutic effects on cancer cells, thus opening a new dimension

for combinational therapy. The antitumor property was observed in both in vitro as well as in vivo studies.[52] QC's anticancer properties are well established in many tumor cells.[56,57] A further report confirmed that QC could activate p53 without genotoxicity through protein stabilization by blocking p53 ubiquitination. This deregulation results from the phosphoinositol-3 kinase/AKT/mammalian target of the rapamycin pathway.[35] QC binds and inhibits proteins involved in multidrug resistance, disrupting the arachidonic acid pathway and affecting the p53, NF-κβ, and AKT pathways.[6] QC offers anticancer potential by downregulating cellular inhibitors of apoptosis protein-1, upregulation of Bax, and cleaving caspase 3 independent of p53. QC activates p53, a transcription factor for cell cycle arrest, cell proliferation control, DNA repair, and apoptosis.[58] Therefore, Quinacrine has the potential to be used as one of the small molecules that could be repurposed for cancer chemotherapeutic management in the near future.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. National Institute for Health. Common Cancer Types - *National Cancer Institute*. August 22. 2018.
2. Zeng C, Wen W, Morgans AK, Pao W, Shu XO, Zheng W. Disparities by race, age, and sex in the improvement of survival for major cancers: results from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program in the United States, 1990 to 2010. *JAMA oncology*. 2015 Apr 1;1(1):88-96. doi: 10.1001/jamaoncol.2014.161.
3. Valcourt DM, Dang MN, Wang J, Day ES. Nanoparticles for manipulation of the developmental Wnt, Hedgehog, and Notch signaling pathways in cancer. *Annals of biomedical engineering*. 2020 Jul;48(7):1864-84. doi: 10.1007/s10439-019-02399-7.
4. Bryant J, Batis N, Franke AC, Clancey G, Hartley M, Ryan G, Brooks J, Southam AD, Barnes N, Parish J, Roberts S. Repurposed quinacrine synergizes with cisplatin, reducing the effective dose required for treatment of head and neck squamous cell carcinoma. *Oncotarget*. 2019 Aug 8;10(50):5229. doi: 10.18632/oncotarget.27156.
5. Oien DB, Pathoulas CL, Ray U, Thirusangu P, Kalogera E, Shridhar V. Repurposing quinacrine for treatment-refractory cancer. *In Seminars in Cancer Biology* 2021 Jan 1 (Vol. 68, pp. 21-30). Academic Press. doi: 10.1016/j.semcancer.2019.09.021.
6. Ehsanian R, Van Waes C, Feller SM. Beyond DNA binding-a review of the potential mechanisms mediating quinacrine's therapeutic activities in parasitic infections, inflammation, and cancers. *Cell Communication and Signaling*. 2011 Dec;9(1):1-8. doi: 10.1186/1478-811X-9-13.
7. Young MD, Eyles DE. The Efficacy of Chloroquine, Quinacrine, Quinine and Totaquine in the Treatment of Plasmodium malarias Infections (Quartan Malaria). American Journal of Tropical Medicine. 1948;28(1):23-8. doi: 10.4269/ajtmh.1948.s1-28.23.
8. Neznanov N, Gorbachev AV, Neznanova L, Komarov AP, Gurova KV, Gasparian AV, et al. Anti-malaria drug blocks proteotoxic stress response: anti-cancer implications. *Cell cycle*. 2009 Dec 1;8(23):3960-70. doi: 10.4161/cc.8.23.10179.
9. Zhan T, Rindtorff N, Boutros M. Wnt signaling in cancer. *Oncogene*. 2017 Mar;36(11):1461-73. doi: 10.1038/onc.2016.304.
10. Lips DJ, Barker N, Clevers H, Hennipman A. The role of APC and beta-catenin in the aetiology of aggressive fibromatosis (desmoid tumors). *European Journal of Surgical Oncology (EJSO)*. 2009 Jan 1;35(1):3-10. doi: 10.1016/j.ejso.2008.07.003.
11. Preet R, Shanmugam R, Mohapatra P, Das D, Satapathy SR, Wyatt MD, et al. Lycopene synergistically enhances quinacrine action to inhibit Wnt-TCF signaling in breast cancer cells through APC. *Cancer Research*. 2014 Oct 1;74(19_Supplement):2777-. doi: 10.1093/carcin/bgs351.
12. Siddharth S, Nayak D, Nayak A, Das S, Kundu CN. ABT-888 and quinacrine induced apoptosis in metastatic breast cancer stem cells by inhibiting base excision repair via adenomatous polyposis coli. *DNA repair*. 2016 Sep 1;45:44-55. doi: 10.1016/j.dnarep.2016.05.034.
13. Kim L, Wong TW. The cytoplasmic tyrosine kinase FER is associated with the catenin-like substrate pp120 and is activated by growth factors. *Molecular and Cellular Biology*. 1995 Aug;15(8):4553-61. doi: 10.1128/MCB.15.8.4553.
14. Hanna A, Shevde LA. Hedgehog signaling: modulation of cancer properies and tumor mircroenvironment. *Molecular cancer*. 2016 Dec;15(1):1-4. doi: 10.1186/s12943-016-0509-3.
15. Nayak A, Satapathy SR, Das D, Siddharth S, Tripathi N, Bharatam PV, et al. Nanoquinacrine induced apoptosis in cervical cancer stem cells through the inhibition of hedgehog-GLI1 cascade: Role of GLI-1. *Scientific reports*. 2016 Feb 5;6(1):1-6. doi: 10.1038/srep20600.
16. Carballo GB, Honorato JR, de Lopes GP. A highlight on Sonic hedgehog pathway. *Cell Communication and Signaling*. 2018 Dec;16(1):1-5. doi: 10.1186/s12964-018-0220-7.
17. Asadolahi M, Nikzamir A, Sirati-Sabet M, Mirfakhraie R, Salami S, Darbankhales S, et al.

Evaluation of the Gene Expression of Hedgehog Signaling Pathway Components in Response to Quinacrine in MDA-MB 231 Cells. *International Journal of Cancer Management.* 2020 Mar 31;13(3). doi: 10.5812/ijcm.92661.
18. Aster JC, Pear WS, Blacklow SC. The varied roles of notch in cancer. *Annual review of pathology.* 2017 Jan 24;12:245. doi: 10.1146/annurev-pathol-052016-100127.
19. Nayak A, Das S, Nayak D, Sethy C, Narayan S, Kundu CN. Nanoquinacrine sensitizes 5-FU-resistant cervical cancer stem-like cells by down-regulating Nectin-4 via ADAM-17 mediated NOTCH deregulation. *Cellular Oncology.* 2019 Apr;42(2):157-71. doi: 10.1007/s13402-018-0417-1.
20. Yang S, Sheng L, Xu K, Wang Y, Zhu H, Zhang P, et al. Anticancer effect of quinacrine on diffuse large B-cell lymphoma via inhibition of MSI2-NUMB signaling pathway Corrigendum in/10.3892/mmr. 2020.11813. *Molecular Medicine Reports.* 2018 Jan 1;17(1):522-30. doi: 10.3892/mmr.2017.7892.
21. Sima J, Zhang B, Yu Y, Sima X, Mao Y. Overexpression of Numb suppresses growth, migration, and invasion of human clear cell renal cell carcinoma cells. *Tumor Biology.* 2015 Apr;36(4):2885-92. doi: 10.1007/s13277-014-2918-5.
22. Diagnostics C. Neurotrophin signaling pathway. Neurotrophin Signaling Pathway—Creative Diagnostics. Available at: Crea-tive-diagnostics. com (accessed on 18 July 2021). 2021.
23. Changchien JJ, Chen YJ, Huang CH, Cheng TL, Lin SR, Chang LS. Quinacrine induces apoptosis in human leukemia K562 cells via p38 MAPK-elicited BCL2 down-regulation and suppression of ERK/c-Jun-mediated BCL2L1 expression. *Toxicology and Applied Pharmacology.* 2015 Apr 1;284(1):33-41. doi: 10.1016/j.taap.2015.02.005.
24. Gallant JN, Allen JE, Smith CD, Dicker DT, Wang W, Dolloff NG, et al. Quinacrine synergizes with 5-fluorouracil and other therapies in colorectal cancer. *Cancer biology & therapy.* 2011 Aug 1;12(3):239-51. doi: 10.4161/cbt.12.3.17034.
25. Jani TS, DeVecchio J, Mazumdar T, Agyeman A, Houghton JA. Inhibition of NF-κB signaling by quinacrine is cytotoxic to human colon carcinoma cell lines and is synergistic in combination with tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) or oxaliplatin. *Journal of Biological Chemistry.* 2010 Jun 18;285(25):19162-72. doi: 10.1074/jbc.M109.091645.
26. Romero L, Andrews K, Ng L, O'Rourke K, Maslen A, Kirby G. Human GSTA1-1 reduces c-Jun N-terminal kinase signalling and apoptosis in Caco-2 cells. *Biochemical journal.* 2006 Nov 15;400(1):135-41. doi: 10.1042/BJ20060110.
27. Kumar M, Martin A, Nirgude S, Chaudhary B, Mondal S, Sarkar A. Quinacrine inhibits GSTA1 activity and induces apoptosis through G1/S arrest and generation of ROS in human non-small cell lung cancer cell lines. *Oncotarget.* 2020 May 5;11(18):1603. doi: 10.18632/oncotarget.27558.
28. Hu JJ, Tian G, Zhang N. Cytosolic phospholipase A2 and its role in cancer. *Clinical Oncology and Cancer Research.* 2011 Jun;8(2):71-6. doi: 10.1158/1078-0432.CCR-08-0566.
29. De Souza PL, Castillo M, Myers CE. Enhancement of paclitaxel activity against hormone-refractory prostate cancer cells in vitro and in vivo by quinacrine. *British journal of cancer.* 1997 Jun;75(11):1593-600. doi: 10.1038/bjc.1997.272.
30. Wee P, Wang Z. Epidermal growth factor receptor cell proliferation signaling pathways. *Cancers.* 2017 May 17;9(5):52. doi: 10.3390/cancers9050052.
31. Mitsudomi T, Yatabe Y. Epidermal growth factor receptor in relation to tumor development: EGFR gene and cancer. *The FEBS journal.* 2010 Jan;277(2):301-8. doi: 10.1111/j.1742-4658.2009.07448.x.
32. Salas E, Roy S, Marsh T, Rubin B, Debnath J. Oxidative pentose phosphate pathway inhibition is a key determinant of antimalarial induced cancer cell death. *Oncogene.* 2016 Jun;35(22):2913-22. doi: 10.1038/onc.2015.348.
33. Guo C, Stark GR. FER tyrosine kinase (FER) overexpression mediates resistance to quinacrine through EGF-dependent activation of NF-κB. *Proceedings of the National Academy of Sciences.* 2011 May 10;108(19):7968-73. doi: 10.1073/pnas.1105369108.
34. Hall A. The cytoskeleton and cancer. *Cancer and Metastasis Reviews.* 2009 Jun;28(1):5-14. doi: 10.1007/s10555-008-9166-3.
35. Samanta A, Ravindran G, Sarkar A. Quinacrine causes apoptosis in human cancer cell lines through caspase-mediated pathway and regulation of small-GTPase. *Journal of Biosciences.* 2020 Dec;45(1):1-8. doi: 10.1007/s12038-020-0011-3.
36. Pertz O, Hodgson L, Klemke RL, Hahn KM. Spatiotemporal dynamics of RhoA activity in migrating cells. *Nature.* 2006 Apr;440(7087):1069-72. doi: 10.1038/nature04665.
37. Nitulescu GM, Van De Venter M, Nitulescu G, Ungurianu A, Juzenas P, et al. The Akt pathway in oncology therapy and beyond. *International journal of oncology.* 2018 Dec 1;53(6):2319-31. doi: 10.3892/ijo.2018.4597.
38. Guo C, Gasparian AV, Zhuang Z, Bosykh DA, Komar AA, Gudkov AV, et al. 9-Aminoacridine-based anticancer drugs target the PI3K/AKT/mTOR, NF-κB and p53 pathways. *Oncogene.* 2009 Feb;28(8):1151-61. doi: 10.1038/onc.2008.460.
39. Gingras AC, Raught B, Sonenberg N. mTOR signaling to translation. *TOR.* 2004:169-97. doi: 10.1007/978-3-642-18930-2_11.
40. Solomon VR, Pundir S, Le HT, Lee H. Design and synthesis of novel quinacrine-[1, 3]-thiazinan-4-one hybrids for their anti-breast cancer activity. *European Journal of Medicinal Chemistry.* 2018 Jan 1;143:1028-38. doi: 10.1016/j.ejmech.2017.11.097.
41. Mantovani F, Collavin L, Del Sal G. Mutant p53 as a guardian of the cancer cell. *Cell Death & Differentiation.* 2019 Feb;26(2):199-212. doi: 10.1038/s41418-018-0246-9.
42. Gurova KV, Hill JE, Guo C, Prokvolit A, Burdelya LG, Samoylova E, et al. Small molecules that

reactivate p53 in renal cell carcinoma reveal a NF-κB-dependent mechanism of p53 suppression in tumors. *Proceedings of the National Academy of Sciences.* 2005 Nov 29;102(48):17448-53. doi: 10.1073/pnas.0508888102.
43. Wang W, Gallant JN, Katz SI, Dolloff NG, Smith CD, Abdulghani J, et al. Quinacrine sensitizes hepatocellular carcinoma cells to TRAIL and chemotherapeutic agents. *Cancer biology & therapy*. 2011 Aug 1;12(3):229-38. doi: 10.4161/cbt.12.3.17033.
44. Das S, Tripathi N, Preet R, Siddharth S, Nayak A, Bharatam PV, et al. Quinacrine induces apoptosis in cancer cells by forming a functional bridge between TRAIL-DR5 complex and modulating the mitochondrial intrinsic cascade. *Oncotarget*. 2017 Jan 3;8(1):248. doi: 10.18632/oncotarget.11335.
45. Changchien JJ, Chen YJ, Huang CH, Cheng TL, Lin SR, Chang LS. Quinacrine induces apoptosis in human leukemia K562 cells via p38 MAPK-elicited BCL2 down-regulation and suppression of ERK/c-Jun-mediated BCL2L1 expression. *Toxicology and Applied Pharmacology*. 2015 Apr 1;284(1):33-41. doi: 10.1016/j.taap.2015.02.005.
46. Liang R, Yao Y, Wang G, Yue E, Yang G, Qi X, et al. Repositioning quinacrine toward treatment of ovarian cancer by rational combination with TRAIL. *Frontiers in oncology*. 2020 Jul 16;10:1118. doi: 10.3389/fonc.2020.01118.
47. Wu X, Wang Y, Wang H, Wang Q, Wang L, Miao J, et al. Quinacrine inhibits cell growth and induces apoptosis in human gastric cancer cell line SGC-7901. *Current therapeutic research*. 2012 Feb 1;73(1-2):52-64. doi: 10.1016/j.curtheres.2012.02.003.
48. Portt L, Norman G, Clapp C, Greenwood M, Greenwood MT. Anti-apoptosis and cell survival: a review. *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research*. 2011 Jan 1;1813(1):238-59. doi: 10.1016/j.bbamcr.2010.10.010.
49. Mohapatra P, Preet R, Das D, Satapathy SR, Choudhuri T, Wyatt MD, et al. Quinacrine-mediated autophagy and apoptosis in colon cancer cells is through a p53-and p21-dependent mechanism. *Oncology Research Featuring Preclinical and Clinical Cancer Therapeutics*. 2012 Nov 1;20(2-3):81-91. doi: 10.3727/096504012x13473664562628.
50. Preet R, Mohapatra P, Mohanty S, Sahu SK, Choudhuri T, Wyatt MD, et al. Quinacrine has anticancer activity in breast cancer cells through inhibition of topoisomerase activity. *International journal of cancer*. 2012 Apr 1;130(7):1660-70. doi: 10.1002/ijc.26158.
51. Das S, Nayak A, Siddharth S, Nayak D, Narayan S, Kundu CN. TRAIL enhances quinacrine-mediated apoptosis in breast cancer cells through induction of autophagy via modulation of p21 and DR5 interactions. *Cellular oncology*. 2017 Dec;40(6):593-607. doi: 10.1007/s13402-017-0347-3.
52. Ashkenazi A. Directing cancer cells to self-destruct with pro-apoptotic receptor agonists. *Nature reviews Drug discovery*. 2008 Dec;7(12):1001-12. doi: 10.1038/nrd2637.
53. Xia Y, Shen S, Verma IM. NF-κB, an active player in human cancers. *Cancer immunology research.* 2014 Sep;2(9):823-30. doi: 10.1158/2326-6066.CIR-14-0112.
54. Bach DH, Park HJ, Lee SK. The dual role of bone morphogenetic proteins in cancer. *Molecular Therapy-Oncolytics.* 2018 Mar 30;8:1-3. doi: 10.1016/j.omto.2017.10.002.
55. Ghebes CA, van Lente J, Post JN, Saris DB, Fernandes H. High-throughput screening assay identifies small molecules capable of modulating the BMP-2 and TGF-β1 signaling pathway. *SLAS Discovery: Advancing Life Sciences R&D.* 2017 Jan;22(1):40-50. doi: 10.1177/1087057116669346.
56. Ortega I, Adam R. State of the art clinical article, Giardia: overview and update. *Clin. Infect. Dis.*. 1997; 25:545-50. doi: 10.1086/513745.
57. Puthia MK, Sio SW, Lu J, Tan KS. Blastocystis ratti induces contact-independent apoptosis, F-actin rearrangement, and barrier function disruption in IEC-6 cells. *Infection and immunity*. 2006 Jul;74(7):4114-23. doi: 10.1128/IAI.00328-06.
58. Friedl P, Wolf K. Tumour-cell invasion and migration: diversity and escape mechanisms. *Nature reviews cancer*. 2003 May;3(5):362-74. doi: 10.1038/nrc1075.
59. Falini B, Brunetti L, Martelli MP. Dactinomycin in NPM1-mutated acute myeloid leukemia. *New England Journal of Medicine.* 2015 Sep 17;373(12):1180-2. doi: 10.1056/NEJMc1509584.
60. Ougolkov, A.V. and Billadeau, D.D., 2006. Targeting GSK-3: a promising approach for cancer therapy?. doi: 10.2217/14796694.2.1.91.
61. Anvarian Z, Nojima H, Van Kappel EC, Madl T, Spit M, Viertler M, Jordens I, et al. Axin cancer mutants form nanoaggregates to rewire the Wnt signaling network. *Nature Structural & Molecular Biology*. 2016 Apr;23(4):324-32. doi: 10.1038/nsmb.3191.
62. Cai J, Li R, Xu X, Zhang L, Lian R, Fang L, et al. CK1α suppresses lung tumour growth by stabilizing PTEN and inducing autophagy. *Nature cell biology.* 2018 Apr;20(4):465-78. doi: 10.1038/s41556-018-0065-8.
63. Jeng KS, Sheen IS, Leu CM, Tseng PH, Chang CF. The role of smoothened in cancer. *International Journal of Molecular Sciences.* 2020 Sep 18;21(18):6863. doi: 10.3390/ijms21186863.
64. Gabay M, Li Y, Felsher DW. MYC activation is a hallmark of cancer initiation and maintenance. *Cold Spring Harbor perspectives in medicine.* 2014 Jun 1;4(6):a014241. doi: 10.1101/cshperspect.a014241.
65. Casimiro MC, Crosariol M, Loro E, Li Z, Pestell RG. Cyclins and cell cycle control in cancer and disease. *Genes & cancer*. 2012 Nov;3(11-12):649-57. doi: 10.1177/1947601913479022.
66. Nowell CS, Radtke F. Notch as a tumour suppressor. *Nature Reviews Cancer.* 2017 Mar;17(3):145-59. doi: 10.1038/nrc.2016.145.
67. Düsterhöft S, Lokau J, Garbers C. The metalloprotease ADAM17 in inflammation and cancer. *Pathology-Research and Practice.* 2019 Jun 1;215(6):152410. doi: 10.1016/j.prp.2019.04.002.
68. Sun J, Sheng W, Ma Y, Dong M. Potential Role of

Musashi-2 RNA-Binding Protein in Cancer EMT. *OncoTargets and therapy*. 2021; 14:1969. doi: 10.2147/OTT.S298438.
69. Loesch M, Chen G. The p38 MAPK stress pathway as a tumor suppressor or more?. *Frontiers in bioscience: a journal and virtual library*. 2008;13:3581. doi: 10.2741/2951.
70. Roberts PJ, Der CJ. Targeting the Raf-MEK-ERK mitogen-activated protein kinase cascade for the treatment of cancer. *Oncogene*. 2007 May;26(22):3291-310. doi: 10.1038/sj.onc.1210422.
71. Vleugel MM, Greijer AE, Bos R, van der Wall E, van Diest PJ. c-Jun activation is associated with proliferation and angiogenesis in invasive breast cancer. *Human pathology*. 2006 Jun 1;37(6):668-74. doi: 10.1016/j.humpath.2006.01.022.
72. Muhammad N, Bhattacharya S, Steele R, Phillips N, Ray RB. Involvement of c-Fos in the Promotion of Cancer Stem-like Cell Properties in Head and Neck Squamous Cell Carcinomac-Fos in the Enhancement of Cancer Stem-like Properties. *Clinical Cancer Research*. 2017 Jun 15;23(12):3120-8. doi: 10.1158/1078-0432.CCR-16-2811.
73. Huebner K, Procházka J, Monteiro AC, Mahadevan V, Schneider-Stock R. The activating transcription factor 2: an influencer of cancer progression. *Mutagenesis*. 2019 Sep;34(5-6):375-89. doi: 10.1093/mutage/gez041.
74. Wang H, Guo M, Wei H, Chen Y. Targeting MCL-1 in cancer: current status and perspectives. *Journal of Hematology & Oncology*. 2021 Dec;14(1):1-8. doi: 10.1186/s13045-021-01079-1.
75. Singh RR, Reindl KM. Glutathione S-transferases in cancer. *Antioxidants*. 2021 Apr 29;10(5):701. doi: 10.3390/antiox10050701.
76. Park JB, Lee CS, Jang JH, Ghim J, Kim YJ, You S, et al. Phospholipase signalling networks in cancer. *Nature Reviews Cancer*. 2012 Nov;12(11):782-92. doi: 10.1038/nrc3379.
77. Zhang S, Xiong X, Sun Y. Functional characterization of SOX2 as an anticancer target. *Signal Transduction and Targeted Therapy*. 2020 Jul 29;5(1):1-7. doi: 10.1038/s41392-020-00242-3.
78. Ivanova IA, Vermeulen JF, Ercan C, Houthuijzen JM, Saig FA, et al. FER kinase promotes breast cancer metastasis by regulating α6-and β1-integrin-dependent cell adhesion and anoikis resistance. *Oncogene*. 2013 Dec;32(50):5582-92. doi: 10.1038/onc.2013.277.
79. Porter AP, Papaioannou A, Malliri A. Deregulation of Rho GTPases in cancer. *Small GTPases* 2016: 1-16; doi: 10.1080/21541248.2016.1173767.
80. Sabatini DM. mTOR and cancer: insights into a complex relationship. *Nature Reviews Cancer*. 2006 Sep;6(9):729-34. doi: 10.1038/nrc1974.
81. Musa J, Orth MF, Dallmayer M, Baldauf M, Pardo C, Rotblat B, et al. Eukaryotic initiation factor 4E-binding protein 1 (4E-BP1): a master regulator of mRNA translation involved in tumorigenesis. *Oncogene*. 2016 Sep;35(36):4675-88. doi: 10.1038/onc.2015.515.
82. Abbas T, Dutta A. p21 in cancer: intricate networks and multiple activities. *Nature Reviews Cancer*. 2009 Jun;9(6):400-14. doi: 10.1038/nrc2657.
83. Konopleva M, Martinelli G, Daver N, Papayannidis C, Wei A, Higgins B, et al. MDM2 inhibition: an important step forward in cancer therapy. *Leukemia*. 2020 Nov;34(11):2858-74. doi: 10.1038/s41375-020-0949-z.
84. Johnstone RW, Frew AJ, Smyth MJ. The TRAIL apoptotic pathway in cancer onset, progression and therapy. *Nature Reviews Cancer*. 2008 Oct;8(10):782-98. doi: 10.1038/nrc2465.
85. Lopez A, Reyna DE, Gitego N, Kopp F, Zhou H, Miranda-Roman MA, et al. Co-targeting of BAX and BCL-XL proteins broadly overcomes resistance to apoptosis in cancer. *Nature communications*. 2022 Mar 7;13(1):1-8. doi: 10.1038/s41467-022-28741-7.
86. Albakova Z, Armeev GA, Kanevskiy LM, Kovalenko EI, Sapozhnikov AM. HSP70 multi-functionality in cancer. *Cells*. 2020 Mar 2;9(3):587. doi: 10.3390/cells9030587.
87. Mercogliano MF, Bruni S, Elizalde PV, Schillaci R. Tumor necrosis factor α blockade: an opportunity to tackle breast cancer. Frontiers in oncology. 2020 Apr 22; 10:584. doi: 10.3389/fonc.2020.00584.
88. Taniguchi K, Karin M. NF-κB, inflammation, immunity and cancer: coming of age. Nature Reviews Immunology. 2018 May;18(5):309-24. doi: 10.1038/nri.2017.142.
89. Wu G, Huang F, Chen Y, Zhuang Y, Huang Y, Xie Y. High levels of BMP2 promote liver cancer growth via the activation of myeloid-derived suppressor cells. *Frontiers in oncology*. 2020 Mar 4;10:194. doi: 10.3389/fonc.2020.00194.
90. Kallioniemi A. Bone morphogenetic protein 4—a fascinating regulator of cancer cell behavior. *Cancer genetics.* 2012 Jun 1;205(6):267-77. doi: 10.1016/j.cancergen.2012.05.009.
91. Samanta A, Sarkar A. Altered expression of ERK, Cytochrome-c, and HSP70 triggers apoptosis in Quinacrine-exposed human invasive ductal carcinoma cells. *Biomedicine & Pharmacotherapy*. 2021 Jul 1; 139:111707. doi: 10.1016/j.biopha.2021.111707.

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